Q7A: Questions and Answers

Section 1A: Background and History

Q. Based on FDA changing of the meaning of "should," does this mean that Q7A will be applied differently in the US than in the EU?

No. The change was made by FDA's attorneys to comply with Good Guidance Practices. There was no change in meaning intended. The change in the definition of "should," was not intended to have any impact on how the guidance is applied either domestically or abroad. Remember, Q7A is a guidance document, but it is not legally binding to either the FDA or the public.

Q. How do you define a "significant structural element" in an API starting material?

A significant structural fragment is that portion of a molecule that contributes to or is responsible for the molecule's pharmacological activity. The original definition talked about an important element. In Q7A the term "element," was changed to "fragment" to avoid confusion with the chemical understanding of "element."

Q. How close can you get to the API and still call it an API starting material?

The company should document the rationale for the designated API starting material. Where in a given process the designated regulatory API starting material comes will vary with each process. One of the difficulties was trying to cover all possible situations, because that's nearly impossible. The decision to designate an API starting material is based on more than chemical logic. It is a pharmaceutical consideration as well. Remember, there is a patient at the very end of every API process who is suffering from a disease, and the goal to provide something to get rid of his illness in a safe and reliable manner.

When you're developing a new chemical process or API process you should be discussing your choice of API starting material with the review division. At some point, you should come in and talk to the reviewers and say, 'this is what I consider to be my API starting material, this is where I consider my API process begins." The reviewers are either going to agree with you or disagree, and they might think that it's further back in the process. But, this is something that you should agree on early with the FDA review divisions, because it's absolutely critical that you have agreement with the Agency as to what you define as your API starting material and where your API process begins.

Q. How early should a company discuss with FDA the company strategy, rationale and what we consider to be an API starting material for filing?

Q7A does not address filing issues. However, you should meet with the review division as early as feasible, to get early input from the reviewers in defining the API starting materials.

Q. If you identify an API starting material vendor, does that vendor need to be audited or qualified?

Section 7.1 states "Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials." The API Starting Material would typically be critical to the process, so you should have assurance of the quality of that API Starting Material. For purchased API Starting Materials, this involves establishing the reliability of the supplier's analysis through qualification of the supplier's test results at appropriate intervals, as described in Section 7.3. API manufacturers may choose to audit the manufacturer of the API starting material, but this is not mentioned in nor is it an expectation in Q7A.

Q. Are internal audit reports mentioned in Section 2.4 subject to FDA review during an inspection?

FDA does not generally review internal audits unless just cause exists. FDA has the authority to look at them, under the statute, if they chose to do so. But they generally do not. Such a request is rare, and actually, by policy, has to be approved at very high management levels within the FDA.

Q. Concerning the distinction that you made between ICH versus VICH for APIs for veterinary products, which standards do the FDA inspectors use in the plants producing APIs for US vet products? Are there any differences seen during a PAI, and which standards should a plant follow?

Since the VICH at this point has not adopted Q7A, FDA investigators may use Q7A in inspecting manufacturers of APIs for veterinary drug use. Any issues or deficiency findings will be brought to the attention of their office of compliance, the Center for Veterinary Medicine. They will then apply what is commonly referred to as regulatory discretion with respect to those APIs for vet use. To summarize, since we lack GMP guidance specifically for APIs for vet use, the best guidance investigators could use is Q7A.

Q. You said that the WHO has now decided to compare the Q7A document with its 1992 API GMPs., I heard previously that the WHO was adopting Q7A with no mention of this evaluation. Is this just a standard procedural issue at WHO or do they have specific concerns, doubts, problems with Q7A?

The World Health Organization (WHO) was an observer/participant during the development of Q7A and agreed that it's more scientifically sound, it's updated, and so forth. The WHO also is a public health agency with a heightened degree of concern for developing countries.
The WHO wants to ensure that this guideline is practical for use by regulators in developing countries where resources are very stretched or even non-existent.

Q. To my knowledge, China, Australia, and India have not had official (observer or participant) status in previous ICH guidance processes. By participating in Q7A, do they agree to be bound by it?

China's representation was spotty during EWG deliberations; sometimes an industry person and sometimes a government person. The regulators in China would have to specifically agree or adopt this document.

India did not have regulator representation. There was a conference in Hyderabad that was the first conference to discuss the document. Even at the point where Q7A drafts were not supposed

to be distributed, officials in India had a copy of the Q7A document and it was the subject of the conference. However, the regulators in India have not yet agreed to adopt Q7A.

Q. As a clarification to this question, will the Indian and Chinese regulators be enforcing Q7A on their domestic manufacturers?

The FDA or their European or Japanese counterparts will definitely be using Q7A in China and India for materials being imported into the ICH regions. Any intermediate or API imported into any of the ICH regions would be expected to comply with Q7A, no matter where it originated. However it is not currently expected that Indian or Chinese regulators will be enforcing Q7A on APIs intended for consumption in India or China.

Q. Since most APIs are manufactured outside the US (80 percent or so), and the FDA's moving to the MRA for inspections, what training is being given to government inspectors outside the US, and what about FDA foreign inspection teams?

We intend to have the same training in Europe as we have outlined here. Nearly all of the associations, including the European inspectors and the European Commission, who are supporting or co-sponsoring this event, are participating. It will be a big move forward for European inspectors and for some parts of the industry, in understanding how GMPs are applied to this aspect of the industry.

Q. Just confirming, the definition of "should" could vary from country to country in the final version, for instance the US FDA versus the EU version. What would you recommend for companies that are international/global? Another person also wanted some practical, down-to-earth words around what "should" should mean. In other words, in here, the person asks, is "should" in ICH similar to "must," is "should" in FDA similar to "good to do?" In other words, I think there's a little confusion around "should."

At least in the United States, the "should" language in any guidance is a safe harbor. If you follow it, you should be found in GMP compliance. If you do something different than what is mentioned in Q7A, then you should have information to demonstrate to an investigator that what you're doing is reasonable. If you're doing what the guidance says, the presumption is you're in compliance and you're doing something reasonable.

The intent of the expert working group was that the definition would be the same in different parts of the world. Both the EU version and the FDA version talk about alternative methods and identify recommendations. The language is quite clear in both versions. Q7A identifies GMP expectations or recommendations for API manufacturing. When we talk about GMP requirements, that's usually referring to a regulation, which is legally binding. So, if something is spelled out in the GMP regulation, 21 CFR 211, that's a requirement, that's legally binding.

Q7A's expert work group provided a lot of examples to help identify what we were looking for. It was not meant to be the only way. If we said, "should," our intent was that it's something that should be done, but you could do it in a different way if there was another option and you would be able to justify it. The guidance has a lot of flexibility in it to recognize the real world.

Q. What are the main differences between the FDA's March 1998 API draft and Q7A?

There are several major differences between the two documents. FDA's March '98 draft guidance covered chemical synthesis manufacturing processes and the later isolation and purification steps of APIs produced by biotech and fermentation processes. The scope of Q7A is broader.

In addition, Q7A has a chapter on agents, brokers, distributors, and all those other organizations. There's also a chapter in Q7A related to biotech and fermentation. Q7A only covers APIs intended for human drug products not veterinary drug applications. There were other issues, such as validation issues, that were either removed or clarified. There were purchasing requirements. There were a number of issues that, quite frankly, made the Q7 negotiation worthwhile for both the regulators and industry.

Q. The new ICH guideline is a major step forward in ensuring the quality of APIs. How does the FDA plan to ensure that they are applied and interpreted consistently by field investigators, and who, when, and how it will be applied to overseas suppliers? Additionally, it is really encouraging to see the support and participation of FDA in this important series of workshops. How does the Agency plan to carry through this commitment within its own organization, for example, training of field staff, key review personnel in the application of Q7A to API manufacturing?

With Q7A in mind, FDA is planning to update its compliance program for APIs, 7356.002F. However, changes in FDA's inspectional or enforcement policies with respect to APIs are not anticipated.

FDA personnel have attended previous sessions of these agency/industry workshops. In addition, FDA held a one-week session training course for 40 or more FDA investigators in December 2001 and is planning a second course in May of 2003. The training includes interpretation of Q7A and how to conduct API inspections.

Q. FDA plans to revise its September 1991 guide to inspection about pharmaceutical chemicals and why the need to revise? Does Q7A not replace the 1991 guide?

Since FDA's publication of the Notice of Availability for Q7A, there's been some talk of revising the September 1991 BPC inspection guide. However, no decision has been made to proceed with this revision since some in the FDA still question the rationale for doing this. .

Q. What does Q7A mean?

Q stands for quality, which is one of the four sections within ICH consultation, 7 is the seventh topic considered under Quality, it's the first GMP topic, but it's the seventh topic considered, and A indicates the first document under the topic of GMP.

Q. USP requires water used in the manufacture of parenterals to be water for injection, WFI. Does Q7A conflict with this?

No. If you go back to the scope of Q7A, it clearly states that the sterilization and aseptic processing of sterile APIs are not covered by this guidance

Q. Now that we have Quality System Inspections and Q7A, can you describe what you envision as a typical FDA inspection of an API plant?

The concepts embodied in Q7A grew from concepts used for years. It will not substantially change FDA's audits and inspections of API manufacturers. It does establish clearer guidelines to assist all parties.

Q. Any background, history on why the accountability for lab records was not included in Q7A? For example, numbered pages in a lab bound notebook or sequential lab sheets that cannot be duplicated.

The accountability of lab records stems from the Barr decision and the falsification of laboratory data. Q7A is an international document; it is not just a U.S. document. It provides good, sound guidance on documentation practices, but it does not specify sequential numbered sheets or the level of documentation that has come to be used in the U.S. for lab records since the Barr decision. Q7A allows flexibility in meeting documentation practices.

Q If the raw material is commercially available, and if this raw material is the API only after purification, so we're basically one step removed, does the raw material manufacturer fall under Q7A?

It sounds like you're bringing an API into your facility and just further purifying it. Does Q7A apply? Yes, because, basically, you're bringing in the active ingredient in an unpurified form and subjecting it to the purification. So, the manufacturer of the crude API would probably fall under Q7A.

Section 1B: Introduction

Q. If the Act does not make a distinction between API and dosage drug product and 21 CFR 211 is a regulation and ICH Q7A is a guidance document, then an FDA investigator may still choose to inspect an API manufacturer using specifically and only 21 CFR 211.

This is part of the reason why we have FDA investigators present in the audience at this training session and we've had them present in the other training sessions of Q7A. It's also part of the reason why ORA and CDER, are sponsoring FDA national training courses to discuss Q7A, and telling investigators and industry the same thing when auditing or inspecting API manufacturers.

However, if you find yourself in this situation pull out the preamble to the 1978 GMP regulations and show the investigator the commissioner's response to comment 270 where it clearly says that 211 does not apply to bulk chemical manufacturing.

Q. Did the Expert Working Group discuss a definition of timely? If so, please comment.

We considered the Barr decision definition of "timely" in terms of closing out deviations within 30 days. If it is not possible to do it within 30 days, then it would be wise to write an interim report. It depends on the issue and the urgency or the health implications of what's timely. If it's a situation with potential health implications for patients down the line, then "timely" is certainly faster than 30 days. If the situation involves a complicated corrective action, maybe it'll take more than 30 days. But you need to think about it in those terms.

Q. If equipment is closed, do you usually need environmental controls?

If the equipment is contained or totally closed whereby the API or intermediate does not see the environment, generally there is no rationale for environmental controls.

Q. When and where do we start applying CGMPs? For example, we may use isopropanol to make the reaction of our API or to purify API. We do not manufacture isopropanol, so does the manufacturer of isopropanol have to follow all the CGMPs that apply to us? Does the manufacturer of any excipient have to follow the CGMPs as we do?

This is one of those examples where using this material, isopropanol, based on its intended use, could be classified as a solvent or an active pharmaceutical ingredient. If the company only uses isopropanol in reactions to purify the API, then clearly, the isopropanol would be categorized as a solvent or a raw material. However, if you are a drug manufacturer and you are receiving isopropanol, and you're producing rubbing alcohol, which is classified as a drug, then under that scenario the isopropanol would be the active pharmaceutical ingredient. That's why we have "the intended use" clause in the Q7A definition because certain materials, depending on their intended use, could or could not be classified as API.

Q. Does Q7A apply to excipients manufacturer?

No, Q7A only applies to active pharmaceutical ingredients as defined in the guidance document.. However, there is other guidance available, such as the voluntary guidance developed by the International Pharmaceutical Excipients Council (IPEC). The inclusion of language dealing with excipients was discussed by the Q7A Expert Working Group, but it was decided to focus on APIs.

Q. How are the FDA investigators actually receiving your advice and what are we doing to provide specific training?

ORA has sponsored some national API training courses for field investigators in addition to allowing agency personnel to attend these workshops.

Q. I've got a question here about critical deviation and non-conformity or non-conformance and why were these not harmonized in the document?

Members of the expert working group thought that it was clearer to use deviations or non-conformances rather than using just one of those terms.

Q. When can we expect the industrial guidelines that went into the development of Q7A to be integrated into the local regulatory agencies. For example, as part of the CFR requirements that would insure compliance.

I assume the person is talking about the various documents mentioned that were used to develop Q7A, the PhRMA document, the FDA's March '98 draft, the PICS document. All these documents have been superseded by Q7A. What's being integrated into the regulatory mechanisms in the three ICH regions is Q7A.

Q. The FDA version of ICH Q7A. Why did the FDA version format the section numbers or leave out the section numbers?

That's basically because of the regulation on Good Guidance Practices (GGPs) which require that FDA guidance documents follow a particular format.

Q. If GMP does not start until the starting material is used in the manufacture of APIs, why then are starting material manufacturers inspected for GMPs?

Starting material manufacturers are not routinely inspected by the FDA.

Q. Are there any guidance requirements within Q7A for starting materials?

Section 1.3 defines API starting materials and states "This GMP guidance does not apply to steps prior to the introduction of the defined API starting material."

Q. Radiopharmaceuticals. Are APIs involved in radiopharmaceutical production? Are radiopharmaceuticals excluded from the scope of Q7A because of their unusual process?

Radiopharmaceuticals are excluded from Q7A because of the uniqueness of those processes.

Q. Can an investigator issue observations based on the Q7A guidance?

All the guidance documents, not just Q7A, clearly state that a guidance document is not legally binding in the way that a regulation is. A binding regulation means that you must comply with it or else you are in violation of the regulation, whereas a guidance document, like Q7A, provides recommendations. You could employ alternatives as long as you show these are equivalent.

Q. For a company involved in production of both APIs and drug products, how should one use Q7A along with other guidance?

For the APIs, Q7A should be used. For drug products, 21 CFR 211 should be used.

Q. Would the acid used to convert a free base into a salt form of a drug substance be considered an API starting material? Significant structural fragment?

No. The acid would be considered a raw material but would typically not be considered an API starting material. Regarding the significant structural fragment, it would depend on the specific acid used, but again typically an acid used only for conversion of a base to salt would not contribute the significant structural fragment to the API.

Section 2: Quality Management

Section 2.1

Q. What is your opinion regarding API manufactured with limited resources in which the quality unit if comprised of only one person?

Section 2.1 states that "there should be a quality unit that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. The quality unit can be in the form of separate QA or QC units or a single individual or group, depending on the size and structure of the organization." So for a very small organization it might be reasonable to have a single person having full responsibility for quality.

Q. "Independent from production." Does having different managers constitute independence? If not, at what point in an organization is it acceptable for quality and manufacturing to report to the same person?

The fundamental idea is not to have conflict of interest. For example, the senior vice president for quality should have the independent authority to approve or require changes.

Q. Is there an outside agency that will certify GMP compliance much like ISO 9000 series?

No.

Q. Should quality units actually develop definitions and examples of deviations and critical deviations?

It is important for each manufacturer to define what is critical to each API process. If you deviate from something that you have defined as a critical parameter, then that becomes a critical deviation.

Unfortunately, as companies continue to run a process over the years, they learn about the process and uncover new factors or parameters that they had not originally identified as critical, that indeed affect API quality. So it's important to continue to update your list of critical parameters with knowledge that you acquire over the years. That's part of the purpose of the Product Quality Review discussed in 2.5.

Section 2.2

Q. Why should rejection of an API not be delegated? In other words, does manufacturing have the right to reject if something goes out of specification?

Section 2.2 (1.) stipulates that the quality unit is responsible for releasing or rejecting all APIs and intermediates for use outside of the manufacturing company and that these responsibilities should not be delegated. The reason for this is that these decisions by the Q.C. unit should not be questioned or overridden by production or other departments.

Although not clearly stated, this section implies that the QC unit can delegate the release or rejection of intermediates used internally by further manufacturing.

Q. Release authority for intermediates can be delegated to production except for intermediates that are sold, what about intermediates that are shipped within companies within the same corporation?

Section 10.2 reads, "APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit (s), and if appropriate controls and documentation are in place." So as long as it's still in the same corporation or a subcontractor, its foreseeable that production could release intermediates provided this is authorized by the quality unit.

Q. If the laboratory is part of the quality unit, must the procedures, test methods, equipment, etc., be approved by the quality unit in addition to the person in the laboratory?

Section 2.2 states that the quality unit is responsible for "approving all specifications and master production instructions, approving all procedures affecting the quality of intermediates or APIs", and "approving changes that potentially affect intermediate or API quality." Q7A simply defines

activities that should be performed by the quality unit. Q7A does not specify who within that quality unit should perform specific activities. So if your quality control laboratory is part of the quality unit, there is no expectation that there be an additional person inside the laboratory who also approves laboratory operations.

Q. In the non-delegateable activities, does that mean that I cannot have a quality control laboratory as an external supplier?

No, that's not what it means. Testing is not listed as one of the responsibilities that should not be delegated. Section 2.2 (1) clearly states that the quality unit should not delegate the release or rejection of APIs. So regardless of who is conducting the testing, it's up to the quality unit to review the results and to make the release.

Q. Do the responsibilities not to be delegated by QA apply to both clinical and commercial APIs? For example, do manufacturing instructions require QA approval prior to commencement of the manufacturing step?

Responsibilities not to be delegated apply to both except where Section 19 indicates otherwise. Manufacturing instructions is one of the areas where expectations are specifically different for APIs intended for use in clinical trials. Section 19 states that the expectation for documentation is different for clinical materials. It does not call for a Batch Production Record. Section 19.5 states, "Production can be documented in laboratory notebooks, batch records, or by other appropriate means." It is the role of the quality unit to ensure that appropriate documentation is kept.

Q. What is the role of the quality unit in approving changes to master production instructions during clinical trials? What is the quality unit's role in reviewing and approving the master production instructions in phase I and phase II?

In section 19.7 under clinical trials, Q7A states: "Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications or test procedures should be adequately recorded." So the role of the quality unit is to make sure that there is a system for recording all changes and tracking when, in the process, those changes were made.

Q. What should approving of contract manufacturers involve?

A contractor, regardless of the activities they perform, is an extension of the manufacturer's operations. Therefore, the manufacturer is still responsible for ensuring GMP compliance for those activities that have been contracted out. Again, just the fact that you contracted an activity does not mean that you no longer have responsibility for that activity. Refer to Section 2.2 (8).

Q You mention the audit expectation for API starting material suppliers. What do you expect from audits of API suppliers by drug product manufacturers?

With Q7A we now have a GMP guidance document that can be used when drug manufacturers audit an API supplier or manufacturer. It's the same document that the API supplier uses, and it's the same document that the regulators use. For the first time in history, we have a GMP document, which both industry and regulators can use, and everybody should have a clear understanding of the GMP expectations.

Q. With regards to quality and production responsibilities, it is understood that the quality unit cannot delegate all of its responsibilities, but can production delegate its documentation review of all documents to the quality unit?

No.

Q. Equipment and computerized systems are not part of the term material, so suppliers of critical equipment and computerized systems do not need to be approved.

That is an incorrect interpretation of Q7A. Section 2.2 (9) states that the quality unit has the responsibility to approve any changes that could affect the intermediate or API. So if the new equipment or new computerized systems could potentially affect the API in any way it should be approved by the QC unit.

Q. Typically an API manufacturer performs quality tests on intermediates. If it passes, then QC will release the intermediate for the next synthesis step. The quality unit then reviews the entire batch records at the end and releases the final API. It seems that Q7A requires that the quality unit review the batch records and test results at each step, prior to moving to the next step. This may not be practical in some cases.

That's an incorrect interpretation of Q7A. Section 6.7, the final paragraph, states that "production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit (s)."

In addition, Section 2.2 (3) states that the quality unit is responsible for "reviewing completed batch production and laboratory control records of critical process steps" before the release of the API for distribution. It is up to the company to define which steps are critical. So the individual release of the intermediates can be performed by production according to systems that have been approved by the quality unit, and the timing for the quality unit review of the batch records is based on the release of the API.

Q. Am I correct though, in terms of that release of intermediates, there is also a requirement that the quality unit review any deviations, so the production group could be releasing intermediates, but only if the intermediate is good, and they need the involvement of the quality unit for deviations?

Yes, the quality unit should review the deviations.

Q. Is there no need for environmental monitoring such as occupational hygiene monitoring for API manufacturing?

Q7A does not address safety considerations for manufacturing either from an OSHA (Occupational Safety and Health Administration) point of view or from an industrial hygiene point of view. So any monitoring that needs to be done to be in compliance with OSHA is beyond the scope of Q7A.

Q. Please further clarify the scope of QA and the approval of master production instructions versus the production review and approval.

Production is responsible for writing and reviewing the master production instructions and for assuring that these instructions contains all the details that production feels it should contain. The Quality Unit is responsible for final approval of master production instructions. .

Q. Q7A says the quality unit should review and approve all appropriate quality related documents. How much scope did the expert group give to this statement? It's easy to see why production and laboratory documents, but what about maintenance documents? Should the quality unit review and approve a procedure that, for example, tells a mechanic how to put oil into a pump? Another example, should they approve housekeeping procedures?

What you really need to do is balance good judgment and common sense. Typically the quality unit should review the procedures having to do with scheduling of preventive maintenance and how the records on these preventative maintenances are kept. Then the quality unit would typically perform a check of some sort to ensure that preventive maintenance is done on time. But the quality unit does not necessarily need to review the detailed procedure on how that preventative maintenance is done. The same thing for housekeeping, where the quality unit should review the procedure defining how often, who's going to do it, that sort of thing, but the details of how it gets done does not necessarily need to be reviewed by the quality unit. The one exception to that would be if you've got micro specifications and the housekeeping really does impact your API .

Section 2.5

Q. Is it ever appropriate for the quality unit to make sure that the Product Quality Review is performed by another group or is this an activity not to be delegated. For example, review of in process controls, critical API results performed by protocol, approved by the quality unit, issued from technical operations, a group that does not report directly to the quality unit.

Q7A Section 2.2 (15) states that the quality unit's responsibility for "performing product quality reviews" should not be delegated. This wording does not imply that the quality group perform all the work. Other groups may pull together the information and data, but the quality unit should at least review that data and make the final conclusions.

Q: What is expected with regard to trending deviations?

Typically that would be done as part of your product quality review. Part of the reason for trending deviations is to look for problems in your processes. Deviations, even the non-critical deviations can be a good indication of the need to make some equipment changes or some sort of mechanical changes so that the operator can follow the instructions without deviating. The deviations can also be a good indicator of when training needs to be done. Q7A is not explicit about trending of non-critical deviations, but it is a good business practice to do so.

Q. Would it be acceptable to use annual product review as an opportunity to determine which processes and products require revalidation?

Certainly. In fact, this is addressed in Q7A Section 2.5 under product quality reviews: "The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken." So clearly it is intended that data from the annual product review could be used to determine if revalidation is necessary.

Q. Who is responsible for making recommendations for corrective actions for revalidation as a result of yearly product quality review?

That would typically be a joint decision between the quality unit, technical services or engineering services or wherever your technical expertise resides and production.

Q. Under Section 2.5, the product quality review, what is the expectation for the review of critical in process control and critical API test results?

What's expected is that you look at the trends. Are impurities increasing or decreasing? Are the test results all over the place? Simply a review of the trend is what is typically expected there. This can be done with a table of data or a graphical plot depending on the amount of data to be reviewed.

Q. Similarly, what is expected in the product quality review for the review of the accuracy of the corrective actions?

What's expected is that you look to see, did the correction that you put in place work? Did the problem recur again or was that correction action effective? The other thing you should look for is whether putting that corrective action in place causes other problems.

Section 3: Personnel

Q. In the past there has always been a difference between the qualified person as defined in Europe and his or her responsibility and the responsibilities deriving from the education of a person are being seen in the U.S. Can you comment whether this continues to exist and is being seen differently? Basically we're looking at the European question of a qualified person versus here.

Q7A does not address the issue of qualified person. Section 3.1 reads, "There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs." In the European Union there is a requirement that the final release of medicinal products (finished pharmaceuticals) be done by a Qualified Person. This Qualified Person is typically a pharmacist. The EU does not require a Qualified Person to release APIs.

In Japan there is a requirement that a security pharmacist has to release all the APIs.

Q7A can be overridden by regional requirements, but the qualified person was intentionally excluded in Q7A. It is important that person have the appropriate education and experience for the processes and products that are being reviewed and released. In some cases it makes more sense to have a chemistry or biochemistry degree than a pharmacy degree.

Q. Does the Q7A Section 3 on personnel directly apply to laboratory and QA personnel, i.e., adequate number of qualifications, etc., or is it intended to apply only to the manufacturing personnel?

. Manufacturing in the U.S. has come to be a synonym with production. Q7A goes back to the use of "manufacturing" in good manufacturing practices. GMPs don't just apply to production; GMPs apply to all aspects of making the API. "Adequate personnel" applies to manufacturing because that's everybody. That's your lab people, warehouse people, everybody that has to do with the control, preparation, production, testing and distribution of the APIs, and it also applies to laboratory.

Q. What personnel are covered by the training requirement?

Training applies to any personnel who are engaged in manufacturing APIs. Remember the definition of manufacturing includes anyone involved in the receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and related controls. It also applies to your maintenance mechanics, anyone who is working with any equipment that affects the API. This also applies to consultants and temporary employees.

Q. Is training using the Internet acceptable? If so, how could it be documented?

You can utilize any form of training that you find to be meaningful. Documentation should include what the training covered, who provided it, how the training was given and to whom.

Q. Does training record maintenance differ significantly from what is specified by 211?

If you compare the language in 211.25 and 211.5 with what's in Q7A, there are no significant differences in terms of the expectations for training. There is more detail in Q7A than in CFR 211.

Q. Can training records for Q7A covered operations be covered electronically without being Part 11 compliant?

Electronic training records should meet the expectations for computerized systems in Q7A, Section 5.4.

Q. Please discuss ways in which investigators will assess whether there are an adequate number of personnel.

When deviations occur, an investigator may question whether enough people are involved in the work or when investigations aren't being completed in a timely manner whether there are enough people conducting the investigations. That's something that each company should look at on a periodic basis. A good indicator may be the time required to complete investigations and implement corrective actions.

Q. Are regulators looking for disciplinary action against basic GMP errors made by trained and qualified operators?

Q7A does not address disciplinary action against people who make mistakes, nor does it prohibit you from taking such action if it's your company's policy.

You should be very careful of overusing "employee error" or "operator training" as a reason for failure in lieu of conducting a real investigation. It's not always the person that's causing the error. Sometimes the equipment is set up in a manner that the person can't do it any other way. Investigators will raise questions about determining the real root cause if you have too many

deviations where the problem is always seen as operator error. Regulators are looking for root cause identification and true corrective action, not disciplinary action.

Q. On training, what is your interpretation of a person qualified to conduct GMP training?

As per Section 3.1, a person conducting GMP training could be qualified by appropriate education, training and/or experience in the subject matter being taught.

Q. Does the fact that training should be periodically assessed mean testing of individuals or watching the individual perform the operation?

It could be done either way. Q7A tells you what should be done, but it isn't specific on how it should be done. One suggestion is to use your product quality review to look for any trends. Are there a large number of errors on a particular operation? Do you have an indication that additional training needs to be conducted? There are a number of ways that you can look for gaps in your training and repeated testing is not always the most effective way to address that. Also a review of your deviations can be used as an indication about the adequacy of your training program. If you're continually writing up deviations and you attribute these to poor operator training, then your training program might need to be improved.

Q. Please expand on the definition of consultant. Can we exclude persons who are contractors that work under direct supervision of company employees?

That description sounds like temporary employees, and you're not excluding them, you're just not calling them consultants. Temporary employees would be covered under Q7A Section 3.1, which reads, "The responsibilities of all personnel engaged in manufacture of intermediates and APIs should be specified in writing. Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMPs as it relates to the employee's functions. Records of training should be maintained."

Q. Please give an example of what qualified means to a laboratory technician. Is it ten years experience? Is it a BS in chemistry? Is it documented training on certain LC and GC analysis or is it some sort of combination of all of that?

As per Section 3.1, a laboratory technician can be qualified by appropriate education, training, and/or experience (e.g. on the job training.) It depends on what that laboratory technician is doing for you. It's up to you to define what you need for the different tasks that are being performed. It's also important that these people keep their training and their education up to date.

Q. Please clarify the meaning of "training should be periodically assessed." Does this mean competency assessment of those being trained, i.e. post-training assessment?

The EWG spent a lot of time talking about what we meant with this language in Section 3.1. Some members of the EWG felt very strongly that you can assess training while others felt that this was not feasible.

One way to assess training is to look at the accuracy with which the employee is performing his/her job. If the employee is making a lot of mistakes or deviations you may need to provide additional training. Some companies use a post-training testing program. There are multiple ways you could assess the adequacy of the training. The objective is to show that the training you are providing is actually being received and implemented.

Section 4: Buildings and Facilities

Q. In a multi-step API manufacturing process, can charging operations for earlier non-critical steps be done outdoors, as long as the last several critical steps are done indoors?

Under Section 4.1 of Q7A, it is very clear that where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors. That is not restrictive at all as to steps. It depends on whether the equipment provides adequate protection of the material.

Q What is the expected frequency of testing of High Purity Water systems, such as Purified Water with Endotoxin Control: daily, weekly, bi-weekly, monthly, etc., for point of use sampling?

Q7A does not specifically address frequency of testing of high purity water systems. The frequency of testing for both endotoxin and microbial testing of water systems will vary from one company to another. A company should assess what is most practical for their particular operation. The frequency of testing for both microbial and endotoxin attributes will depend upon the design of the water system, the quality of the source water and other factors

Q. For Intermediate processing, comment was made that the processing of potentially toxic, i.e. pesticides, was not that significant an issue. Can a company support such an activity?

Yes. Some APIs may actually be derived from an intermediate that is a pesticide or an herbicide. This is possible at an intermediate stage. (Section 4.4)

Q. Is Purified Water or Water for Injection the quality of water you are requiring or recommending for use in API production?

As per Section 4.3, "water used in the manufacture of APIs should be demonstrated to be suitable for its intended purpose." So, it is up to the manufacturer to determine what quality of water should be used at various stages of the API process and establish appropriate specifications. Potable water is the minimum quality of water to be used in API manufacturing. (Section 4.3)

Q. Permanently installed pipe work identification: would documentation be a P&ID, or would a process flow diagram be an adequate substitute for labeling individual lines?

It depends. Q7A Section 4.2 states, "permanently installed pipe work should be appropriately identified." It does not address how this should be accomplished. It's up to the manufacturer to determine this. The identification should typically be visible to the persons (operators) working in that area.

Q. Which engineering steps during the planning of a new API plant should be kept, documented, and verified?

Q7A does not get into that level of detail. Sound engineering and scientific practices should dictate what data should be retained.

Q Does the manufacture of API's require the establishment of air quality standards, HVAC systems specifications to insure no dust migration during the charging of components used in API manufacturing from one reactor to another?

Section 4.2 of the guidance states that "adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment."

If the API process is essentially a closed-system, this would minimize the need for establishment of air quality standards and specific area classifications.

Q. Drug product manufacturers rinse manufacturing equipment with purified water. Should API manufacturers rinse finishing equipment such as mills and blenders with purified water?

Q7A does not specify the quality of water that should be used in any process or cleaning step. Once you determine what quality of water is suitable for a particular step, you might want to use the same quality of water to rinse the equipment. (Section 4.3 & 5.2)

Q. Is microbiological control in the environmental clean room necessary if the room is not used for injectable grade products?

Section 4.2 states that if microbiological control is necessary, your facilities should be designed to minimize the possibility of microbiological contamination. Sterile APIs are outside the scope of Q7A.

Q. The new EMEA note for guidance on water has some clauses around APIs and water qualities that are tighter than the Q7A guidance. How should companies interpret these two guidances?

The Q7A expert working group had extensive discussions over a number of meetings around the world about the quality of water, and the final wording recognizes that in many circumstances there was not a good justification to expect more than potable water quality.

We considered a lot of issues and opinions when developing this language, but the bottom line here is whenever you're asking about the quality of water, you always have to ask what is the water being used for? If you're using potable water at a very early process step, its impact may be minimal, even if you're using it at a later processing step, its impact may be minimal. As per Section 4.3, the manufacturer basically needs to determine that the quality of water they're using at any particular step is suitable for its intended purpose.

Q. Regarding closed systems for APIs in the same room allowing for multiple products to be manufactured in that same room, is that just different lots of the same product or different chemical entities or reactions?

It is uncertain what the question means by the "same room" in an API facility.

Section 4.1 states that facilities should be designed to minimize potential contamination and cross contamination. That's the intent. There is no reason why you could not have different processes or different intermediates or APIs processed side-by-side in closed reactors.

Obviously, a packaging operation is a different scenario. Having side-by-side packaging operations without some sort of a barrier or containment between the lines is not an acceptable GMP practice. The intent is to minimize cross contamination from one process to another.

Q. We've heard Europe has defined a fourth level of water purity called highly purified water, which seems to be aimed toward the production of APIs. What impact will this have on the other ICH regions and Q7A if any?

Q7A, like any GMP document, does not define standards. API manufacturers should establish adequate specifications for process water, but Q7A does not define or specify the use of purified water, highly purified water, or WFI. This is outside the scope of Q7A.

Q. Does the manufacturing facility need to be qualified to be at least class 100,000 for API manufacturing?

No. See Section 4.2.

Q. Section 4.4. For material of high pharmacological activity or toxicity, dedicated production areas should be considered unless there is validated inactivation or cleaning validation. Is there an amount or a method for determining if your compound is considered highly potent?

Q7A does not define potent or a potent compound. There are some definitions in the OSHA requirements in terms of the various containment areas. (Section 4.4)

Q. Would validation of critical HVAC controls be expected if there were a separate validated alarm and monitoring system?

As per Section 4.2, all utilities that could affect product quality, to include heat, ventilation, and air conditioning systems, should be qualified and appropriately monitored.

Q. In design and construction, is there any topic under the subtitles regarding local hazards because of adjacent units, adjacent companies, which are involved in non-pharmaceutical operations? Say dyes for the textile industries or rubber industries and the like that are located in the same chemically zoned industrial district as the plant?

No. Q7A does not specifically address this issue. However, Section 4.1 states that buildings and facilities used to manufacture intermediates and APIs should be located, designed and constructed to minimize contamination or cross contamination. So if you're in an area in which for, one reason or another, you believe there is a possibility of contamination from a neighboring chemical plant, then you have the responsibility for ensuring that the facility, equipment and the process is protected from potential contamination.

Q. If you're using electronic systems for control of materials, exactly what physical segregation or physical separation of products and areas is needed?

Section 4.1 states there should be defined areas or other control systems for a variety of activities. If you have an adequate documentation or electronic system that provides appropriate control and handling of materials, there's not an expectation for physical separation of the materials. In addition, Section 7.2 states, "A system should be in place to identify the status of each batch." This can be a documentation or computer system.

Q. For nitrogen gas, which is being used for vessel-to-vessel transfer. What qualification is required? Anything besides IQ, OQ and PQ?

Section 4.2 states, "All utilities that could affect product quality should be qualified and appropriately monitored, and action should be taken when limits are exceeded." So in addition to qualifying a system, there should be some sort of monitoring.

Q. What does adequate protection in Section 4.1 and adequate filtration in Section 4.2 mean?

Q7A does not address this because it's up to the manufacturer to determine what is adequate protection for their particular processes. Section 4.1 states, "Where the equipment itself, (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors." If it's a reactor, and it's completely closed, that's probably fine. If it's equipment that you are opening outside to sample or to introduce materials, you may need some temporary protection where the system is being opened.

Q. There are several questions here that relate to standards for clean room classes and are asking about regulations or specific guidances that identify either where they're needed or about design requirements for room classifications, Class 10,000, etc.

Q7A does not define standards for clean room classes nor specify classes for API processes or steps. Within the United States, no regulation or guidance has been issued defining the types of clean rooms or room classifications for APIs.

Section 5: Process Equipment and Cleaning

Q. Wherever possible, food grade lubricants and oils should be used. Does that mean it's okay to get into the batch?

The reason that was put in to Q7A is that you should be using materials that will cause the least amount of harm if a small amount gets into your batch. If, however, you have catastrophic seal failure and a large amount of lubricant gets into the batch, you really should investigate this as a deviation and determine its impact on the quality of the API or intermediate. Yes, that does mean that small amounts may get into your batch, but it is not intended to imply that you don't investigate failures or process deviations

Q. What do you recommend in terms of status indicators for production equipment? Give me examples.

As per Section 5.2, "Equipment should be identified as to its contents and its cleanliness status by appropriate means." This can be accomplished by physically labeling the equipment or by computer controls.

Q. Regarding equipment identification. Is it considered necessary to identify transfer lines with direction of flow?

It might be an issue for safety, but it is not addressed in Q7A.

Q. What was EWG's thinking along the lines of consumable items such as inline filters, O - rings and gaskets? Is there an expectation that they are treated as job aids or equipment?

It would be reasonable to regard them as part of the equipment and include these in the equipment change control procedure. If you exchange these items and they have a different composition, different material, they can have a significant impact on the intermediate or API.

Q. Is the performance of preventive maintenance required for each piece of GMP equipment?

Any piece of equipment is subject to wear and tear and a company should have a preventive maintenance program for all pieces of equipment. It doesn't make a lot of sense to buy a very expensive piece of equipment and not have some type of scheduled maintenance of that equipment. Again, this is one area where good common sense practices dictate that this is a good thing to do. It will minimize sporadic or catastrophic failures of equipment, and it will maximize the use of that equipment and its shelf life.

Q. Under preventive maintenance, is it acceptable to let certain equipment to go to failure, such as piping, manual valves, etc?

As per Section 5.2, "Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment." If manufacturers allowed equipment to run until the equipment broke down without concern for maintenance, the company management would bring it to your attention well before the regulators would. Some regulators would conclude that periodic or frequent equipment failures due to lack of a preventive maintenance program is a GMP deficiency.

Q. Are flexible hoses that are repeatedly used considered major equipment, therefore requiring maintenance?

Flexible hoses are not major equipment, but they should be adequately identified, maintained and cleaned. Section 5.2 emphasizes that "written procedures should be established for cleaning equipment and its subsequent release for use in manufacture of intermediates and APIs."

Q. Does Q7A provide for the matrix approach to equipment cleaning validation, or are companies expected to perform a separate cleaning validation for each compound?

Yes. Section 12.7 states: "Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the same process cleans the equipment, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability."

Q. Is it expected to establish a maximum time elapsed from the end of processing to cleaning? Give some examples where this is not appropriate.

According to Section 5.2, procedures should include "establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate." Each company should evaluate the need for establishing maximum elapsed time based on the difficulty of cleaning the equipment after prolonged standing. The GMP issue is to assure that your

cleaning procedure is capable of removing residues that remained in the equipment for an extended period of time after its use.

Q. Is there an expectation to establish time limits for clean equipment before that equipment needs to be recleaned?

Once the equipment is cleaned, it is important that you protect the equipment from contamination. Section 5.21 states that there should be an "inspection of equipment for cleanliness immediately before use, if practical." There is no expectation for a time limit after cleaning.

Q. Cleaning methods - are you looking for the active ingredient, the raw material, and by-product in the cleaning methods?

Generally in cleaning validation you are attempting to remove residues of the compound previously manufactured in the equipment and cleaning agents, if these are used.

The objective is to look for compound residuals that shouldn't be in the next intermediate or API. Anything that you don't expect to be there is what you're trying to find and remove from the equipment. Obviously, if you don't use cleaning agents, then testing for cleaning agents would not be an issue. However, if a company uses a solvent as a final rinse for a piece of equipment, and that same solvent is used in the next process step, they would not be expected to test for residuals of this solvent.

Q. Does the ICH provide guidance on the determination of cleaning limits, residual limits?

Calculation of cleaning limits is not addressed in Q7A. Section 12.74 emphasizes that residue limits should be "practical, achievable, verifiable and based on the most deleterious residue." The limits can be established "based on the minimum know pharmacological, toxicological, or physiological activity of the API or its most deleterious component."

Q. What is the group's opinion of detergent cleaning versus solvent cleaning?

This issue is not addressed in Q7A, although it was discussed by the EWG. If the solvent used to clean equipment is the same solvent that will be used in the next manufacturing step, it would not be of concern. If you are using a detergent for cleaning equipment or a solvent that is not used in the next step, cleaning methods should demonstrate removal of residuals from the detergent or the solvent.

Q. Solvents used for cleaning equipment. May these be recovered?

According to Section 14.4, "solvents can be recovered and reused in the same process or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse." This includes recovery of solvents used for cleaning. Of course, you should establish appropriate test specifications and quality criteria for the recovered solvents.

Q. Visual and analytical verification after cleaning, is one exclusive to the other?

Section 12.7 states that "equipment cleanliness can be monitored by analytical testing and visual examination, where feasible." Visual examination can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis." Generally, some combination of analytical testing and visual exams are employed.

Q. For a non-sterile API intended for use in a sterile drug product, what level of equipment sanitization and/or sterilization is expected and how verified?

This issue is specifically addressed by Section 12.7 which states that "equipment cleaning/sanitation studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern."

The primary issues with a non-sterile API intended for use sterile drug products are the possibility of microbial and endotoxin contamination of the API and subsequent incorporation into the drug product. Endotoxins, once in the API, are generally not removed by drug manufacturing processes.

If you're producing an API that is susceptible to microbial contamination or supports microbial growth, it may be prudent to sanitize or sterilize equipment to minimize microbial and endotoxin levels.

Q. Is cleaning validation expected to take place when the first batches are produced for commercial use (process validation), even when such batches are produced on a pilot or small scale?

Section 19.3 emphasizes that during all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use." Due to the nature of the manufacturing equipment used (e.g., laboratory glassware, small scale equipment or pilots scale equipment that is easily disassembled for cleaning and inspection), validation of equipment cleaning methods is not expected.

Cleaning validation is expected, as per Section 12.7, once API batches are produced for commercial use.

Q. Is cleaning qualification sufficient? Would cleaning validation be expected once the API manufacturing was commercial and not clinical?

Section 12.7 emphasizes that "cleaning procedures should normally be validated." This applies to API commercial processes.

Cleaning or any validation is pretty much recognized as being generally inappropriate for APIs for Use in Clinical Trials. Section 19.3 states: "…procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use."

Q. Regarding use of equipment for pre-clinical and clinical, is it allowable to use the same equipment for both as long as all operations are conducted under Q7A and as long as the worse case scenario is considered for cleaning?

This could be acceptable as long as you have adequate cleaning procedures to remove residues of the previous material from the equipment and those procedures have been shown to be effective.

Q. Is cleaning validation required before the API starting material?

No. Section 1.3 (Scope) of Q7A states "this GMP guidance does not apply to steps prior to the introduction of the defined API starting material."

Q. What is the minimum adequate interval for monitoring a validated cleaning process?

Section 12.7 emphasizes that "cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production." It is up to the company to define the interval for monitoring.

Q. After calibration and/or maintenance of a process unit, is it required to clean the unit before use for processing?

This is not specifically addressed in Q7A. However, using a common sense approach, if the calibration or maintenance of process equipment exposes the equipment to the environment or introduces contaminants, it would be prudent to clean the equipment before use.

Q. Vendors of new equipment often ship you a vessel that has been polished. Often they do not know the chemical constitutes of the polish or of the gases. Our approach to cleaning, in this case, is use of a non-polar solvent to remove organics followed by a polar solvent to remove inorganics. Is this acceptable?

First of all, we have not discussed this kind of cleaning within the expert-working group. What you have just described is a perfect example of how to use scientific knowledge, and it sounds like a good approach for dealing with this situation. .

Q. Please elaborate the definition of dedicated equipment. Equipment used on a campaign during six months can be considered dedicated during this period. Does cleaning validation apply if change of product is forecasted?

Dedicated means that it is used solely for one product and only this product is manufactured in this equipment. In the case of the six-month campaign, it's still a multi-purpose facility. As per Section 5.2, equipment assigned to continuous production or campaign production "should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of microorganisms)." It is up to the company to define the appropriate intervals for cleaning equipment. During this six-month campaign, there may have been cleaning between batches, in addition, appropriate cleaning should be conducted after the campaign is finished to prevent cross-contamination. It would also be appropriate to consider validation of the cleaning at the end of the campaign.

Section 5.3

Q. Do you need to calibrate non-critical equipment?

Normally you calibrate the instruments, not equipment. Section 5.3 of Q7A addresses calibration of critical instruments, but it may be wise to calibrate any instrumentation because measurements may have an impact on the overall process. The calibration program may look different for non-critical instrumentation.

Q. Is it the expectation of Q7A that equipment should be calibrated before and after a preventive maintenance is done on a piece of equipment?

There is not necessarily a link between the calibration of instruments and the preventive maintenance. If the preventive maintenance affects the calibration, then calibration should be done afterwards.

Q. What types of controls are expected if the calibration of equipment is contracted to outside agencies?

No different controls than what would be expected in-house. Any contractor providing a GMP service is an extension of your own company, and there are the same expectations. It's just who's doing it, and you still have the responsibility to insure that it's done correctly.

Section 5.4

Q. Regarding computer validation, is it necessary to second check all data into the computer system or only the critical data?

Section 5.4 explicitly limits this to critical data and not to all data.

Q. Revalidation of computerized systems. What is required for computerized materials management systems used to monitor receipts, sampling testing or release of materials?

There is no formal necessity for routine revalidation of computerized systems. The need for revalidation is based on changes made to the system.

Q. Does Q7A consider 21 CFR Part 11, and what is the regulatory status for compliance when inspecting an API manufacturer? Does Q7A specifically address or imply compliance requirements?

Restated, the question is asking whether Part 11 applies to API manufacturers. This question should be addressed from both the legality and practicality perspectives. Part 11 is the regulations that set forth the criteria under which the FDA considers electronic records, electronic signatures and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper. Section 11.1(b) states that the regulation applies to (1) records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations; and (2) electronic records submitted to the agency under requirements of the Federal Food, Drug and Cosmetic Act and the Public Health Service Act,

even if such records are not specifically identified in agency regulations (this generally applies to NDA's or ANDA's submitted electronically to the agency)

Herein lies the legality issue. Part 11 cannot be imposed on API manufacturers because in the United States we lack a GMP regulation specifically covering the production and control of active pharmaceutical ingredients that sets forth records requirements. Q7A is industry guidance, not a regulation. It is not legally binding and does not establish requirements. .

However, from a practical standpoint, I would not run to the bank with this. If you are an API manufacturer with an established paper record and manual signature system and are contemplating or engaged in converting to an electronic records and electronics signatures system, would you not consider it prudent to assure that this new electronic records system is trustworthy, reliable, and generally equivalent to your paper records and handwritten signatures executed on paper? If so, would it not make sense to follow Part 11 as guidance to provide this assurance?

Section 5.4 of Q7A includes the following expectations for computerized systems:
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- Computerized systems should be validated
- Installation and operational qualifications should demonstrate the suitability of hardware and software
- Controls to prevent unauthorized access or changes
- Record of any data change made, the previous entry, who made the change and when the change was made
- Change control for modifications to hardware, software and any other critical components

In addition Q7A gives you some flexibility as it allows for recording of data by a second means in addition to the computer system. This allows you for example to manually record temperature on a batch record in addition to the instrument recording.

Q. Master batch instructions written by a word processor using something like Microsoft Word, then printed, reviewed and approved as a hard copy, which is signed and dated. True or false, is this an electronic record?

Q7A (section 5.4) does not define what constitutes an electronic record. But from a Part 11 perspective, it depends on is how you are using that document.

Section 6: Documentation and Records

Q. Section 4.2 requires utility system drawings be available. What level of documentation/drawings is expected? Are piping and instrumentation diagrams sufficient, or are drawings showing actual dimensions expected?

Basic diagrams showing the flow and the tracking of the particular piping throughout the facility have been adequate to this point in time. But, identification is the bigger issue. In most cases, the engineering diagrams that the company has obtained from their engineering companies (i.e., the companies responsible for designing and constructing the equipment and installing it) would suffice for inspectional purposes. It is important that those engineering diagrams be current and that they actually show what's in place in the plant at that particular moment. Linking your change control program to updates to your engineering drawings is key to keeping them current.

Q. The CGMP regulations for drug products, 21 CFR 211, specify a written record of major

equipment cleaning, maintenance, and use shall be included in the individual equipment logs. Q7A does not specify individual equipment logs, only records. Does this mean individual equipment logs are no longer necessary/ expected for API manufacturing?

Section 6.2 states that "records of major equipment use, cleaning, sanitation, and/or sterilization and maintenance, should show the day, time (if appropriate), product, batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance. If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately."

It certainly seems to imply that if it is not dedicated, then you don't have those two options. You only have the option of having it as part of the batch record.

This is one area where the EWG was attempting to address the uniqueness of API manufacturing. In many API plants, the entire operation is often controlled from an operation or a control room, where you have an electronic board or some type of automatic control system and the operators sit there and push buttons to control the process. Imagine if, before a particular piece or reactor was to be used, the operator had to stop the process run down to the second floor to get the equipment use and cleaning log for that particular reactor. This doesn't sound reasonable. From the GMP perspective, it's important that equipment cleaning and use be documented. Where it is documented is up to the company.

Q What microbial controls is the manufacturer required to have in place for an API used in clinical trials for parenteral drug product even if the manufacturer has no responsibility for the end use of the API?

The same controls that any private company would be expected to have in place since it is an API. In today's global market, it would be hard to conceive that an API manufacturer would not know the intended use of the API provided to a customer. Particularly, in the clinical trial arena the API manufacturer knows what company is going to receive that API. In many cases, this is the same corporation, because of your new drug substances, new APIs, both the API and the final product are developed by innovative companies. The responsibility to ensure the API is appropriately controlled for use in a parenteral would lie with the Drug Product manufacturer.

Q When making corrections to documented entries, the only requirements are to sign, date, and leave original entry readable. Was there any discussion when writing Q7A to also record the reason for the change? Will field investigators expect this?

The EWG did discuss it but decided not to include it in Q7A. While it might make sense to record the reason, there was concern about how to word the requirement and how it would be interpreted. (Section 6.1)

Q. Please expand on what is acceptable as true copies. Do you mean actual reproductions in place of originals, scanned records, or validated computer system accepted by the FDA?

Yes, these all would be true copies; also microfilm, microfiche. Typically with a true copy like that, someone has reviewed the original and the copy and has signed a document somewhere that indicates that a review has been done and that this is a true copy of the original. (Section 6.1)

Q Should an Equipment Use Log be maintained for non-dedicated equipment? Should it include listing which piece of equipment was used for that particular product at that particular moment?

Section 6.2 of Q7A clearly states, "If equipment is dedicated to manufacturing one intermediate or API, individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately." Thus, it is up to each company to define the format for maintaining these records.

Q Does the list of raw materials need to include a list of filters and other commodities? Does Q7A require control of durables and consumables?

Q7A does not specifically categorize filters as a raw material. It is important that the batch documentation record the specifics of the filters used to facilitate subsequent investigations. (Section 6.3)

Q. Is there a list or reference available that defines objectionable organism?

When we talk about objectionable organisms, we're really thinking of the intended use of the product and what organisms would be objectionable based upon that intended use. One example is a topical ointment that is placed over an open wound. If you had Pseudomonas contamination in that ointment, that would be objectionable. So, objectionable really ties into the intended use of the drug product and whether it the presence of that organism would be objectionable given that intended use. USP identifies indicator organisms, pathogens that should be tested for under certain circumstances.

Q Why was the validation protocol not used as a source document for defining critical parameters?

Different companies put that documentation in different files. In some companies, that information is in the development report; in some, it's in the validation protocol; and in some, it's in engineering source documents. We did not try to reference specifically which document would identify, what was critical. It was the EWG 's opinion that the validation protocol was too late for defining what would be critical. By that point, the development reports should have already identified from R&D and from engineering what they pre-define as critical areas of concern. (Section 6.4)

Q What degree of validation should be necessary when data is recorded on a computer and a second system, i.e. paper batch record? Differences could exist in the degree of accuracy on the computer versus the paper. Also, in deciding if a deviation is critical, would one normally expect to see what requirements are critical versus non-critical pre-defined in the production instructions? If not, what justification would you expect to see?

With the exception of significant figures and timing, there's not going to be much of a difference, normally. Many bulk manufacturers record the data electronically from their distributed control system, and then have critical steps manually recorded by operators for a second check. In addition, it makes sure that the operators are focused on these important readings. Certainly companies are not prohibited from having two systems operating at the same time.

Q. Section 6.5 says, " . . . should include complete information relating to production," yet clarification to 6.3 says " . . . short document for recording results;" please explain the discrepancy.

While it is not specifically mentioned in the Q7A document, some companies have chosen to control their documents in this manner. The white box that was shown on the slide said that there's no one right way to do it. You can have all of the instructions on one document, and then you can have a short document that would have the same numbers, so you just record the results. That's what is meant by short, as opposed to having blanks throughout the instruction where you would record the results, and each completed batch record would be a copy of the instruction and the results together

A similar situation occurs in drug products regarding the requirements of 211.188(b) where it says, "documentation that each significant step in the manufacturing, processing, packing, or holding of the batch was accomplished." A good example would be documenting an integrity test on a .22-micron filter. In some companies, in the batch record, it will say perform the integrity test following procedure so-and-so, and the person then goes and looks up the procedure. Other companies will detail the actual procedure in the batch records.

Q In deciding if a deviation is critical, would one normally expect to see what requirements are critical versus non-critical pre-defined in the production instructions? If not, what justification would one expect to see?

Remember the definition for critical. If it were something that affects the quality of the API, you would probably want to include it in the batch record.

Q. Is there a distinction between a significant and a critical step? Q7A does not define "significant."

Q7A does define critical, and what you will probably find as you're doing your process validation or going through your development reports is that there are a lot of variables with different levels that they will contribute. What EWG tried to address in Documentation and Records, is the critical steps. For your own process consistency, you will probably keep records of steps in addition to the critical steps. But, we have not stated that there is a second signature required, for example; the level of documentation is not the same. You will probably have subsets, such as key parameters, or significant parameters, or whatever.

Q If a data entry were missed, not done directly after performing the activity, is noted and corrected subsequently, i.e. the next day, would you expect a deviation report, in addition?

It is important to know what kind of data we're talking about, but you've probably got to have someone in Quality look at what you're doing (i.e., what it is you're putting in later). So, first, what it is; and second, how do you know that's the correct number the next day? Typically, that would be written up in the format of a deviation, because then you could have all the signatures on the appropriate page.

Q. What are the expectations for second-person review of data entry in the laboratory including weighing, adding, etc.?

Section 6.6 of Q7A indicates that the review of laboratory records should include "the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards." Typically, second-signature on weighing in the laboratory is not done for GMP reasons; if you're handling narcotics or controlled substances, that's a totally different issue. In order to review accuracy, there typically has to be a check on the calculations. Review for completeness would be to confirm that all of the work has been done, and everything has been filled out fully. Compliance with established standards would be accomplished through comparison of the result against the expected result.

Having a second person always watching over your shoulder to witness everything you do is an unreasonable expectation. This could create havoc in the laboratory and probably impede the proper and efficient analysis of materials and drug products in the lab.

Q What is the difference between official and established specifications? Are these terms interchangeable?.

That is an example of putting in wording to allow the EWG to reach consensus. "Official" was meant to refer to the specifications that would be in the Pharmacopoeia, and "established" being the ones established by the company. "Official" could also mean specifications that are submitted in a regulatory submission to the regulatory bodies.

Q. (Section 6.4) To what level of detail should the manufacturing master production instructions be written with the assumption that the operator has a Ph.D. or is totally ignorant?

The instructions are written not based on intelligence level, but are written with a level of detail such that the operation can be carried out and that in reviewing at a later time, you can know exactly what the history of that batch was. Some of the detail may be included in area SOP's rather than being specified in the master production instruction.

Q. A batch record should be checked before it is issued to production. Can this check be done by production or must it be done by quality?

Q7A (section 6.5) says that the quality unit must check the master production instruction, but for the batch production record, it is silent on who much do the check. Therefore, either quality or production could do this.

Q. Does batch record generation software have to be Part 11 compliant? Can Microsoft products be used to generate these batch records? Do batch record generation programs have to be validated?

Q7A-Section 6.5 says that the batch production record should be checked that it is an accurate reproduction. (Note: See section 5.4 for other questions related to Part 11 compliance.)

Q. Should raw materials have traceability so as to establish the raw material history, etc.?

Yes. Section 6.3 recommends that you show where the raw material was used.

Q. Would you expect to see an official document from the API manufacturer describing the starting material and its position in the synthetic pathway?

Yes. Section 1.3 states that the company should designate and document the rationale for the point at which production of the API begins. Generally the starting material is identified in the regulatory filing. An inspector would probably ask for some documentation describing the starting material and showing the process itself.

Q. Cleaning records, maintenance records don't appear to have to be reviewed or checked anymore by a second person or supervisor. Is this true?

(Section 6.2) There is no specific expectation in Q7A that cleaning records and maintenance records have a second signature of verification. Q7A , section 2.2 tells us that quality is responsible for making sure that effective systems are used for maintenance and calibration of critical equipment. What that says is that it's incumbent on quality to make sure that the system is indeed effective, and if you are having a number of deviations or problems with maintenance or calibration, than maybe that's something that your quality unit would want to consider, but that is not mandated. Further, section 8.1, Q7A states that other critical activities should be witnessed or subject to an equivalent control.

Q. Review of critical process steps. Is the complete review of the batch record for a critical process step, meaning a synthetic step, or is it a review of the critical variables within the critical step?

Q7A (section 6.7) places the responsibility on quality for reviewing critical steps. It leaves you, the flexibility to determine what you define as the critical steps.

Q. Will API firms be held accountable to these guidelines even though operations were conducted prior to effective date of Q7A?

I guess the person is asking whether or not FDA will retrospectively enforce Q7A. During an inspection, inspectors typically evaluate GMP compliance. Now the only time that this might become an issue is if they're looking at batch records for batches that were produced before the implementation of Q7A. But frankly, much of what's in Q7A is not new.

Q. In which document does one designate the API starting material, the drug master file or some other filing application?

At least here in the states, a DMF or the NDA/ANDA could be used. However, it may vary in the other ICH regions.

Q. Is it necessary to complete any investigations including out-of-specification investigations (OOS), prior to release of product?

Q7A (section 6.7) suggests that all deviations, investigations and OOS reports should be reviewed as part of the batch record before the batch is released for distribution. Critical deviations are investigated and documented. Deviations are documented and explained.

Q. As a repackager of APIs, we use an expiry date only when one is given by the manufacturer. However, in a recent inspection, the investigator insisted that all APIs

should have an expiry date. We believe this to be incorrect and would like to know what argument we should use to defend the fact that most APIs do not have an expiry date.

It would be recommended to say that you have a retest date, not an expiry date. Following Q7A, you should indeed have that date either on the label or on your certificate of analysis.

Q. Is it expected to have a complete graph or printout of the whole process batch attached to the batch record for a critical or significant step?

Q7A (section 6.5) states that if it is critical to your process, then you would want to have a record of the appropriate parameters. That record could be an electronic record or that record could be a paper printout that you would attach to the batch record. But either way, you would be able to access that record and you would also need to show if it is a critical parameter that the results of that were reviewed as part of the batch review.

Q. Since results for critical process parameters must be recorded, must the API manufacturer identify critical process steps and parameters in the batch production record?

Q7A (6.5) states that the actual results are recorded in the batch records for critical process parameters. Minimally, critical steps should be identified in the validation protocol (see section 12.2).

Q. Must the intermediate and API storage containers be identified in the batch production records? Must critical materials be identified in the batch production record?

Yes. Section 6.5 says you should describe the containers in which the intermediate or API will be stored. Section 6.4 also requires any special storage conditions be incorporated in the master production instructions. Regarding critical materials, all materials should be described in the batch record.

Q. Corrections have to be signed and dated. How about the original entry? Seems logical that both be dated.

Yes, both should be dated. Section 6.5 says that each significant step in the batch production record should be dated.

Q. What is the Q7A definition for deviations? For example, if one forgets to sign and date a step, but the same person goes back at a later time and signs and dates the step, does a deviation need to be written?

In the glossary, deviation is defined as the departure from an approved instruction or established standard. Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented. Q7A allows the company to determine the extent of the investigation or explanation. This allows for simple deviations like transposing numbers to be easily corrected and noted. Similarly, if you forget to sign and date a step, you would write directly on that sheet later that the step was completed and the line was not filled out at the time.

Q. Does 9.4 label information apply to API samples submitted for laboratory testing?

No. Section 6.6 talks about what you should have in your laboratory records.

Q. Is it acceptable to delegate the batch record review of non-critical process steps to production, reviewing completed batch records and lab records of critical process steps before the release of the API?

Section 6.7 says that non-critical steps can be reviewed by production following procedures that quality has approved. Critical process steps should be reviewed by quality.

Q. Should the time of execution of each step in the batch record be recorded?

Q7A is not specific on this issue. Section 6.5 says that appropriate time should be recorded for significant steps. That's one of the reasons that your production and your quality group should be involved in the initial approval of your master production instruction. There are steps that the time matters on, there are other steps that the time doesn't matter on, and that's a decision you need to make for each particular process.

Q. Is black ink pen, which looks like photocopying, acceptable for filling in data in batch records?

Yes, black would be acceptable. There is no specification in Q7A as to the color of ink that's used. However, entries should be indelible (section 6.1).

Q. Equipment cleaning and use records. For multi-use, non-dedicated equipment, is it acceptable to have these records as part of the batch record or is a separately maintained record required.

Q7A allows you, in the definition of should, to use an alternative means if you can show that the alternative means gives you an acceptable level of quality. Q7A does not specifically recommend a use log. So one could work through the batch records, in a reasonable period of time, to find the answers to any questions on equipment cleaning and use.

Q. Does the section on equipment cleaning and use records (section 6.2) apply to lab equipment in the laboratory. For example, HPLCs, balances, GCs, etc.?

Section 6.2 on Equipment Cleaning and Use record was intended to apply to the equipment used in the production of intermediates and API. However, the documentation that you would keep on HPLCs, balances, GCs, etc., is covered in Section 6.6 under lab records, which asks for you to keep complete records of any calibration on laboratory instruments.

Q. For an existing registered process, is the starting material listed in the drug master file registration the starting material for Q7A?

It would be recommended that you review your legacy processes and determine what the starting materials are according to Q7A.

Q. Control data requests that you retain data on the preparation and testing of reference standards. Since many of the reference standards are purchased, how can one accomplish this?

(Section 6.6) The records for purchased reference standards should be retained. For in house materials like, standard solutions that you're actually preparing, you would retain the records on the preparation and testing.

Q. Is it appropriate in a batch record to have large spaces, i.e., pages, for handwritten comments to be entered to document observations, etc., as well as spaces for entering data, i.e., tables.

Q7A does not prohibit it. Typically in a process under development, you would have large spaces for recording observations. In a process that's moved to commercial, you typically do not see that amount of open space in a batch record for recording observations. However, you may have a special situation where that makes sense. It's not typical, but it may make sense in your operation.

Q. Does every operation in a critical step automatically become subject to QA record review?

Q7A (section 6.7) states that records of critical process steps should be reviewed and approved by the quality unit before release. It is up to the company to determine how to review each step.

Q. If an API has an impurity, does the dosage form manufacturer have the responsibility to identify it if the API manufacturer provides a C of A? Which of the two does FDA hold legally responsible?

Q7A does not address dosage form manufacturer responsibilities nor does it address associated legal liabilities.

Q. Does a batch numbering system need to be sequential?

No, Q7A (section 6.5) only says it should be a unique batch or ID number.

Q. Do isolated synthetic intermediates intended for use in the next process step need to be quarantined and released by the quality unit?

No. As Section 6.7 tells you, Quality can delegate to the production unit the responsibility and authority for release of intermediates. So unless the intermediate is being sold, it does not have to be released by the quality unit according to Q7A.

Q. Could you provide some additional comment regarding the filing requirements for alternative rework processes, and if prior approval is required for recovery procedures?

It is best to discuss these issues with the filing agency as part of the filing strategy.

Q. Do all record keeping and traceability requirements apply for brokers to chemicals and intermediates before the API starting material?

Q7A does not apply to the process chemicals and intermediates prior to the API starting material regardless of the source.

Q. Slide 6.26 requires the investigation of deviations and results of release testing after the completion of each significant step. Usually release testing and deviation investigations take longer than it takes to complete each significant step. Is it acceptable to include this documentation in a report after completion of the batch instead of after each significant step?

Yes, that can be done after the completion of the step. What Q7A tells you in Section 6.7, is that this should be completed before the release of the batch.

Section 7: Materials Management

Q. What is the difference between evaluating suppliers of critical material in Section 7.1, and the supplier approval evaluation discussed in Section 7.3? Does Section 7.3 pertain to all materials or just critical materials?

Section 7.3 regarding sampling and testing of incoming materials is pertinent to all materials. Section 7.1 says that you should have a system for evaluating the suppliers of critical materials. Section 7.3 describes what that system should include.

Q. Sampling and testing states that, "No testing necessary for special materials if . . ." Please define special materials in this context.

This language was used in Q7A Section 7.3 specifically to allow you to justify why you would not be testing a certain material. It could be that it is a material that is not necessarily highly toxic or highly hazardous, but it is a very specialized material. The supplier has very specialized testing ability and testing procedures, and you do not have that particular capability. What Q7A says is that for special situations, you can justify taking it on the vendor's Certificate of Analysis. Obviously, you would have developed some sort of confidence in your vendor to do that testing.

Q. Regarding Alternate method for rejected material, is it okay not to have a separate area?

Section 7.4 specifies that a quarantine and control system exists for rejected materials. How that is accomplished should be justified and can be done in numerous ways.

Q. Where do gases fall, i.e., nitrogen for the blanket, as a raw material or process aid? Do they require material management control, quarantine, ID testing, etc?

Most would considered it to be a processing aid, which is a material used that does not participate in the reaction. In most cases, companies probably do not do extensive testing on incoming nitrogen. (Section 7.3 & Glossary)

Q. Under Section 7.3, third paragraph, "describe other special materials." These are materials excluded from testing. Does the company define the special materials? If so, on what basis?

Yes, the company should be defining that something is a special material, that no additional incoming testing will be done, and the reason why they are not going to do it. (Section 7.3)

Q. What is an appropriate system to allow a material's use while still under quarantine? What makes a conditional release appropriate?

Q7A says that you can use material prior to its release or prior to its completing testing, as long as you have an appropriate system to allow its use under quarantine. It does not define what has to be in that appropriate system. It would certainly seem that an appropriate system should be procedurized, so you should have a written procedure that says what you are going to do. Obviously, if you are going to have a written procedure, then it has to be approved by the quality unit. The system will probably only permit use of material for which you have good data; material for which you do not suspect that there is any problem. You are just waiting to complete the

testing, or validation studies, or something like that. A critical part of the system is that you really do have a good system to "flag" the material in which this unreleased material is used. So if there is a problem, you know exactly where it was used. You also then have a system to make sure that, prior to release of the material in which this unreleased material has been used, there is a way to verify that the unreleased incoming raw material or the API really was released before the final product goes out. Those would certainly seem like some of the key things that would have to be in an appropriate system, but Q7A does not specify what those characteristics have to be. (Sections 2.1 and 7.2)

Q. When incoming materials are mixed with existing stocks, for example, solvents. How can a distinctive batch or receipt number be meaningful for purposes of tracking materials used in a specific production batch? And, how useful is assigning batch numbers to such materials when they are mixed?

First of all, the intent of Q7A (section 7.2) was that you need to be able to track batch history and raw material history. The distinctive code will enable you to track your material and show what's mixed with what, and that it's been released and properly controlled.

Q. Would you do an ID test, such as IR, on polyethylene bags for API packaging, or could you rely on vendor label ID?

It should be based on the company's judgment. You decide what to do. Some companies routinely do an IR ID on the bags to make sure they really are polyethylene and do measurements on them to be sure they are the right thickness. (Section 7.3)

Q If a material is received from another site within your own company, say a site in another state, do you need to perform an ID test of the material upon receipt?

Q7A allows for not performing an ID test for material being transferred between units of the same company. (Section 7.3)

Q. What is the expectation for auditing and qualifying a producer of an API starting material from a manufacturer of material made for both industrial and API applications?

Q7A does not address and does not cover in its scope the manufacture of API starting materials. Q7A states that there should be a system for evaluating suppliers of critical materials." If a supplier can be adequately evaluated without an audit, an audit clearly is not required. (Sections 7.1 and 7.3)

Q. For a non-dedicated tanker, if a Certificate of Cleaning is utilized to assure no cross-contamination, does verification of cleaning need to be performed?

This is addressed in Section 7.2, which states, "if bulk deliveries are made in nondedicated tankers, there should be assurance of no cross contamination from the tanker. Means of providing this assurance could include one or more of the following: certification of cleaning, testing for trace impurities, audit of the supplier.

Q. What type of laboratory controls and testing are typically expected of labels and secondary packaging containers? Is visual inspection sufficient?

Q7A recommends conformance to specifications, but leaves it up to the company to set them. More companies do simple visual inspection than anything else. Of course, that doesn't mean that your quality group or your manufacturing or even your purchasing group that's spending good money on these materials may not want something additional done in terms of adhesiveness or water resistance or anything that you think is important, but for most companies it's simply a visual inspection. (Section 7.3)

Q. Is it necessary to physically separate the rejected material or is labeling sufficient?

Section 7.4 states that rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing. It is not an expectation that it has to be physically separated, but a reliable system should be used. That could be by spatial separation; it could be by locked cage; it could be by labels; it could be by chains; it could be by computer system, as long as it is reliable to prevent unauthorized use.

Q. Do you need separate areas for materials in quarantine or under test?

There's no expectation under Q7A. The operative section here is actually the definition of quarantine in the glossary: "The status of materials, isolated physically or by other effective means pending a decision." So Q7A is quite specific, it does not have to be spatial or physical separation. (Section 7.2)

Q. How do you validate a method for a toxic or a very dangerous raw material?

You do not have to. Q7A section 7.3 on raw materials states that toxic or very dangerous raw materials do not have to be tested. You can accept them on the certificate of analysis. (Section 12.8 & 7.3)

Q. Is it necessary to audit a supplier?

No. Section 7.1 says that you should have a system in place for evaluating the suppliers of critical materials. It does not mandate that it be an audit.

Q. There is no specific definition for critical raw material. Should we combine the definition for raw material and the definition for critical to come up with the criteria?

Yes, that's exactly the way it was intended. You may notice that throughout Q7A there are many uses of "critical": there's critical raw materials, critical steps, critical parameters, and none of those are defined as composite terms. The intent is always to take the definition of the specific item and add on to it the term critical that is defined in the glossary to make the composite definition. (Section 7 & Glossary)

Q. Why aren't bulk deliveries of chemicals used in API manufacturing held to the same standards as APIs? There is no validation of clean outs for non-dedicated tankers.

Incoming raw materials are not held to the same standards as APIs because raw materials are not covered under the scope of Q7A. However, Section 7.2 does expect that you have assurance that no cross contamination is occurring, and that could be done by certificate of cleaning, an

audit of supplier or testing of the material. So there is concern, but there's no expectation in Q7A that you have validation of raw material suppliers or their processes.

Q. Is statistical sampling a lot for raw materials used for production of APIs sent to Europe?

There are no regulatory restrictions on raw materials used for APIs in Europe. Q7A specifies that samples should be representative, so statistical sampling should be acceptable. (Section 7.3)

Q. There is no expectation in Q7A to have to audit starting material suppliers. It was also stated that starting material suppliers should be qualified. Does this mean that vendor qualification does not need to include an audit?"

Q7A has no expectation for conducting audits of API starting material manufacturers. It's not even a requirement in 21CFR211. The only expectation is that you qualify raw material vendors, and what is mentioned in 211 and Q7A is verifying the laboratory test results that are provided to you on the typical analysis. (Section 7.1)

Q. If Q7A does not apply to API starting materials, is it necessary or mandatory to, first of all, audit manufacturers of API starting materials? And B, if an API manufacturer decides to audit the manufacturers starting materials, against which document should the audit be conducted?

There is no expectation in Q7A to audit a manufacturer of an API starting material because Q7A is very clear and states that the document does not apply to the manufacture of an API starting material. In general, API starting materials are subject to the sections of Q7A regarding qualification of a raw material vendor, and an API starting material supplier should be qualified like any other raw material supplier. The language in Q7A does not specifically talk about and does not mention auditing as a function. It talks about verifying the laboratory test results from your vendor by doing your own testing in house and comparing your laboratory test results against the test results received on a Certificate of Analysis. That doesn't prohibit you from auditing an API starting material manufacturer if you feel that there is a need, in your particular situation. (Section 7.1)

Q. What type of proof would be required by an investigator to verify that a supplier has been designated an approved supplier? Would he or she ask for copies of audit reports if audits were performed?

Section 7.3 of Q7A says that supplier approval should include an evaluation that provides adequate evidence that the manufacturer is going to consistently provide material meeting your specification. That certainly could be a past history of incoming materials. It could include an audit, but Q7A does not have that expectation. One should be prepared to share the information on which you based your approval.

Q. I have a whole series of questions asking about various materials and whether they should be construed as raw materials or process aids or whatever. We had a question earlier on nitrogen, here's one on resin and one on argon.

According to Q7A, the only difference in how materials are classified, is that an identification test can be eliminated for some process aids. But for everything else, you have the same expectations. So, it really doesn't matter how a material is classified. For all materials, you should have an agreed upon specification, an approved supplier, incoming testing with that one

exception of an ID test, and a supplier Certificate of Analysis. Section 7.3 states that processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, etc., etc. You can declare materials other than processing aids to be special materials on which you don't have to do testing. Q7A simply says that you should document and justify why you're doing it.

Q. How do you test ID for a gas like argon for which there's no compendial ID test and the manufacturer says this is controlled by their industry by different fittings?

It may be very appropriate for you to define that as a special material, for which you are not going to do any incoming tests because you know the reliability of the supplier, and it's not necessary. For a resin, it may also be very appropriate for you to declare that a special material. (Section 7.3 & Glossary)

Q. The questioner is asking about the conclusion that no testing is necessary for toxic materials if transferred within the company's control, but non-toxic materials transferred within the company's control would need to be retested and tested again.

That's interpretation is erroneous. Q7A clearly states that transfers within company control of material toxic or not, do not have to be retested. (Section 7.3)

Q. An API manufacturer performing sampling of its starting material within a room not equipped with any type of air handling system. In addition, there's no environmental monitoring. Is this acceptable?

Section 7.3 states that sampling should be conducted at defined locations and by procedures designed to prevent contamination of materials sampled and contamination of other materials. There are not necessarily any requirements for environmental monitoring, unless the material that you were sampling was so sensitive that you needed that environmental monitoring to prevent the contamination of that material.

Q. Also, no log is kept of the raw materials sampled. Is this acceptable?

There's nothing in Q7A that requires a sample room log. Your records should have the date on which material was sampled, and your procedure or records should have identified where it is sampled, so you can probably identify what happened in that room. The fact that there's no expectation of a sample room log in Q7A does not necessarily mean it is not a good practice, and your company may have logs of sequences and times in which things are sampled. (Sections 7.3 & 6.3)

Q. Do distributors of raw materials need to be approved and put on an approved supplier list? What is needed? Is an audit needed?

Q7A states you should have a system for evaluating the suppliers of critical raw materials. It's also written in the document that the agent and so on should transfer all the quality or regulatory information to the customer, including the name of the manufacturer. Q7A does not include an expectation of an audit. (Section 7.1)

Q. Does three-batch testing of raw material have to include all tests listed on the supplier Certificate of Analysis? If your company's specifications do not include all of those listed by the supplier, would it be acceptable to test to you specifications?

When Q7A refers to complete testing, it is referring to complete testing against your specification. It is well recognized, particularly, for solvents that are sold in many industries, that the manufacturer will list on their Certificates of Analysis lots of things that may be of very little consequence to you as the API manufacturer. So this is where it's important that you set a good specification, and the complete testing that's done should be against your specification. If this is questioned during an audit, you may need to justify why your specifications are different from the suppliers, but you should have the underlying science, when you set the specification, to be able to do that. (Section 7.3)

Q. May raw materials delivered in tankers be mixed in silos with old batches of the very same raw material after a limited ID testing is performed? Date and time of mixing and identity are, of course, well known.

Yes, such mixing under the proper controls is allowed. There's more to it than the ID testing because you've also established some history on that supplier. (Section 7.2)

Q. Are we expected to QC release polybags, drums and containers and plastic scoops used to scoop and sample APIs?

First, you don't have to have QC (i.e. the quality unit) release it, because, the release of raw materials can be delegated. However, you would be expected to have a release mechanism for packaging materials, so that would include polybags, drums, and containers that are providing protection. Plastic scoops are different. Q7A does not have an expectation for that. If it's critical to the operation, it might be appropriate to have some sort of an evaluation to ensure it's the right item. For many of these materials, and particularly for drums and containers, the evaluation may be nothing but an inspection that it really is the correct material and not damaged. (Section 2.2 & 7.2)

Q. You mentioned accepting starting materials by performing an ID test in accepting the Certificate of Analysis from a qualified supplier. Could you elaborate on expectations regarding full and reduced testing?

Like 21 CFR 211, Q7A allows a manufacturer to accept COAs on materials provided they establish the reliability of the supplier's analysis by qualifying the supplier's test results at appropriate intervals. Section 7.3 of Q7A states, "Complete analysis should be conducted on at least three batches before reducing in-house testing. However, at a minimum, a complete analysis should be performed at appropriate intervals and compared with the certificates of analysis." (Section 7.3)

Q. By full analysis on batches of raw material in order to qualify a vendor, does this mean all the analysis reported on the vendor's C-of-A or just the analysis we deem critical, i.e. assay, melting point, water, etc.?

As a minimum, a complete analysis should be performed at appropriate intervals and compared to the certificate of analysis. The basic intent here would be verifying all the test results reported on that Certificate of Analysis. But Q7A is a guidance document and alternatives may be appropriate. If there are some parameters on the Certificate of Analysis that are not critical to

your use of the material and you chose not to analyze those, you should provide justification. (Section 7.3)

Q Is it necessary to sample raw materials in a controlled environment?

It depends upon the raw material and what you're going to be using it for, as well as where you're going to use it. Now, if you're talking about that a raw material going into a synthetic process, sampling in a controlled environment is not required. If you're going to use a raw material in the final crystallization after the filtration, then the answer is yes. So, you really need to examine the particular stage of the process and the expectations in order to make the proper choice. (Section 7.3)

Q Storage conditions are listed on raw materials for reasons unrelated to GMP, i.e., some solvents are listed at store below 72°F to avoid high vapor pressures that could cause spills upon opening. How might non-GMP-related conditions be delineated to avoid inspector confusion?

To deal with that, you almost need to try to deal with your supplier and ask them to make it clear as to why that condition is on their label. This has been an issue with some regulatory inspectors. The best way to deal with the situation is to try and get the supplier to make it clear that it is a safety issue or an environmental issue, and not an issue impacting GMPs. If you can't, then you're going to be faced with having to convince somebody scientifically that you're correct. (Section 7.4)

Section 8: Production and In-Process Controls

Section 8.1

Q. Prior to issuing for use, batch production records should be reviewed, dated and signed to prove that it's the correct version. Can the production department perform this check or does QA need to do it?

Production can perform this check based on procedures that have been approved by the quality unit.

Q. Are detailed recipes on the PLC level seen as part of the master instructions? If yes, is review and approval required?

Yes, the instructions in your PLC are considered part of your master instruction if that is what is controlling your process, and you need to be very careful about the approval of those instructions and also of the change control on those PLC instructions.

Q. In Europe, it is common to require only a single signature for critical manufacturing steps. In the batch records, Q7A requires a second person to verify. Which system will prevail in Europe?

Q7A states in 8.12: "critical weighing, measuring or subdividing operation should be witnessed or subjected to an equivalent control". Q7A goes on in 8.13 "Other critical activities should be witness or subjected to an equivalent control." This is one of those areas where Q7A is trying to address the uniqueness of API manufacturing recognizing that many times API processes are

handled or controlled by a common control panel. Operators may be sitting in a control room pushing buttons to add reagents or solvents to reactors or tanks. Imagine how cumbersome it would be if the operator had to run down to the tank and make sure that the acid was actually added to the tank. That is not an expectation in API manufacturing. That's why Q7A allows an equivalent control. The equivalent control may be a printout from an instrument showing the amount of e.g. reagent added. In API manufacturing a lot of the processes are in closed systems, many times it's difficult to actually have a second person verify a particular operation and sign off on the batch record. That's why Q7A allows equivalent means of doing this.

Q. If the QC laboratory releases the bulk of the raw material and then the material is subdivided, does QC have to release it again?

Not typically. There may be situations where your quality unit has set up something special, but there is nothing in Q7A that calls for a second release of material after subdivision.

Q. Do you need a second signature for all weighing operations?

No. What Q7A says is critical weighing, measuring or subdividing operations should be witnessed or subjected to an equivalent control. The printouts from balances or printouts from mass flow meters or electronic records can be used for that the equivalent control. Q7A does not, even for the critical operations, always expect a second signature.

Q. Does the second review of a critical processing step need to take place at the time the step is performed? Does the supervisor review following the unit operation meet this requirement?

Sometimes there's no way to review it after the fact, and that's part of why Q7A put in the allowance for electronic or other means of verifying the critical steps. For example, if you're adding a liquid, you may have a printout for your mass flow meter as to how much liquid went in. That together with what the knowledge of what was actually hooked up can be your second verification. So you need to have some justification if it is a critical step and you're not doing a review at the time.

Q. For yields and ranges, how do you define appropriate ranges for yield, the percentages?

You can define the expected yield based on the weight coming out of the process or you can define it as percentages. You can do it either way. Yield is an indication of how your process is running. What Q7A is asking is to make some markers for yourself as to how you expect that process to run. If you're process is outside of those markers that you've set, you look at what is different about the way it ran that particular time.

Q. If the yield and the quality of an API improved drastically over time without explanation, to what extent should it be investigated?

It's very typical for yield and quality to improve as you get more experience with a process. I would tend to look at, in the annual product review, the trend that your yields and qualities are going and make a determination then if you want to adjust any of the ranges. However, if you start getting purities above normal, you need to take a look at your standards.

Q. Would the agency expect you to adjust your ranges to include the new values?

The annual product review, would be the time that you should consider adjusting those ranges.

Q. And that wouldn't necessarily trigger a revalidation?

No.

Q. How are OOS results in yields dealt with at process start-up for a new campaign? Specifically, how should atypical results be dealt with when they are due to hold ups or…in the initial batch at start-up?

This is not specified in Q7A, but typically you do have a lower yield for the first batch that's going through the equipment because it tends to coat the equipment. A possible approach is setting a lower yield for the first batch in the campaign.

Section 8.2

Q. Relative to Section 8.2 on time limits, does stability of a batch under certain processing conditions need to be established by laboratory studies or historical processing data in order not to have to specify time limits? Do max hold times need to be established based on historical data or laboratory stability studies?

Typically you would use is your historical data. For a new process you could establish a tentative hold time. As your database grows and you have additional data on a product at those conditions, you could extend the hold time.

Q. What, if any, stability is expected to be performed on intermediates processed in house? A side question on that is it expected to have retest dates for intermediates that do not leave the company?

Q7A does not have an expectation for a stability program for intermediates other than those intermediates that are being sold. It does not have an expectation for a retest date for intermediates other than those that are the being sold. Q7A states in Section 8.2: "Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use." What are being asked for here are appropriate conditions. Appropriate in this case would refer to both conditions and the length of time. It's not a retest date, it's not a stability program, but there is an expectation that you make sure it is okay to use either through past knowledge or testing prior to use.

If there is concern regarding suitability, it can always be tested just before use. That's why Q7A did not include stability testing and applying retest dates or expiry dates to intermediate as an expectation.

Q. Please comment on holding times for intermediates or APIs and the difference between holding times and time limits.

These are not specifically defined in Q7A. Based on the discussions in the Expert Working Group - time limits are generally established for completion of process steps whereas holding times generally relate to maximum times that a material may be held or stored before reuse or reintroduction into the process.

Q. The other part of the question was, comment on holding times for intermediates or APIs.

For APIs, Q7A does not refer to holding times but rather to retest dates and expiry dates, mostly retest dates. Holding times are generally applied to intermediates, with the exception of those that may be marketed or distributed. For an intermediate that's distributed, Q7A expects a retest or expiry date, but for intermediates being held in house for further processing, the expectation is for holding times. Retest dates and expiration dates are not an expectation for intermediates, but rather holding times.

Q. If we have other ways to measure the process (e.g. temperature, in process tests, pH, etc), do we have to specify a time limit?

Not necessarily. There are a number of reactions that do not have time limits in which the process is controlled by other means.

Q. What if a step has no specified time limit in the master production record, but you have an unexplained process delay? While waiting to make a solvent change, if you know that there's no quality impact, then what sort of deviation or documentation would be expected?

Even though you do not have a time limit in your master instruction, if you do have an abnormal delay, this is a deviation that should be evaluated. You want to use your science and your good common sense. If it were way out of the range from where you normally operate, it would be wise to document that.

Section 8.3

Q. How does Q7A deal with the addition of seed crystals to induce crystallization with respect to: amount of seed needed and used, type, i.e. particle size distribution of seed material, and documentation.

This is a very specific situation that Q7A does not address. However, Q7A says you have to describe and document your process. Seed crystals would fall under the definition of material, which is a general term to denote raw materials, process aids, or intermediates. If the seed crystals are critical to the API quality, then it should be considered a critical process and controlled appropriately.

Q. For a critical process parameter, what is the appropriate method of monitoring, continuous or manual? (Section 8.3)

Either method is appropriate or both.

Q. Section 8.3 regarding OOS. For example, the illustration, your target was to drive to an LOD of 2%, and after a number of hours, the LOD is at 2.5%. Further drying cannot drive the LOD lower than 2.5. Shall the 2.5% be considered as OOS?

Section 8.3 says, "OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process." If your process will not achieve the limit, then an investigation is appropriate to determine whether the problem is a bad result from the laboratory or whether it is process related.

Q. For what deviations are OOS investigations required: in-process test monitoring, excursions outside the historical range, environmental, critical quality impeaching, intermediate impurity tests (final impurity okay)?

As described in section 8.3, "out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process." The in-process tests that you do where you are processing to a result are not normally handled under OOS. For example, if you're drying to a Karl Fischer of two percent and your first result comes up at four percent, your batch record typically tells you, dry two more hours and take another sample, or whatever the specific details are. That is an example of an in-process test to a limit, and that would not need an OOS.

Q. On production and process controls, if carry over from batch to batch is allowed, how would you address an issue of raw material related recall?

That's one of those business risks. If you subsequently find out that there is a problem with a raw material, you will have to evaluate every batch that raw material could have affected regardless of how small an amount of raw material went into the batch.

The risk is real, but the chance of a recall caused by a raw material is far less a risk in API manufacturing than it would be in dosage form manufacturing.

Q. Is it possible to blend some different OOS batches to have a sufficient quantity of products to perform reworking or reprocessing?

Yes. Theoretically, you could blend OOS batches before you started reprocessing, but it might be just as logical to charge the amount that you were going to reprocess into the reactor and not go through the blending operation. (Section 8.3 & 14.2/14.3)

Q. If centrifuge loads are not blended when they are combined, is it necessary to evaluate centrifuge load uniformity during process validation, i.e., first, fifth, tenth load?

That's something you are going to have to determine based on knowledge of your process. If you tend to form impurities when your crystal is in the liquid longer, then obviously your later centrifuge loads may have more impurities than your first centrifuge loads. If that is something you have reason to believe may happen, then you should probably take a look at that either during your development of the process or during your process validation. But this is why we

wanted to be very clear that combining of multiple centrifuge loads in a dryer was not considered blending. On a routine basis, Q7A does not expect that you will do testing of centrifuge loads prior to recombining those in a dryer.

Q. In a continuous process involving several purification steps, must all the intermediates be released prior to going into the next step provided each step has its own protocol and article number and that the process consists of a series of those steps?

Q7A (section 8.3) allows, especially at the intermediate level, for the manufacturing arm or research arm to test and release. Depending on what your internal written procedures say will drive who's going to do the testing and release. It may not even be in the filing. The filing would tend to drive it, but it could also be driven by your own internal procedures

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Section 8.4

Q. When you discussed blending and identified process steps that were not blending steps, are you suggesting that the not blending steps are simply part of the normal process?

Yes, that is exactly what is being suggested.

Q. Why would it not be acceptable to blend two batches of material, one with a high concentration with one with a low or out-of-spec concentration, if the reason for the low concentration is understood and the batch has no quality-related defects?

FDA has traditionally viewed blending of out-of-spec batches with material that is in specification as an act of adulteration, disguising a defect in a batch by blending it with another batch. The guidance in Q7A basically encourages companies to correct a situation by reprocessing or reworking, not by blending.

Q. If we're at a step where we can get a good feel for the final quality of the batch, the last step before concentration and drying, we know that the batch will not pass release testing, we could conceivably mix this batch with another superior quality batch so that in the final step, the final material will pass. Would this be considered blending an OOS batch?

It would be considered devious and it is difficult to imagine a situation where it would be considered and acceptable practice.

Q. What does "appropriate testing of each chemical batch before blending" mean?"

Q7A states in Section 8.4 that out-of-spec batches should not be blended with other batches for the purpose of meeting specifications. Appropriate testing is needed to ensure that no blending of OOS material is occurring. This does not imply that you have to do the full set of USP testing, for example, both before and after the blend, to look for things like heavy metals, residue on ignition, things that historically have never been an issue. One would typically include tests where variability is seen, for example, impurity test, assay, moisture, etc.

Q. If a batch is broken into several fractions and then recombined, is it necessary for all the individual fractions to pass the final in-process specification?

The 2nd paragraph under 8.4 is very important: "Out-of -specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending."

In order to answer the question above, there are a number of things that you need to take into account, and that's why Q7A does not say you must do full release testing prior to blending. Some of the things you should take into account include: At what point is the batch broken into pieces? What happens to those pieces separately? That's why Q7A refers to appropriate testing.

The section on blending addresses blending of the API. It addresses blending of intermediates, if those intermediates are intended for sale, otherwise you are continuing with the process and typically that is not considered a blending operation.

Q. What is the difference between combining fractions from several batches for further processing, which is an activity not considered blending, and blending of tailings from batches of the same intermediate or API, which is considered blending. Please clarify it.

Q7A makes a distinction between further processing and blending. In the case of further processing you are continuing to process in house, and you are going to do subsequent testing. One example of combining fractions from several batches for further processing is charging multiple batches of intermediate into the next step of the process.

Q7A addresses blending from the point of view that you are selling the product, your intermediate or API. If you take pieces of more than one thing and put them together to sell them, what do you need to do? You need to test those pieces before you put them together, you need to ensure that you are not blending out of specification material, you need to do stability studies on final blended material if there's any reason to believe that blending could affect the stability. So there are a number of expectations specific to blending.

We addressed blending in Q7A partly because the term has been commonly used in our industry. At the time Q7A was being developed there was a lot of discussion within FDA about blend uniformity, about what size sample you should take for blend uniformity, about the fact that blend uniformity testing should be done on every batch. That is applicable to drug product only, it is not applicable to APIs. That was why we addressed blending in Q7A to be very clear that blend uniformity testing was not applicable to APIs.

Q. If you combine two crystallized batches for drying, do you have to test the wet material against the full specification?

The answer is, no. You don't have to test it against the full specification. You need to use your knowledge of the history of the product. Where have you historically had problems with failing? For most compounds you would typically look at impurities rather than the full specification. But you need to make an evaluation for each process based on your data. If you don't have history, if you're just starting up a process, what should you do? The same, start with looking at the impurities in each batch.

Q. Is there any limitation for the lot size of a blended lot based on the Q7A? For example, the lot size should not exceed the capacity of the blender?

Q7A does not speak specifically about lot size. The important thing is making sure to use good, sound science. Q7A depends upon good, sound science. You don't want to exceed the capacity of any of your equipment, particularly your blender.

Q. Is it acceptable to blend second crop material with first crop material?

If second crop material meets all of your release specifications and is within your filing, then it is acceptable to blend that material.

Q. Is mixing a centrifuge heel material with the next batch not blending? If we don't consider that blending, how should that be handled?

Carryover of centrifuge heel is not considered blending. That is typically considered carry over of material from one batch to another.

This carryover is typically handled during process validation. You look at the amount of material that's left in the centrifuge, and then depending on the product and how stable it is under centrifuge conditions, it may make sense to take a sample of the centrifuge heel during validation and look at the impurities. That is normally covered in validation and your development and engineering people need to help you set up.

Q. Can heels from dryers, and the example that's given here is 60 kilos, be left inside the equipment between batches of the same campaign?

You need to have data to support how long that heel can remain in the dryer. Sixty kilos sounds like a lot to consider carryover, but you may be talking about a very, very big dryer. So that's a specific question that's hard to answer in general, but the general answer is dryers are one of the areas that you want to be careful because the material that is left and carried over is subjected to repeated heat ups and cool downs. But once you have the data to show how many heat ups and cool downs your product is stable through, you can leave material in there and carryover to the next batch based on that data.

Q. If you blend a tailing into another batch and then retest the blended batch, if you have a policy that is based on retest dates given after the testing, then wouldn't the blended batch get a retest clock in this case?

It's up to you to set the point that you are calling the retest date for your batch. Make sure you're using good science and good common sense. If you have a highly stable product, then it may be okay to set your retest date based on the testing date. If your product is not highly stable, it could appear that you are trying to extend the retest time beyond what would typically be allowed. So just take a look at your own internal practice, and ensure it makes sense from both a common sense approach and also from a good science approach. Typically, the date for a blended batch should be based on the date of the oldest material that goes into that batch, and it seems to try to circumvent that by setting your date based on testing after blending.

Q. Section 8.4 says that batches should have been tested prior to blending. Do you strongly recommend doing it prior to or is it possible for the company to take a business risk and test individual batches at the same time that blending operation is taking place?

Typically you should test individual batches before blending. If you choose not to test individual batches before blending, you need a justification (written) to explain your rationale for any tests you are NOT performing before blending.

Q Is it only required for critical steps to be witnessed or should all steps be witnessed?

The expectation is that only critical process steps be witnessed because those are the steps that by definition are going to have the quality impact or an impact on the quality of the API. Section 8.1 says that "critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control."

Q. Do you need to perform homogeneity tests on two acceptable batches that have been blended into one batch?

Typically, the homogeneity testing is done during blender validation.

Q. Is mixing of two or more batches of intermediate allowed, one of which might be OOS, into solution when reacting the next stage? Assume a weighted average meets the specification.

Q7A, section 8.4 says that OOS batches should not be blended with other batches for the purpose of meeting specifications. It is allowed to mix two or more batches of intermediates into a solution, but if you have a specification, it is expected that all batches of intermediate would meet that specification.

Q. This one applies to chromatography fractions and if your specification is 90 to 100% for the potency, is mixing of fractions with a potency less than 90% allowed if the final potency of the blended fraction meets the not less than 90% purity requirement?

Unless you have something special in your filing that would allow for blending of the subpotent material, than it would subject to what Q7A says about needing to meet specification. You set the specification, so if it is a special case, than you probably have something either in your specification or your filing for that.

It is fairly common for chromatographic purification that the first fractions are going to be much purer than the final ones. Therefore, manufacturers have in process controls that the final fraction(s) coming off are below the specification that the pooled material is going to have, but that would be in their filing.

Section 8.5

Q. The section on impurities relates only to process-related impurities. Does Q7A address impurities that arise from contaminants external to the process, for example, brine inclusion into a batch from a condenser failure? If not, where is this addressed?

It's the second paragraph in 8.5, under contamination control, "Production operations should be conducted in a manner that prevents contamination of Intermediates or APIs by other materials."

Your condenser fluid would fall under the "other materials." Contamination should be treated as a deviation, and should be investigated and documented.

Q. Would the agency expect a maximum residual carry over from a previous batch to be specified and validated? What other rationale could be used for demonstrating that residual carryover does not affect final API quality?

Section 8 does not call for validation or rationalization. Section 8.5 asks for adequate control of that carryover such that you do not adversely affect the impurity profile.

Q. All agree for closed system environmental monitoring room classifications are not necessary. What about where a finished API is isolated and packaged?

Section 8.5 states: "Production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials." Then it goes on and says precautions to avoid contamination should be taken when APIs are handled after purification. So if after purification the API is exposed to the environment, you need to consider and actually implement, appropriate controls to avoid any contamination of the API. What those controls entail is really up to you. Whatever you feel is appropriate and will accomplish the intended purpose.

Q. Under what conditions can quality typically delegate authority for releasing Intermediates to production?

As described in section 8.3 of Q7A, "in-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record." Section 6.7 further states "production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s)."

Section 9: Packaging and Labeling

Q. What's the minimum amount of information required for the labels on containers of starting materials when they are received prior to API manufacturing?

Section 7.2, "Upon receipt and before acceptance, each container or grouping of containers of material should be examined visually for correct labeling, including correlation between the name used by the supplier and the in-house name, if they are different." That's essentially all that has to be done. That's the only reference in here to material that has to be on the label for incoming starting materials. This is an answer that pertains to what is required with regard to GMPs.

Just to clarify one thing, Section 6 does not describe what needs to be on the labels of materials that are coming into you. It does describe what kind of records you need to keep about those materials.

Q. Does the FDA have any objection to storage and shipment of APIs in polyethylene lined fiber drums?

I'm not aware of any. I think it's up to the manufacturer to demonstrate that the packaging is suitable for the product and that they have conducted stability studies to support this container.

Q. 9.2 states that containers should not be additive beyond the specified limits. This imputes the need to evaluate packaging for interaction with the API. On the other hand, that additive of packaging implied is not a concern so long as the API is not altered beyond its specification. Please clarify how an API manufacturer might justify not evaluation product/packaging interactions.

That's part of why your stability program puts material up in the same packaging material that it's typically shipped and stored in.

Q. What kind of ID test is acceptable for packaging materials, such as polyethylene bags, lined drums? Is the shipping document of packaged material used in lieu of a C-of-A?

If it contains all that information normally found on a Certificate of Analysis, then that's probably adequate. If it's just something that's saying, we're shipping you a polyethylene bag, or it just says you're receiving a truckload of polyethylene bags, it's probably not. In fact, the Certificate of Analysis in reference to the specification and meeting those requirements may be adequate.

If you look at Section 7.2, the first paragraph, there's a sentence there that says, "Materials should be held under quarantine until they have been sampled, examined, or tested, as appropriate, and released for use." The bags may be an example of material that you may not test for; you just might simply examine it before use and determine that it's okay.

At least fiber drums, you probably aren't testing; you're probably examining your drums. Q7A does not specify what kind of ID test you could do on polyethylene bags, but IR is often used.

Q. A packaging/labeling question; transport of API outside the facility, can boxes containing API be sealed with tamper-evident tape, or must the inner bottle or container be sealed?

The guidance is basically asking that you put a seal so that you can tell whether or not someone opened it and did anything to the material under normal conditions. The answer, in my opinion, is that's fine. If you use unique tape and can tell if it had been opened, you've certainly satisfied the intent of the guidance.

Any measure you can take to ensure the integrity of that material while it's in transport is most beneficial to you and to your clients. There are many ways of doing that, not only of using seals that have specific designs, which may be hard but may not be impossible to imitate. Some companies use some kind of markings that, under normal lighting are not visible, and are only visible under UV lighting or special lighting conditions to mark containers. The persons receiving this material know that if they look for those markings in specific locations with special lighting, if it's missing, that's usually an indicator that that's not their original material.

Don't forget that the Agency is very concerned about the potential for counterfeit APIs. So, obviously, if you make it difficult for somebody to hide a change in the material, you make it much more difficult to put something else into your box or your container.

Q. Section 11, what do you test for labeling?

Section 11 states that "All specifications, sampling plans, test procedures should be scientifically sound, appropriate to ensure that . . . and labels conform to established standards of quality and/or purity." So, whatever you are determining is appropriate, to determine that it's of suitable quality should be in the specifications. Certainly, some that come to mind, depending upon what they are, pre-printed - again, testing and inspection, these are synonymous - it doesn't have to be a chemical test, but certainly the label copy, the color of the print, if it's a self-adhesive, that there's adhesive on it. Some of these things which are fairly obvious, but in essence, all the things that you require of your supplier to make sure that they get it before you're going to pay them are the things that you're going to want on your specifications and your acceptance criteria.

Q. With regard to packaging materials, Q7A does not make a distinction between inner and outer containers. If you have written procedures for the inner containers that actually come into contact with the API, do you also need written procedures for the outer containers, such as fiberboard boxes that do not actually contact the API? An example of the inner container might be glass jar or vial.

If your company is paying good money for something, you probably want some sort of acceptance criteria to make sure it is what you want. Packaging material is defined in Q7A as, "material intended to protect and Intermediate of API during storage and transport." If the material is not being used for that intent, if it is simply being used to ease the transport and, in fact, you're saying the glass bottle is the thing that is really protecting the API, then under Q7A, that's not covered and that's not considered a packaging material. Again, some of these are common sense

Section 11.1, under lab controls, tells us that, "all specifications, sampling plans, test procedures should be scientifically sound and appropriate to ensure." To packaging materials, "the testing or examination that would be appropriate to ensure" that an outer package conforms to what you need will probably be a lot simpler.

Q. Can you perform accelerated stability studies on an API to extend the retest date if running room temperature studies concurrently? And, the statement is made, "Drug product firms do this routinely, to place a two-year expiry date on the product."

Going back to one of those slides, way back in the first session, if Q7A does not prohibit something, it's probably okay to do it. Q7A does not prohibit running accelerated studies. It does not recommend, or it does not require, it is not an expectation that you'd run them. And, if the person feels that running those accelerated helps meet the requirement to provide, in terms of retest dates that should be based on evaluation of data derived from stability studies, and that's part of their stability study, to help them get the data on which they could make a sound judgment, then it may be appropriate to do it. There's nothing in Q7A that would prohibit it or would say that the data generated from that was not scientifically sound and could contribute to the decision.

But just remember that Part 211 says that any tentative expiration date assigned to a drug product based on accelerated data must always be verified by shelf-life studies. While this applies for drug products, it may be applicable to APIs as well.

Q. Is that in the GMPs?

211.166(5)b says, "Accelerated studies combined with basic stability information on the components, drug products, and container closure system, may be used to support tentative

expiration date, provided full shelf-life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf-life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration is verified or the appropriate expiration date determined."

Again, that is talking about expiry dating. The question related to retests, and the question again, the person talking about retest was not saying this would be the only data, and they would not have any real shelf-life data. This would be in addition to, and help them justify.

Q7A tried to address specifically the Good Manufacturing Practices. Typically, the stability development studies are a function of the filing requirements, which are addressed in Q1, which does talk specifically about how stability development is done. Since Q7A is a Good Manufacturing Practice document, it is saying you've already done the things you need to do for filing, and this is what you would do on an ongoing basis. So, the stability that's addressed in the laboratory section of Q7A needs to be the ongoing after filing.

Your stability program could be dealt with in your filings up front. In other words, if you've got a commercial product that you've filed for, you could get agreement from the reviewing branch up front to a special approach to a stability program, and that should become then a moot point from a GMP perspective. That's your option that you can work on developing.

Q. Would you elaborate on your last slide in packaging stating if a container seal breach occurs or a label is missing recipient will be alerted to the possibility of contents being altered? The first question is who should do the alerting? A missing label can occur in transport and originator may not even know it.

You should have a unique seal that is obviously missing or broken. Nobody has to physically alert the party, they just have to look at the container upon receipt and see that something is wrong. That was the intention of that expectation in the guidance.

Q. For packaging and labeling issues, is material transferred to and from contract manufacturers still considered control of the API parent firm?

The expectation for you, as the primary manufacturer, is the same whether you are making it or your contract manufacturer is making it. Transfer to and from each location becomes the ultimate responsibility of the primary firm.

Q. If a validated automated warehouse is used for inventory control of materials and/or product, does this type of system provide adequate control or access to labeling material or are additional controls for separate storage areas required for printed materials?

Yes, it can, but it really does depend upon how you operate and what you're doing.

Q. I've got a question regarding the labeling that I discussed for materials that are subdivided in Section 8.1. For any material with hazardous specification, is Q7A in line with OSHA or other safety requirements for labeling or how does Q7A deal with the safety?

Q7A specifically does not address safety issues. Q7A addresses CGMP issues related to maintaining the identity of the material and keeping the information that you need for further use

of the material. Safety controls are the responsibility of the manufacturer and governed by national laws.

Q. This has to do with inspection of packaging and labeling facilities for APIs. Is this intended to be the same level as for drug product line clearance? Can production personnel carry out this check, and does the requirement apply to API only or also to isolated intermediates?

The intent of the EWG here was to assure that the procedures exist to prevent the mislabeling or mix-up in the labeling. Any organizational unit can actually conduct it. You have that flexibility.

Q. Why do you have to take all markings off a container that you might reuse?

The problem is that you may have planned to reuse it in the exact same operation, but then all of a sudden, you don't consume it, you put it off to the side, and somebody goes and picks it up and brings it into a different operation. That's why you need to remove all labeling and old labeling from every container before you change over.

Q. Labeling requirements in Section 9 seem excessively complicated where one batch of API requires label performed every few months. Can this system be simplified, i.e., fill in the blank labels? So they must be talking about product for clinicals.

Section 9 does not require any complicated reviews or procedures. It merely establishes the need for procedures.

Q. API labeling. For APIs manufactured, pre-validation for clinical products, is it required to include a statement limited for investigational use like what's required for clinical products?

Section 19.2 states "labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use."

Q. Someone stated that the quality unit must inspect packaging materials. Can that be delegated?

There is no requirement that packaging materials be inspected by the quality unit. That is one of those expectations that can be delegated.

Q. You mentioned that name and manufacturer and address must be on the label. Would the name and address and the distributor be acceptable?

No because the intent was traceability. Go back to the Haitian situation.

Q. Section 9.3 states that an example of a printed label needs to be included in the BPR. Does this requirement apply to hand printed labels?

Yes. How a label is generated makes no difference. Make a photocopy and attach the photocopy.

Q. Why did Q7A expert work group allow the option of a retest date being placed on the Certificate of Analysis or the container label?

The retest date allows for the user to extend the usability of the product. An expiration date does not allow for extension of use. For this reason expiry dates were mandated for label use as C of As are not always readily available.

Q. Q7A does not seem to differentiate between intermediate and API labeling. Is there a difference? Can you use generic labels that operators fill out?

If it's not being sold, your ability to label is really driven by your own procedures. If you're going to be selling the intermediate or the API, than you need to comply with Q7A.

How do you arrive at your retest or expiry date?

You define it. Quite frankly, that is your decision to make, put it in writing, put it in your procedure and consistently use it.

Q. Please clarify reused containers cleaned according to documented procedure. Does this include secondary containers?

Yes

Q. Does the label information, as defined in 9.4, apply to starting materials and components used to manufacture API as well? Particularly the retest date on a label or CA?

If you look at the title of Section 9 itself, you will see it says packaging and identification labeling of APIs and intermediates. Now one of the things that you can bet on is if we mention API and we say nothing about intermediates, the intent of the expert work group was it was going to be only for APIs. If we say both, than it is both. Now you will see this throughout the document. There are sections where we explicitly mention one or the other or both. If we don't say anything about either, it would probably generally apply to both.

Q. Is Section 9.3 on label issuance and control, applicable for intermediates?

The answer to that is yes.

Q. Regarding packaging materials. To what standards should they be cleaned?

You have to look at if it's a contact surface. It certainly has got to be cleaned to comply with the contamination requirements of Q7A, not just the requirements of the packaging sections.

Q. Are there any requirements for labeling of drums of in process materials? These are temporary labels for moving material from one step to another.

There are not specific requirements. It falls under the same section of labeling of intermediates and APIs. You define the procedure in your written procedures.

Q. Q7A Section 9.4 makes a "requirement to use tamper evident packaging for shipments outside the company control." True or false?

The intent of the EWG was that you'd be able to tell whether those containers were tampered with.

Section 10: Storage and Distribution

Q. Is it acceptable to store equipment-cleaning logs and use logs in a single location such as a supervisor's office rather than in close proximity to the corresponding equipment?

As long as the records can be filled out in a timely manner when the activity is actually performed, there is nothing in Q7A that mandates where cleaning records are to be stored.

Q. What does another unit exactly mean in the distribution procedure? 10.2?

The intent there was to allow, company A with a manufacturing operation in one location to ship to another manufacturing operation in another location when both are operated under an effective quarantine control systems. It doesn't necessarily have to be two plants of the same company. It can be subcontractors. For example, if an intermediate was going out to a contractor who is doing the next step and then being returned to you that would be possible. That's why the term was used, "under company control" as opposed to "the same company".

Q. Is there going to be an attempt to harmonize water monographs in the future?

This has nothing to do with Q7A, but yes there will be an effort to harmonize.

Q. If storage conditions are not defined on the label, what is the assumed ambient temperature? What is ambient temperature? How is it defined since it varies by geography and times of the year?

Ambient is not used in Q7A.

Section 11: Laboratory Controls

Q. Are formal stability studies required for an Intermediate that you are planning on holding?

Q7A does not expect formal stability studies or monitoring studies except for the finished API, except where the intermediate is to be transferred outside of the control of the manufacturer's material management system. (Sections 11.5 & 11.6)

Q. Slide 11-11 indicates that a formal testing program is not needed to establish "use by" dates. Does this mean that the lab does not need to establish limits by a formal program for reference standard solutions or HPLC testing, where the standard solution is not prepared fresh each time?

It is not necessary to have a formal monitoring program to establish "use by" dates, if you use good, sound, scientific judgment. (Section 11.1)

Q. If material is being shipped, can the retest date be on another document that is shipped with the material instead of the C-of-A or label?

Q7A says that the retest date should be on the label or certificate; it does not say it must be. If you have a system that provides an equivalent level of quality that you can justify, then that is probably all right, but you should be able to justify that it works equally well.

It also has to work equally well for the persons receiving it. Obviously, they have to know about it and know where that information is. (Section 11.4)

Q. Whose responsibility is it to obtain the stability information for a filing, i.e. IND, NDA, ANDA, the API manufacturer or the dosage form manufacturer? Does Q7A take a position on this?

Q7A does not establish or assign filing responsibilities.

Q. For starting materials that have no pharmacopoeia monograph, are test methods required to be formally validated or can methods be justified on the basis of scientific logic?

All controls should be scientifically sound. All critical controls should have validated methods. (Section 11.1 and 12.8)

Q. For an API intended for a parenteral drug product that is lyophilized, is it sufficient to test the API powder for moisture content? Do microbiology/sterility issues need to be addressed?

These are reviewer questions, dealt with at the time of filing with the reviewing branch. They are not issues for Q7A. Whether or not there are established specifications for these parameters would already have been determined in the filing. It should be noted that for an API that is obviously intended for parenteral drug manufacturing, microbiological and endotoxin issues are relevant. (Sections 11.1 & 11.2)

Q. Please explain the difference between specification and action limit. If there are no differences, why are both terms used?

An action limit is just a limit. A specification includes both a test method and a limit. In some cases, an action limit and specification may be same. They may differ in cases where a manufacturer establishes tighter controls than those included in the filing. A specification indicates the acceptance or rejection criteria, whereas the action limit usually indicates a point at which some action could be taken to prevent a subsequent specification failure. (Section 11.13)

Q. Final product APIs - if the impurity profile changes as a result of scaling up, but still falls within required specifications, what is the status for this API?

The API is expected to meet are pre-determined specifications. However, if the impurity profile changes due to changes in manufacturing, including scale up, the impurity profile change should be evaluated to determine its impact on the suitability of the API. (Section 11.2)

Q. When, if ever, is parametric release of Intermediates allowed, either to skip testing or reduce testing?

If parametric or skip lot testing is in compliance with the registration and allows compliance with the intent of Q7A, there is nothing in Q7A that prohibits either parametric release or skip lot testing. (Section 11.2)

Q. Shouldn't all APIs intended for sterile use normally have a specification for microbiological content?

A specification for microbiological content is not explicitly mandated by Q7A. Q7A expects that a firm can justify whatever is included or not included in specifications. (Section 11.2)

Q. If the inspector asks you to provide the basis for using a three-month-old reference solution in the stability testing of a specific API, what experience and scientific judgment do you defend the utilization of that material?

Data and experience supporting the "use by" dates should be adequate. (Section 11.1)

Q. Section 11.2, Pharm Forum recently proposed AMC (Aerobic Microbial Count) specifications for all API. Is this appropriate?

If the question is asking if it is appropriate that there be microbial limits on all APIs, Q7A does not say it is appropriate for all APIs; Q7A says, "where appropriate." (Section 11.2)

Q. Is an API brought into the country without an expiry date or a retest date on the label of C-of-A considered misbranded? And, is it held on entry in customs?

Q7A is a guidance document and does not address issues of regulatory misbranding or customs procedures. (Section 11.4)

Q. You mentioned that validated methods are not required for raw material testing. Does this mean from Step I materials to the raw materials that enter the final API production step, even the API starting material? Are tests other than ID also required?

Yes. Often raw materials used in APIs are commercially available, technical grade commodity items for which the test procedures are either in a compendium or provided by the supplier. You are probably not going to find many companies that have those raw material tests validated, even for raw materials that are going into the final step. (Sections 12.8 and 11.1)

Q. (Section 11.2.) Should specs be set for non-critical Intermediates?

Section 11.2 clearly states, "For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications." There is no distinction made between critical and non-critical.

Q. Can a retest date be extended without stability data? Can you think of a situation where that might occur?

No, stability data is needed. However, a formal stability program is not necessarily required. If incoming material was tested, and the material is retested at the retest date, you've tested at two points. If the material is still stable, you could extend that retest period for some reasonable time. (Section 11.6)

Q. (Follow-up from floor) That would depend upon the stability of the material?

Yes, you should have stability indicating assays and you would have to know that you are looking at all the parameters that are subject to change. (Section 11.6)

Q. What happens if it is not possible to identify an impurity? A new one or one detected…? What happens if it's just not possible to identify the impurity?

If the questioner means that they're not able to identify its chemical structure and name, that's not a requirement, and Q7A talks of identified and unidentified impurities, and certainly other ICH documents (Q3B for example) on impurities talk to impurities that are identified by a characteristic like a retention time. You do not necessarily have to identify its chemical structure when you have an impurity. (Section 11.2)

Q. FDA's March 1998 draft GMP guidance for API manufacturing defined for antibiotics the use of expiry date. Q7A does not have this recommendation, is this difference existing or not?

FDA's March 1998 draft GMP guidance for API manufacturing tried to reflect the then current practice of assigning expirations dates for many antibiotics. FDAMA (FDA Modernization Act) essentially eliminated the regulations that required expiration dates for many antibiotics. Q7A came along post-FDAMA, so you don't see that language. But there's no conflict between Q7A and national laws. National laws still would prevail in this international agreement if they exist. (Section 11.6)

Q. Are retains of raw materials used to make APIs necessary or required?

It's not an expectation. Q7A does not require that raw materials be retained. Bear in mind also the fact that while Q7A does not require it, it does not prohibit it. If you have an API starting material and you're interested in that for your own purpose, there's absolutely nothing that precludes you from deciding that it's a good practice for your company. (Section 11.7)

Q. Is there a conflict of retest date definitions among ICH, Q7A and Q1A with respect to immediate use?

The definition for retest date in Q7A is the date when a material should be re-examined to insure that it's still suitable for use. In Q1A, it says essentially the same, but then it says for use immediately. The Q7A EWG discussed how companies interpret immediately. We didn't think that it was prudent to include this particular term "use immediately" because it's subject to so much interpretation in the industry. We approached it from the perspective that it's up to the company to justify how long they're going to use this material after they've reassigned a retest date to that material.

The other thing that we discussed within the EWG was the practice within the API industry of setting a retest date, comparing the test results at the retest date to the original test results and then extending the retest date. (Section 11.6)

Q. Is the retest date calculated from the manufacturing date or from the release date?

Q7A does not specify. It's up to the manufacturer. You will find both of those approaches in various companies. Some companies do their original retest date from the manufacture date; some do it from the date of release. You should describe your approach in your procedure. (Section 11.6)

Q. Do we need to keep reserve samples of starting materials used in API manufacturing? Do they need to keep samples of intermediates if they're not marketed?

Q7A does not have an expectation for reserve samples of raw materials or intermediates, other than intermediates that are being sold. (Section 11.7)

Q. Can the user assign retest dates later than manufacturer's expiration date?

No. That's not the intent of Q7A. The expiration date that has been assigned by the API manufacturer, and the user should not be extending it. (Section 11.6)

Q. Can new retest dates continue to be assigned if material remains?

Yes, if your material can be evaluated, and if that evaluation shows the material is expected to remain suitable for a period of time, a new retest date can be assigned. This isn't intended as a substitute for a good material management system, and so there probably comes a point where there's concern about continuously extending retest dates. If you are the API manufacturer and you are extending retest dates, you need to extend the retention period for the batch records as well. (Section 11.6)

Q. If a process has several purification steps and the first step fails to meet specifications, but this can be corrected by adjustment in a subsequent step, is an OOS investigation needed for this first step?

An OOS result is an out of specification result for the specification that you set at that first step. Theoretically you set that at the level at which you think it needs to be investigated. If it exceeds your specification, regardless of where it is, you should investigate it. (Section 11.1 & 8.3)

Q. This is in regard to a slide 11-5 in laboratory operations, which said that you had to have a procedure for sampling. Was that referring to a sampling procedure for obtaining a bulk sample from the lot or was that referring to sampling that bulk sample for use in the laboratory?

This is referring to the sampling within the laboratory to get the testing sample. In the section on material management, Section 7.1, general controls, it states there should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, etc., of materials. So, there should be procedures for both samplings, but they are described in two different sections: one for the sampling of the materials and one for the sampling of the laboratory test sample. (Section 11.1)

Q. Is there a chain of custody for reference standard materials?

Chain of custody is normally a legal term in which you have something and you really know who has an item at every moment, with people signing for receipt and transfer. To the extent that the term "chain of custody" is normally used, Q7A does not expect it for reference standards. Section 11.1 states that records should be maintained regarding the storage and use of standards. So you should make sure that it is being stored and handled correctly. If you are shipping the standard half way around the world from a central location, you probably want some sort of information regarding its handling or some way of knowing that the standard is still acceptable. (Section 11.1)

Q. We test water for endotoxins for a non-sterile API that is sold for further processing to produce a sterile product. Should we also test the API itself for endotoxins?

It would probably be a normal expectation that there would be an endotoxin limit on an API that is being used for making a sterile injectable product, unless there's something unusual about the material or process. If you have an endotoxin specification, you have to test for it. However, if you've been able to convince the regulators in your filing that you do not need that specification for endotoxins on the API, then there's nothing in Q7A that says you have to test. (Section 11.2)

Q. Is there an annual inspection expectation for retention samples similar to the ones expected or required for drug products?

No, it was very intentionally left out of Q7A. It was thought that annually inspecting a retained sample of a drug substance for visible deterioration did not add a lot to the overall quality assurance system. (Section 11.7)

Q. Is the expectation for retention samples for bulk drug product, for further packaging, not in the final package, the same as for APIs in Q7A?

No. Q7A pertains only to APIs. Bulk drug tablets or capsules for further packaging are covered by 21 CFR 211. (Section 11.7)

Q. If retention samples are stored in more protective conditions, they are no longer representative of the product in the market. In the case of a complaint from the customer, how can we defend our product in the market with samples stored in better conditions than the product itself?

You have to understand what the purpose of a retained sample is. This is stated in Q7A, Section 11.7 -- the packaging and holding of reserve samples is for the purpose of potential future evaluations of the quality of the batch, not for future stability testing purposes. It's your stability studies that are intended to show that your material is going to remain suitable on the market. Bear in mind, there is absolutely nothing to prevent your company from deciding that it's your policy to have retained samples in a trade package or in a simulated trade package. Those are options within Q7A. That's perfectly acceptable to do, but it's not required. A company can choose to use a more protective package. (Section 11.7)

Q. If the API manufacturer must retain a sample of each batch - and so must the drug product manufacturer under 21 CFR 211, - can the API manufacturers retained sample satisfy both requirements?

The purpose of the retained sample for the API manufacturer is to retain an authentic sample of the material representing its quality at the time it was shipped out. The purpose of the retained sample for the drug product manufacturer is to retain a sample of the material as it was received. In most cases it is unlikely that the API manufacturers sample can satisfy both. On the other hand, there could be a plant in which APIs are made in one half of the plant; drug products are made in the other. In that situation, one retained sample could be enough. (Section 11.7)

Q. Please give some examples of when an expiry date rather than a retest date would be required for an API.

When the government requires it. The whole concept of expiry date has, historically, in the API field been driven by antibiotic regulations that require expiry date. That is the main example of use of an expiry date on an API. The other example would be an API that is stable for less than two years. Again, that would be determined at the time of filing. (Section 11.6)

Q. Should companies maintain accountability of reference standards in the QA labs, i.e. a log of every use amount and date of the reference standard, that is reconciled with the amount of reference standard received. Is this a general expectation?

Section 11.1 of Q7A says, "Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations." There is no specific mention of the need for use log or a reconciliation regarding reference standards.

Section 12: Process Validation

Q. Does Q7A address the need for product-specific Master Plan or the Validation Master Plan?

A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units. Q7A doesn't address product-specific or Master Validation plans. It's really the company's judgment what you do with the Master Plan. The Master Plan could be for an Intermediate or API, a class of API, or for an entire facility. (Section 12.2)

Q. Is the need for Design Qualification (DQ) addressed in Q7A?

Section 12.3 defines Design Qualification, as "documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose." Q7A is probably one of the first GMP documents where you see design qualification. The EWG had a reason to put it in there - to send the message that process validation really begins with the design of an adequate manufacturing facility.

Q. Are charging operations, even of non-critical materials, considered as critical steps that must be documented and verified?

Section 8.1 states, "Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Other critical activities should be witnessed or subjected to an equivalent control." Due to the nature of API manufacturing, when you're charging liquids or solids, usually a printout out from a flow meter or weight-cell would suffice as an indicator that you

charged the appropriate amount of reagent, or catalyst, etc. Alternate means may also be appropriate.

Q. Can approval of the IQ/OQ protocols be delegated if the template document has been approved by quality?

Section 2 is very specific. Reviewing and approving validation protocols and reports are listed as activities that should not be delegated. Someone in the quality unit should review the protocol. Would the questioner like to clarify "template?"

Q. (Audience) We have generalized templates and from there we will take that and add the specific information for the equipment to those templates. We're wondering if the original templates are signed off after the additional information has been added to the templates, do we need to have an additional review by quality prior to the execution of the IQ?

It depends. If you have a standard format that you use every time you are writing a validation protocol, you don't have to reinvent what section goes where. If you've got that much information in the template, then signing the template probably meets the expectations in Q7A.

Q. What are the expectations for qualifying equipment? For instance, does the OQ need to go to the limit that the piece of equipment is capable of running, or can it just go to the typical operating conditions, i.e., temperature, pressure, etc.?

Section 12.3 defines Operational Qualification (OQ) as documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

Q. Drug Product Manufacturers may produce placebo product during the PQ-phase to demonstrate the process and equipment are functioning prior to manufacturing commercial product. What is expected in performing a PQ in an API facility?

It may be difficult to run a "placebo" batch in API processes. Many companies may run solvents or a water batch to simulate the API process. In other instances, a company may go directly to a validation phase after IQ/OQ, without the benefit of a true PQ.

Q. What is the difference between "witness" and "verify" in Q7A?

Generally, the term "witness" means a second person present at the time the operation occurred. In comparison, verify is usually conducted after-the-fact through review of supporting documentation. For example, a weight can be verified through review of a scale printout, but one cannot confirm which material was charged without witnessing the act. But, Q7A is actually silent in defining "witness" and "verify".

Q. Can you give examples of appropriate documentation or other alternate means to indicate the status of equipment?

(Section 5.1) Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified. In addition, Section 5.2 indicates "Equipment should be identified as to its contents and

its cleanliness status by appropriate means." Major equipment should have a unique equipment number on it, for example, your reactors may be numbered R40, R41. In your batch record or on your control panel in the control room, if you have a distributed control system as referred to, an Operator should be able to see what's happening with R40 and what is in it at any particular moment

Q. Does Q7A address process development reports?

Q7A does not specifically address the need for process development reports. In Section 6.1, it does indicate that summary reports be available regarding the development history, scale-up and technology transfer of the API process.

Generally, during development of the API, the R&D group writes a report that includes all the fundamental information that drives your eventual manufacturing on a commercial scale and your process validation. Regardless of what you call those reports, (they may have different names in the industry), the bottom line is that a company should have some level of documentation showing that the process has been fully developed and transferred to the commercial facility.

Q. Does the quality section need to signoff/approve the validation reports in addition to validation protocols?

Yes. This is discussed in Section 2.2, item 10. The Quality Unit's responsibilities should include "Reviewing and approving validation protocols and reports."

Q. Could you elaborate on section 12.6? Would a change in the source of an API starting material require revalidation?

Section 12.6 states, "Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation."

Revalidation of an API process may be warranted if the change in the API starting materials is deemed significant. If the Impurity Profile of the Starting Material is significantly different from that previously validated, this may warrant additional validation studies to ensure that the API process can eliminate any increase in or new impurities in the API.

Q. A company wants to manufacture a blend of chemical actives, where no chemical synthesis extraction occurs. This blend is then sold for use in the manufacture of a consumer product. Is this blend considered an API or does API starting material manifest itself?

This example goes beyond API manufacturing. What you're doing is you're combining various actives for purposes of manufacturing a drug product or some consumer product. For example, if you are in fact taking various actives and combining those in order to produce a consumer product, that's formulating.

Q. In Section 8D in your presentation, is validation data required in support of blending?

Section 8.4 states, "Where physical attributes of the API are critical, APIs intended for use in solid oral dosage forms or suspensions, the blending operation should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process." If it is for a liquid, it's generally not an issue. But, if you know it's going for a solid oral dosage form or a suspension, those physical attributes could be critical to the performance of the drug product.

Q. If the only specification not met is expected yield, is blending still acceptable?

Although not addressed by Q7A, a blend not meeting the expected yields may be acceptable. Typically, if you're starting a campaign and charging to a clean blender, you may experience low yield on the first batch due to material adhering to equipment surfaces. After that first batch, an investigation would be expected into why the yield is low

Q. Is it acceptable to blend multiple lots that do not have a physical property specification to meet a blended lot physical property specification, example bulk volume particle size? If the material is out of specification for physical properties, can it be blended with other lots to meet these specifications? In all cases, appropriate validation would be conducted.

As an example, a manufacturer may have an API that they're selling to multiple customers, and a particular customer for some reason has provided you a particle size specification. So, this is now a customer-defined specification that you get when the order comes in and is within the range of particle size distribution of the process. Thus, to meet the new, tighter criteria, selected batches chosen and blended. This results in a batch that meets the desired specification of the customer.

This appears to be within the expectations of Section 8.4 of Q7A, provided the individual batches selected are within the manufacturers initial specifications. While the justification for doing such a blending would need to be carefully developed, it does not appear to represent dilution of a known quality problem for the materials that would not be permitted under Q7A.

Q. In the presentation on Section 12.4: Approaches to Process Validation, the expectation of having at least one validation batch completed at the time of the Pre-Approval Inspection was mentioned. Is this stated in Q7A?

While not specifically discussed in Q7A, section 12.4 states, "Prospective validation of an API process should be completed before the commercial distribution of the final drug product manufactured from that API." Thus, validation of both the API process and the Drug Product process should be completed prior to commercialization of the Drug Product.

During the Pre-Approval Inspection, a key focus of the inspection is the evaluation of technology transfer. As such, production experience at a particular site provides some level of confidence that the process has been adequately transferred and will operate as described. Production and Inspectional history at the site may also play an important role in reinforcing this confidence.

Q. What kinds of validation work need to be done for a validated API process that stopped producing for five years and produces again? No process or equipment changes are made. Do we need to do stability tests again?

Q7A would not expect revalidation if you haven't changed anything. Your change control system should still be operating. If you've made no changes to what you're going to do, and it's the same

facility with the same equipment, Q7A does not mandate another series of extra work. Now, if you're a conservative manufacturer, you may want to do some additional work, additional testing to assure that the process will still produce API in a consistent manner. But, by no means does this guidance require that additional work if nothing has changed.

Q. Should process parameter ranges used during validation be tighter than the filed parameters applied to routine commercial production operation, e.g., the full range supported by development?

Section 12.1 of Q7A states, "The critical parameters/attributes should normally be identified during the development stage or from historical data, and the necessary ranges for the reproducible operation should be defined." Normally, the full range of processing parameters that are listed in the filing are wider than those challenged during validation. These ranges are normally established in the development lab or in the pilot plant to show that acceptable product can be manufactured. Many companies chose to operate within tighter ranges (e.g., target process parameters, typical ranges, etc.) during routine production.

Q. One of the most critical words used in Q7A in Q7A is "critical." Is it not essentially implied in Q7A that there be documented bases for identifying critical materials, critical steps, critical operating parameters, etc., whether or not it be called a product development report?

With respect to validation, Section 12 of Q7A says that you should validate critical process steps. Each company is responsible for defining what steps are considered critical. During an inspection by a regulatory agency of a company's validation packages, it would be reasonable for the investigator to ask you how you determined which of the steps in your eight-step synthesis are critical, and how you determined the critical process parameters. It is expected that data are available to show that the critical process steps are in fact critical and support by the range of critical process parameters.

Q. Can process deviations be used to expand the validation critical process parameter ranges, for one deviation, multiple deviations?

Q7A does not specifically address this issue. In some cases, deviating batches may suggest the need to expand the previously validated ranges. Data from these batches may supplement the available information and allow the company to define what additional validation work may be necessary.

Q. What is an acceptable mechanism for confirming the suitability of an alternate source of a starting material?

Section 7.1 of Q7A states, "Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control." Section 13 states," The potential impact of the proposed change on the quality of the intermediate or API should be evaluated."

Q. It's not uncommon for a company to have two suppliers of a starting material. They're now going to validate the process and they want to make sure that their validation encompasses material from both suppliers. What do they need to consider.

Assuming that the company has done some preliminary work to show that their two suppliers are delivering material to the same specification, and that both will work in the company's API process, it would be prudent to use material from both suppliers in their demonstration batches. With the criteria that the starting materials from both suppliers met the same specifications and all quality attributes are satisfactorily met for the API, this should support he use of either supplier.

Q. Are requirements for GMP compliance, in fact, less stringent for API manufacturers versus dosage form manufacturers: less validation, less cleaning validation, less detailed documentation? Is there any basis for individuals to interpret Q7A this way?

Q7A recognizes that there are fundamental differences between the manufacturing processes for API and Drug Products. GMPs are no less important in API processing. GMPs are applied differently to APIs because of the nature of API manufacturing and the differences in API manufacturing.

Q. In Q7A there are lots of definitions provided in the back. Why are there no specific definitions for prospective or concurrent validation?

Various Agency and Industry groups have been talking about validation for more than 20 years. The 1987 Drug Process Validation Guideline issued by CDER and ORA clearly defined the terms prospective validation, retrospective validation, but not concurrent validation. When writing the sections in this document, the EWG did not feel it was necessary to redefine these terms or to include the definitions in this document.

The guidance does not define what these different approaches to validation are, but it does tell you how to apply them to API processes. That was the intent.

Q. Is retrospective IQ/OQ required for existing equipment that was installed longer than 10 years ago, and has complete preventive maintenance records? In other words, does a formal IQ/OQ document need to be generated or do the PM records and change control suffice?

IQ/OQ for existing equipment differs from that conducted for new equipment. For existing equipment the IQ documents what is currently installed in the facility. It would not be expected to go back to when the equipment was originally installed and document what was done. There's really no need to do the OQ because the OQ would be the historical data that you've generated with the use of that equipment over the years, demonstrating that that equipment is working satisfactorily.

Q. Would you apply the statement of IQ/OQ to existing analytical instruments?

Section 12.8 of Q7A states, "Appropriate qualification of analytical equipment should be considered before initiating validation of analytical methods.

Q. Does Q7A address the need for PQ in new pilot-scale equipment prior to validation?

Q7A defines performance qualification as "documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications." One of the key phrases in this definition is "when

connected together," because you may have done some work on the individual pieces in the pilot plant like the reactor or centrifuge, but you haven't run the process all the way through the entire train. Some companies may choose to perform a solvent batch as part of the PQ.

Q. There's a similar question here in talking on IQ/OQ/PQ, if a PQ is performed on a piece of equipment, would you need re-qualification on a yearly basis, or is an one-time PQ acceptable if the equipment remains the same?

If the equipment is not changed in any way, there would be no expectation for you to do another PQ.

Q. In defining the critical process steps to be validated, are there ways that you have seen companies avoid the analysis paralysis of reasoning that all steps could be critical and therefore seek to validate all steps?

Section 12.1 of Q7A clearly states, "Validation should extend to those operations determined to be critical to the quality and purity of the API. It is left to the API manufacturer to determine which steps are considered critical in their process.

Q7A does not expect you to validate non-critical steps, nor are you expected to validate each subsequent step in the process once you initiate validation. This later point is reiterated in section 1.3 of Q7A, where it states, "it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical."

Q. To add on to that, could there be steps filed that are not critical?

The filing should be a complete description of the intended process and should define which steps are considered to be critical process steps.

Q. A batch of new API is produced prior to validation. Can this batch be used for commercial distribution after completion of validation of the API process?

If the process used to manufacture the specific API batch is consistent with the validated process, this may be considered acceptable.

Q. Please discuss re-validation as it relates to scale-up. If the same equipment is used, is there any restriction on how much the scale can be increased prior to re-validation? If similar but different equipment were used, would re-validation be required?

This is not addressed by Q7A, nor does the guidance place any restrictions on scale-up, either before or after validation. The potential impact of the proposed change on the quality of the intermediate or API should be evaluated through the company's change control procedures.

Q. Is it acceptable to validate at a scale less than that of the commercial process (e.g., 10%)?

The 10% rule originated from FDA's Generic Drug Branch for purposes of submitting bioavailability and dissolution data for solid oral dosage forms. It does not apply to API and Q7A does not specifically address scale-up.

Q. How is blending of small batches to increase batch size different from combining fractions from several batches of intermediate for further processing?

Further processing, in this context, would be taking multiple batches of an Intermediate and moving these forward in the process. Taking those batches into the next step for processing is not a blending operation.

Q. Please explain why combining several centrifuge loads from a batch is not considered blending in Q7a.

The glossary in Q7A defines "batch" as "a specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval." In API manufacturing, it is common to process material coming from one reactor through various centrifuge loads because of capacity limitations of the equipment, or various drying loads because of the same reason. This is still considered one batch. They are sub-batches of the same material coming from one reactor. When these sub-batches are brought back together, this is considered a mixing operation. If portions of different batches are combined, this is considered blending.

Q. Q7A is titled "Good Manufacturing Guidance for Active Pharmaceutical Ingredients". Why does it not include the reference to "current" as in 21 CFR 211?

The scope of Q7A includes a statement "For the purposes of this guidance, the terms current good manufacturing practices and good manufacturing practices are equivalent."

Q. In general, do in-process test methods need to be validated?

Section 12.7 of Q7A states, "the degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process." For example, a pH measurement used for in-process control would generally not be validated. The pH meter would be properly qualified/calibrated and standard solutions used would demonstrate that the pH meter is functioning properly. However, there would not be a formal analytical method validation. Additional guidance is provided in ICH Q3A and USP.

Q. For the cleaning of dedicated equipment in a facility dedicated to the manufacture of a single API, is visibly clean an acceptable criterion for cleaning validation, i.e., no requirement for specific determination of the API?

Yes, visibly clean may be acceptable if we're talking about a dedicated facility. The concern is not cross-contamination. In a situation like that, the concern is the potential for carryover of material left over in equipment to subsequent batches and the possibility that that material may degrade. Instead of being focused on cleaning validation and avoidance of cross-contamination the issue really is being on the alert for carryover of degradants. (Section 12.7)

Q. May Equipment qualification and equipment validation be used interchangeably to mean the same thing?

No. The term qualification is typically applied to equipment, and the term validation is typically applied to processes, methods or systems. The Glossary of Q7A defines these terms as follows:

Qualification
Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Validation is a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Q. Is it necessary to validate the process in the manufacture of an intermediate?

It depends on whether it is critical. According to Section 12.1, manufacturers should validate steps determined to be critical to the quality and purity of the API. Identifying critical process steps should be based on sound scientific reasoning. Not every process step is critical nor can all process steps be not critical!

Q. What is an acceptable yield range? ±20%, ±30%, where would somebody find an acceptable yield range?

This is not specifically addressed by Q7A. Section 8.1 states that "actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data." Previous data may be your development data or it may be for processes that you've been running in the plant for a number of years, it's your historical plant data.

Q. Can the ranges for expected yield be set post approval with biotech products where as little as three to four API batches at scale may have been produced and historical data sets will be very small?

. You should not necessarily be locking in on a firm yield range until you have enough history to know where the yield range should be established. Remember, deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches, as per Section 8.1. Thus, it's got to be a meaningful range. You don't want to conduct investigations all the time if there's no real meaning to it.

Q. Should process validation be performed at full production scale or can it be performed at one-third or one-tenth commercial scale?

You should usually perform process validation at the scale that you will be manufacturing during routine production.

Q. If the theoretical yield of a synthetic process is 20 kilograms, is that the batch size or if the typical yield is 16 to 17 kilograms, is that the batch size? On your batch record, what do you call the batch size? The yield or what gets charged or the amount of starting material?

That's up to you to define. Some companies define their batch size based on what they charge in, other companies define their batch size based on what they get out.

Q. Is it necessary to perform a trend analysis for the yield analysis?

No. Q7A is silent on that issue.

Q. Is it necessary to investigate yield discrepancies not associated with critical process steps?

Firms can investigate anything they deem necessary. However, Section 8.1 addresses deviations in yield associated with critical process steps. These should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

Q. Would a clean-up procedure be considered critical, and then, therefore, it would have to be validated.

It depends. You define where and when cleaning validation is required based upon sound scientific reasons.

Q. You have a validated process. Do we need to disqualify a previous process validation and repeat the process validation after product failures?

Depends on is what caused the product failures. If the failures were due to process variability it would be prudent to correct the problem and revalidate the process.

Q. Please clarify or give examples of increasing GMPs over multi-step processing of APIs. Certainly most parts of GMPs such as personnel and facilities are either meeting or not meeting GMPs.

In Step 1 you may be using a simple pH to monitor reaction progress while in Step 4 you use pH plus HPLC.

Q. In the case of a contract manufacturer producing an API for a client abroad, must the process be validated entirely by the contractor or can it be partly done by both parties?

API manufacturers are expected to validate critical process steps that are critical to the quality and purity of the API. Neither Section 12 nor 16 specifies the responsibilities of either party. This should be decided upfront and specified in the written contract or formal agreement between the company and its contractor, as specified in Section 16.

Q. Is it acceptable to validate drying using an LOD spec target without regard to drying time? If so, does this mean significant time differences between batches would not be considered deviations?

Yes, it is acceptable to validate the process based on drying to a target LOD value. But you should be concerned about extremely long drying times if you have seen any indication that the product will degrade at elevated temperature or if such an extended drying time could cause a problem with the API.

Q. Regarding Q7A, is there a need to validate in process analytical tests that are used to monitor reaction progress?

Section 12.8 of Q7A says that analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. However, the section clarifies that "the degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process."

Q. Are shipping validation studies required for APIs?

This is not addressed by Q7A.

Q. Should analytical methods used in commercial scale validation to be validated?

Yes. See Section 12.8.

Q. This has to do with biological assays. The question is do biological assays need to be validated?

Yes. All analytical methods should be validated as per Section 12.8.

Q. During clinical trials, is it acceptable to transfer the analytical methods to quality control for conducting of stability testing and for release testing prior to final validation of the method being completed? Does analytical need to continue the routine executing of the method until final validation?

As per Q7A, you define how and what your firm will do. Chapter 19 defines specific guidance regarding the manufacture and control of APIs for use in clinical trials. Specifically, Section 19.8 states, "While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

Q. Is there a need to define environmental control specification for API processing area and powder handling area such as particle…micro-biological and so on?

Section 4.1 states that facilities should be designed to minimize potential contamination and to limit exposure to objectionable microbiological contaminants, as appropriate, where microbiological specifications have been established for the intermediate or API. In addition, Section 8.5 states, "production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials." However, Q7A does not define specific environmental specifications for API processing areas or powder handling areas. Development of such requirements is based upon your own scientific studies and local regulatory requirements.

Q. Does a reprocess of non-conforming material require validation?

Q7A does not mention anywhere that you should validate a reprocessing. Obviously, if it's a critical step, than the expectation is that it would have been validated initially, and if you repeat in the reprocess a critical step, there's really no expectation to revalidate it because it's already been validated.

Q. Also, does the reprocess of non-conforming material require an investigation?

According to Section 2.1 critical deviations should be investigated. All others deviations should be documented and explained. So the non-conformance would need to be documented and explained. If the non-conforming material is an API then an investigation should be done.

Q. Can a process step be defined as small as a single instruction in a batch record?

Q7A does not make this distinction. You define what is a step during your process development and regulatory filing.

Q. Should analytical methods used to test residuals such as TOC or HPLC methods be validated?

Analytical methods should be validated in accordance with Section 12.8.

Q. If a company dries to an LOD specification, doesn't that imply the drying process is not validated?

Well it depends. It may not be validated based on drying times. The validation of the drying process is defined by development and whether it is a critical step. It is very common in API manufacturing to dry to a LOD specification and not based upon a fixed time.

Q. Are firms expected to have a product development report to identify the critical steps and critical parameters of the process to yield an acceptable product and limit impurities?

Section 12.1 says that critical process parameters and attributes should be identified and documented during Development. A development report is not specifically mentioned. However, documentation of critical process parameters and attributes is expected.

Q. If a reaction temperature ranges from 60 to 70, do you run validation batches at 60, 65 and 70 or three at 65?

The objective of process validation is to generate evidence of consistency. You can only show consistency by producing multiple batches in exactly the same way. So in this example, you should try to run all three batches at the target value of 65 degrees. You normally would have already tested the temperature ranges in the development phase. So if you've already done that beforehand during the development, there's no expectation to challenge the defined ranges during the actual process validation.

Q. If, during a process chemical validation, one validation batch fails due to an assignable cause, equipment malfunction, how many validation batches are necessary to demonstrate consistency and/or to complete the validation, one more lot or three more consecutive lots?

Q7A Section 12.5 says three consecutive successful batches. When a mechanical or human error occurs, Q7A allows for judgment in deciding how many additional batches should be run to show consistency of the process.

Q. What is the expectation on performing process validation without the qualification or validation of utilities that are in contact with the product? Examples, steam, nitrogen.

Q7A is very clear in saying that qualification should be conducted before process validation, not afterwards. Refer to Section 4.2.

Q. When you perform a process validation, should the equipment instruments be calibrated immediately after the completion of the validation runs?

Refer to Section 12.3. Equipment calibration should be done as part of your equipment qualification program, and again, that's normally performed before you initiate process validation.

Q. You've done your qualifications, you've calibrated all of your equipment, now you've done your batches, and do you have to do immediate post-calibration of the instrumentation?

Q7 is not specific on this issue. From a very business oriented perspective, it depends on the history that you have on that particular equipment and how long it will remain in calibration. If you have any reason to believe that the calibration may have drifted, then you may want to recheck it, but if you have a good history on the equipment and you know that your calibration and preventative maintenance schedules are adequate, this may be satisfactory.

Q. What is the expectation on facilities that are old and do not have DQ? Do we need it before performing process validation?

No, if the facilities are old, you would not be expected to redo DQ.

Q. Why was steaming sterilization validation not included in the guidelines?

Section 1.3 states that Q7A applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The actual sterilization of APIs, the subsequent aseptic manipulations and aseptic filling, packaging and labeling is not addressed by Q7A. These activities are generally regulated by drug product GMP regulations in the three ICH regions.

Q. Is your process validation starting point defined of your choice of your API starting material?

Remember the two fundamental concepts that are embodied in Q7A. GMPs begin to apply with the introduction of API starting materials and manufacturers are expected to validate critical process steps. So we're talking about two different things here. The API starting material, once that's introduced into the process, that's where GMPs begin to apply in the API process, but that's different from validating critical process steps. You should identify your critical process steps in your API process and validate those critical process steps. So in general, it's not related.

Q. In a new facility, can you start process validation prior to completion of water system validation that will run for several months to a year?

This is not specifically addressed in Q7A. However, for a new water system, both regulators and industry generally recognize that there are various phases to validating the water system. Phases 1 and 3 generally last one or two months, and then you enter a third phase that may last up to a year. During this third phase, you're trying to show that the water quality is consistent throughout the seasons and any other variations. Provided there is an appropriate ongoing testing program as part of the validation, it is typical to use water during the final phases of validation of the water system.

Q. Should raw material testing methods be validated?

It's not addressed in Q7A and it's not an expectation in Q7A.

Q. Is there a limit to the number of times you can retest an API if the API stays within specifications?

This is not addressed by Q7A.

Q. Please elaborate more between concurrent and prospective validation. Is it only related with final release of the batches for commercial use? And question two, do we need to specifically include the batch number on validation protocol or specifying number of batches is enough?

The major difference between prospective and concurrent is that when you prospectively validate, you do not release the batches to the market until you have completed the validation project and you've shown consistency of the process. Once you've shown consistency, then you can release the batches. With concurrent, you haven't shown consistency and you're releasing the batches through the market based on extensive testing. You won't be able to show consistency until you produce multiple batches, and that might take some time, maybe a year or two down the road. Those batches are released during that time based on extensive testing.

Regarding the second question, whether or not you need to specify the batch number on the validation protocol. No, the validation protocol normally includes the number of validation runs. The batch numbers for validation will be specified in the validation report, not in the protocol.

Q. For submission of the PAI, FDA needs one batch produced or one validation batch, can a demo batch be acceptable for that if a validation protocol already exists for future commercial campaigns?

Yes, as long as the future batches will be produced by the same process as the demo batch.

Q. One could argue that a computer system used for process control and process automation is equipment and therefore subject qualification and not validation. Can you comment on this?

You could qualify the individual components of the system and then validate the entire computer system once it's been connected. So you qualify the components, but then the entire system, the entire computer system, everything connected, working together, that's what you should validate as the computer system.

Q. What type of validation is required to demonstrate effective separation of GMP and non-GMP production operations within a single facility? Specifically if HVAC systems are separate and design minimizes potential cross contamination?

This is not addressed in Q7A.

Q. Is it recommended to qualify analytical equipment used in QC/QA labs that don't perform methods validation if the QC/QA lab used calibrated equipment and performed systems suitability at time of use?

Section 12.8 states that "appropriate qualification of analytical equipment should be considered before initiating validation of analytical methods." In addition Section 12.8 also states "the suitability of all testing methods used should nonetheless be verified under actual conditions of use". So even if the method validation is done elsewhere, the method needs to be shown to be suitable in the lab where the testing is done. It would be reasonable to expect qualification of the analytical equipment as part of this. The calibration and system suitability you describe can be used as part of the qualification.

Q. Is it a requirement that analytical methods be validated prior to process validation?

Yes, it is logical and preferable that you validate analytical methods before initiating process validation to have confidence in the data generated during the validation study. In reality it often happens that analytical validation is not fully complete at the beginning of process validation. However, in such a situation any changes to the method would have to be investigated as to the impact on the process validation.

Q. Do we have to validate the mother liquor recovery process?

. It depends on what step in your process you are recovering the mother liquor from, and where that recovered intermediate or API is introduced back into the process. You should validate a mother liquor recovery process like you would validate any other purification step, to demonstrate that you're removing impurities. So you look at what level of impurities is that process capable of removing and define what is critical as far as process parameters for those impurities removal.

Q. If one of the validation batches fail, can a company redo one more batch to the validation for three consecutive batches, need to be repeated?

It all depends on the reason for the non-conformance. If it's not related to process variability, then perhaps one additional batch may suffice. In any case, the failed batch, reason for failure and resulting decisions should be included in the validation report.
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Q. Consider synthetic steps A through B to C to D and then that produces the API. If B and D are critical, than are all the intermediate steps from B onwards validated or only the critical intermediates B and D?

According to Q7A, you're only expected to validate critical process steps.

Q. As you are aware, API processes can be extensive, and Q7A requires that you identify critical process steps and validate them. Is it required to justify why all non-critical steps are not critical in the process development report?

While it's not an expectation, it's probably a very good idea.

Q. If we have a lot of API manufactured at another parameter other than the target, but within the range, should we use or should we do an investigation?

If the API lot was manufactured within the established validation ranges for critical process parameters, it could be released for use provided it meets established release specifications.

Q. Is it required to perform an IQ to a piece of equipment that has been operating normally for a long time?

For existing equipment, your IQ documents what is currently installed in your facility. There's no need to go back 20 or 30 years to when the equipment was originally installed. You just document what is currently installed. So it's less of an IQ.

Section 13: Change Control

Q. Are change controls needed for critical and non-critical raw material changes?

Yes.

Q. If you are evaluating a technical change in production and the yield and/or quality are not improved or even affected, what do you do with the batches involved? Can they be sold?

Theoretically, yes. When you make a change, the difficulty is to show that it has no impact on the quality, especially on those parameters that you normally do not measure, like physical and chemical parameters. From this point you have to do some studies anyway.

There's also a non-Q7A issue, i.e. does that change affect your regulatory filing? You may have a change that doesn't affect the quality of the product, but it may affect the registration filing.

Q. If the quality unit is required to approve changes that impact product quality, who decides if a change impacts the product quality?

This is something that you have to solve in your own organization. In some companies the quality units are always involved in the changes. Other companies have different levels of change. Changes that are not initially reviewed by the Quality Unit should be addressed during internal audits.

Section 13 (change control) expects a formal procedure. And any formal procedure would have to be approved by the quality unit. This procedure should define what changes need to be approved by the quality unit and which ones do not need to be approved.

Q. If an API process is confidential and is described in a master file, how should the API producer deal with informing customers of a process change?

Confidential information doesn't have to be disclosed to customers.

However, Section 13 says, "current dosage form manufacturers should be notified of changes from established production and process control procedures that can affect the quality of the API." So the expectation is that drug product customers should be notified of any changes that could affect API quality.

Q. If one is not sure whether or not a change might affect the quality of the product, to what extent should one involve the quality unit to be on the safe side?

Quality Unit should be involved in all changes that could affect the quality of the product.

Q. When assessing if a change has had an affect on product quality, what criteria are used to evaluate any change in the impurity profile?

The impurity profile should be compared against historical data.

Q. If a part or a piece of equipment fails and is replaced by a functionally equivalent, but not identical part, will this be classified as a change? For example exchange of 304 versus 316 stainless steel construction.

Yes. The example is a change. But how the change is handled is subject to definition within the company. The example is a material change that might have an impact on the quality, or not. The Expert Working Group tried to build in the maximum freedom. It's now up to the companies to define the best way to handle it.

You have to deal with all changes, but not all changes have to be discussed by a committee consisting of people from the quality unit, registration department, marketing department, drug product manufacturing and so on. Then within the system you have to identify at which level certain departments are going to get involved.

Q. Regarding the requirement that first batches have to be evaluated after a change, is this for every change or just major changes? For instance, a change in wording for clarity in manufacturing batch instructions would need evaluation?

No. There must be a system to categorize changes and the level of review needed for each category of change in place that is excluding such changes from review. The simplest change would be e.g. an editorial change in a document.

Q. When should customers be notified of change? Before or after implementation?

Normally the customer should be informed before the changes are introduced for commercial manufacture because he has to evaluate the impact in the drug product, and there may be also registration issues.

Section 14: Rejection, Reuse, and Reprocessing

Q. Some drums of an API were in a room next to a smoky fire. There's no visible damage to the inner packaging, although the outer drums were sooty. 211 specifies that the drug product would need to be destroyed. What would the recommendation be with respect to the intent of Q7A in destruction or reprocessing? The material still meets the established specifications.

Q7A Section 4.5 - Returns - may address the issue, although this may not be returned material. It says, "If the conditions under which returned Intermediates or APIs have been stored or shipped, before or during the return, or the condition of their containers casts doubt on their quality, the returned Intermediates or APIs should be reprocessed, reworked, destroyed, as appropriate."

You have a little more flexibility with APIs because, if there's any concern regarding its quality, you could reprocess it, rework it, or destroy it.

Q. If, as you say, material can be reprocessed at its retest date, what new retest date should be given to the reprocessed API? If retest is five years, can you reprocess at five years, then wait another five years to the next retest date?

Yes. Chemistry is chemistry. If you're going to do a physical manipulation then "it depends," comes into play. If you're going to repeat the original process of crystallization/purification there's no reason to expect to see something different. If you get something different, then you have an out of control process. If you know your chemistry, and the material was good for five years the first time, it should be good for five years the second time.

Q. When we do a retest for customers, they frequently ask why we can't re-start the shelf life. After some explanation, they accept why, but then they ask the question, how long can we keep the raw material before it must be consumed?

It depends on the impurity profile and the stability data that you have on the compound. You should use sound science and your good judgment.

Q. In order to use reprocessing at retest date, what type of provision, if any, must be in the NDA? What must be done in the NDA or supplement to allow rework?

This is a filing issue and not the subject of Q7a. However, if we remember the '87 guideline correctly, reworks need to be filed. Reprocessing, by definition, is using the same already filed process, so you really don't have to do very much if you're going to reprocess; you just have to keep your records. But, rework, absolutely, is a filing issue.

Can we go back to that earlier question about reprocessing for a minute? Be sure to look back to the documentation section. Be sure that you retain all records related to this material. Be sure that no records have been destroyed due to their age. All records must be kept for the new period. We've had some cases in the past when we found that old records have already been destroyed. Obviously, at that point, the material is no longer suitable.

Q. I believe that the ICH guideline on stability and the FDA guideline on stability have said, upon retest, the material should be used immediately, something to this effect. I believe this contradicts the Q7A intent and I think the whole industry intent.

We tried to address that in the presentation. The ICH guideline you are referring to is directed at the dosage form manufacturer. If you look back at the slides, we talked about assigning retest dates by the API manufacturer, and talked about assigning additional retest dates by the dosage form manufacturer.

The EWG was didn't know what was motivating that segment of people that are pushing for testing of an API immediately before use. If you've got stability data that allows you to keep this material in use, and it's good for a year, to require a dosage form manufacturer, while it's within that year period, to test it the day before they use it is unrealistic and impractical. It's not a sound scientific argument.

ICH tells us that, wherever possible, definitions should be the same between different guidance documents so that there is not confusion. But, in some cases in Q7A, there truly were unique situations, where the expert working group felt that there was justification for having a different definition. The EWG discussed at length the fact that it does not conform to the other definitions, because it does not include the phrase requiring that it be used immediately. However, the EWG felt that the difference was justified and necessary.

Q. Does Q7A address the traceability of reprocessed/reworked batches?

You saw on the slide that both reworking and reprocessing should be adequately documented, controlled, and monitored. Documentation means that you should be able to show traceability where appropriate. "Batch production records prepared for each Intermediate and API should include complete information." Complete information would be anything that has happened to that batch.

Q. Slides 14.10 and 14.11 -It is understandable that you cannot validate a single rework, so why shouldn't Q7A be stronger regarding the need to do more intensive testing, including stability testing, on reworked batches? For reworked batches, are stability studies necessary; what instances would require stability studies?

We felt within the expert working group that since reworking is a non-routine activity, and there are so many possible scenarios under which a company may attempt a rework procedure, it was necessary to just have a general statement and leave it up to the manufacturer to determine what testing would be appropriate. But, the bottom line is, and the intent here is that you need to show, whatever you do, that the reworked API is of equivalent quality to that produced by the original process. How you do that is really up to you.

Stability testing of reprocessed material was not mentioned because the manufacturer uses the already accepted process. However in Reworking you introduce a new process and that is why "if warranted," is in the document.

Q. What is meant by additional analytical methods under rework? Shouldn't you already know what your methods are? Is it appropriate to create new methods for a process just because it is reworked material?

Most analytical methods and most specifications are established based upon what is normal. What your process is, what your synthetic route is, and the impurity profiles that come out of it can all have an impact. But, when you change solvents and you change conditions to the point where it becomes a rework rather than reprocessing, Q7A expects you to examine whether or not you need to use a different method that you may need to develop.

Q. For a reused container, does the documented cleaning procedure need to be validated? Is there an expectation of a monitoring program for solvents stored in bulk, and the frequency thereof? Is there any expectation for the monitoring of critical parameters using continuous chart recorders or two manual operator documentation of a specific time period?

If it's a product contact surface, it's certainly more critical. Whether it needs to be validated is going to depend upon whether this is storing a critical material. Is it a finished API; is it an Intermediate, or what? Certainly, you need to have data that shows what you've chosen to be in contact with is acceptable. Your company may need specific information to tell you whether or not

it should to be validated. If it's not critical, it probably doesn't need validation, but it certainly should have data to show that it's suitable.

Monitoring can be done on a continuous basis or manually - either one. We don't mandate which way you need to do it. You need to do some kind of monitoring for the quality. If you could do that automated, online, and record that, so be it. There's nothing that says you can't do it that way.

We'd like to go back to this question about reuse of containers. Common sense usually applies in many of these situations. You do whatever you think is necessary in order to accomplish the task at hand.

There are certain things that are intuitively obvious that you really should validate, and there are things that are common sense driven that tell you, you do your testing, and you make sure it works. Put your dollars and your emphasis on the things that are really meaningful.

Monitoring and storage of solvents stored in bulk should be described in procedures established by the firm. If Q7A requires certain things, they need to be followed. If no requirements are described, there is no need to perform extra work.

Q. If in-process nonconformance results are not documented as such prior to continuing the process, how will you know that a change is indeed required in the process? How many chances at reprocessing do you get to conform to specs prior to rejection of the lot?

The purpose of the in-process test and the specification is to monitor the process and to make adjustments to the process. Take for example, a hypothetical case in which you might take a sample to measure pH against an in-process pH specification and it doesn't meet your in-process pH specification. Do you have to stop the process at that point and try to determine why it failed pH in the first place? Not necessarily, if it failed pH, it failed pH. It needs to be adjusted until the proper pH is achieved. This is not reprocessing, it is processing to a specification. Since this is not reprocessing, you would continue to monitor and adjust the pH as necessary in order to meet the specification for the Intermediate or API.

Regarding reprocess a batch, it actually makes little scientific sense to say you need to limit the number of times you can do it, at least from a product or material perspective. Generally, where synthetic chemistry is involved, reprocessing improves material quality since you are doing multiple purifications. For someone to try to scientifically object to reprocessing something more than three times, or 10 times, or 100 times, makes no sense. Certainly for biological systems, further manipulations could lead to product quality degradation and multiple reprocessing could be undesirable.

The question becomes what knowledge is lacking that causes repeated reprocessing. Why this is potentially important it is not immediately nor should it be a GMP issue. It is an important economic issue.

Q. Can you reprocess expired API?

Q7A does not prohibit you from doing that, but you should gain concurrence from the regulatory agency before proceeding.

Q. A rework can be beyond the filing process. Our current expectation is to update the

filing for the rework process prior to release. To update the filing, we must validate the rework, requiring multiple runs. How does this correlate with the Q7A GMP expectation of no validation required and only run one run?

It's quite difficult to validate a rework procedure because, in most cases, you're lacking numerous batches to be able to show consistency of that rework procedure. This is basically a filing issue, but at least from a GMP perspective, it's quite difficult to validate a rework procedure because you're lacking multiple batches that failed for the same reason.

Reworking always required a prior approval and re-processing didn't. We think we've got a lot of people reinventing definitions and reinventing what was originally agreed upon, and things will start to fall out as you shake the trees. But, you're going to need to explore with the reviewing branch when you start to get outside of the GMP part and get into the filing issue.

Section 14.3 says: "the batch should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that it's equivalent." This is a good example of where you would use concurrent validation. You should agree up front with the Center exactly what testing you are going to do. That should be written up in a protocol. You should then run your one batch according to the rework procedure and write it up as an interim report that is retained. Once you and the Center have agreed, you would release that reworked material. Your concurrent validation report for this one batch would sit on the shelf, hopefully forever. If a similar problem occurs where you would want to use that same rework procedure, then that would be added on to the original protocol, and a second report should be written at that time. So, while it's not possible to document the consistency, and we all hope that we never have a lot of opportunities to do rework, we should still capture all the additional testing and controls.

Q. Is it allowable to recover, and presumably use, API from expired drug product and, if so, what data is involved?

Once that drug product has expired, you can no longer use it. So, in most cases, that's destroyed.

Q. The question, though, I think, was specifically, if you recover the API from the expired drug product, if you've gone beyond the expiry date of the drug product, does that also mean that the API has expired?

If you've gone beyond the expiry date of the drug product, it's going to take some very special permission from the Center in order to recover that API. Most likely, they would not approve it.

Q. Is it permissible to have an optional reprocessing step, for example a re-slurry, as part of the manufacturing instructions, where the decision on whether or not to reprocess would be based upon an evaluation by testing of the purity of the in-process material?

This is a common practice. Many API processes have an in-process check (for purity, etc.) before continuing or initiating a re-crystallization or a reprocessing step. This check enables you to determine whether or not you have bet specifications to proceed. It's built into the batch record; it's part of the established process. It's triggered if the purity in-process specification is not met. If met, you proceed to the next step.

Q. Would a solvent recovered as an azeotrope for use in the same process be required to be tested before its re-use according to Section 14.4, especially if this is from a continuous process?

The Q7A refers to this as being controlled and monitored. I don't think that necessarily says that each batch has to be tested. I think part of that is the reliability of the process and how much risk the manufacturer is willing to take. The monitoring in that case could be the monitoring of the temperature of the azeotrope for distillation.

The exact quote here is, "solvents can be recovered and re-used in the same process or in different processes, provided that the recovery procedures are controlled and monitored," "to ensure that solvents meet appropriate standards before re-use or co-mingling with other approved materials." You've got a decision to make. The answer generally is you need to make sure the material meets your requirements. If your requirements are simply satisfied by temperature controls, fine. But, you need to establish those requirements and, quite frankly, it would be a very unusual process that you would not already know it was good at the time you went to use it. But it is possible you just have to make that decision whether you're satisfying this requirement.

A lot depends on the design of that solvent recovery system. For example, if you design a solvent recovery system where the recovered solvent is then sent to a vessel and stored there, then it might be feasible that you would implement some type of batch testing of each vessel of recovered solvent. But, if it's a continuous process, obviously, that would not be feasible, so you have to have other controls in place to provide you that assurance regarding the quality of that recovered solvent.

It's more important to recognize that you could have different requirements for the recovered solvent than you did for the virgin solvent. That especially becomes true when we start talking about azeotropes.

Q. Does Reprocessing need to be validated and, if so, is concurrent release appropriate? Then, the statement is made that this practice could result in validation packages remaining open for long periods of time. Why don't you address that, and there are a couple of other twists I can throw in if you don't have enough fun with that one.

If you recall the definition for reprocessing in the API arena, that's taking a batch that either conforms or non-conforms and putting it back into the process, and repeating steps that are part of the established process. Now, if your established process was validated, then we don't see a need for re-validating the reprocessing. If, for example, the original crystallization process was validated and your reprocessing step is a re-crystallization, than we frankly, do not see a need for re-validating that re-crystallization step. It's already been validated. If the step is not originally validated and used for reprocessing it should normally not require validation either. Validation of a step is driven by whether the step is critical or not.

Q. Do you need to re-validate the same re-crystallization step for different reasons for reprocessing? For physical contamination? For out-of-spec particle size? For out-of-spec LOD?

If you're going to change the process, there's no question; if you have to change what you do, you need to validate it. But, if you're not going to change it, and you're just going to go right back in, exactly the way you were doing it the first time through, you may need comprehensive additional testing, and analysis, and monitoring. But, you do not usually have to validate it.

The process is designed to do something. If you have not already demonstrated that the process will do something, like reduce a given impurity, then if you're going to repeat a recrystallization to remove an impurity, to change a particle size, to do something that you have not already

demonstrated that that process does, that is something that has to be validated possibly as a rework.

Q. For material that has reached its retest date, what is the generally accepted length of time the retested material can be distributed for commercial use past that date? Evidently, they mean you retest it at that date, it passes, and it looks okay, still hits specs. How long can you redistribute that material? Do you have to establish a new retest date? What procedure do you use to do that?

It depends. Normally, additional testing is done when something hits its retest date or nears its retest. If you look across the industry, you'll see numerous options in terms of how firms do this. The real issue here is to have whatever you do in a written policy, so that it's clear as to how you're going to deal with retest dating. The bottom line is, there are various options for establishing your retest period. "An API expiry or retest date should be based on an evaluation of data derived from stability studies." And, obviously, "those stability studies should be done using stability indicating methods."

Q. If you subject the final API to reworking with a different solvent, where do you draw the line between being in compliance with GMPs and being out of compliance from a regulatory standpoint? Would you need to update your certificate of analysis to test for the additional solvent and notify the drug manufacturer of the reworked batch? If not, why?

Being in GMP compliance and being out of compliance with your filing is kind of no mans land, because if you're out of compliance with what you have filed, you're not in a position to sell the material. The requirements of the Agency relative to filing requirements are the driver when it comes to rework. Use of another solvent is a trigger to notifying a user of an API and requires the use of the rework section of Q7A.

Q. For rework and reprocessing, Part 211 requires changing batch numbers to make it evident that the batch has been reprocessed/reworked. Is this still a requirement for APIs under Q7A? It's very burdensome when reprocessing occurs based on in-process testing.

Q7A does not specifically require or state how you would number either your first batch or your reworked/reprocessed batch. It does say that you must have unique batch identification, and that the batch must be traceable through all of its history.

Q. Would you provide a definition of adulteration in terms of Q7A, for example, if a rubber band falls into a tank at the beginning of a process and can be removed and shown to have lost no extractables and not impacted product quality, is it adulteration? Can removal be considered a deviation or reprocessing?

First of all, adulteration is when it's not manufactured in accordance with Good Manufacturing Practices. The elastic band we're talking about is more related to contamination.

Section 5.1 says, "any substance associated with the operation of equipment, such as lubricants, heating fluids, coolants, should not contact Intermediates or APIs, so as to alter the quality of the APIs or Intermediates beyond the official or other established specifications. Any deviation from this practice should be evaluated to ensure there are no detrimental effects on the material's fitness for use." Wouldn't you think, by extension, when you're talking about something that comes in contact with the process, even if it's not part of the equipment - it's an elastic, a polybag

in which the material was stored that comes in contact - you would evaluate it the same way, that it's not detrimental and it does not alter the material beyond its specifications and its suitability for use?

In that particular example, if you are using a lubricant and you get some of that lubricant in your API, under this section, as long as it does not alter the quality of the API beyond its established standard, then what you have is some contamination, but it would not be considered adulteration at that point.

Q. If the requirements for traceability and quality specifications for an API are so critical, then why is Q7A only guidance without the weight of a regulation in the U.S.? Are there any plans for implementation of these regulations into an actual regulation in the future? If not, why not?

ICH does not write regulation, regulations are written by individual countries.

Q. How often should SOPs and policies be reviewed? Is there a maximum time limit? For example, one, two, three, four, five years?

Not specified under Q7A. You establish such periods by your own SOPs. You do have to follow your own SOPs.

Q. If the reprocessing step is not in the filing, can the product be sold on the U.S. market, assuming that the reprocessing procedure is validated?

There is usually a general statement in the filing that says companies can reprocess or repeat steps. However, this should be clarified with you local regulatory agency.

Q. How should rework/reprocess be addressed for products still in clinical phase where no license yet exists to permit these activities?

You should have appropriate controls and documentation whenever you reprocess or rework an API. You should keep accurate records, and you should show that the scientific staff directing your development work has authorized and approved these activities. They should all be properly recorded and documented so that one can look back through your laboratory notebook and understand exactly what happened and how you processed that material.

Your scientific management should have determined that the reworking/reprocessing procedure is appropriate. There is greater flexibility permitted under Q7A for materials still under development.

Q. Is there a limit to the number of times a given batch of API can be reprocessed?

This is not specified in Q7A. If reprocessing happens often, then it may need to be placed into the filing itself. However, this is usually not a serious issue from a GMP perspective, since multiple reprocessing would normally increase purity.

Q. If an API is returned by a customer for non-quality reasons, example, inventory levels, etc., and the customer sends documentation stating that the API was handled to GMP, could the API be resold without reprocessing?

This would be addressed by the section in Q7A dealing with returned materials where it says that if there are any doubts regarding the quality of the returned API, for example, if you notice evidence of tampering with the returned material or say the material originally had seals, factory seals on the containers, and these have been broken, which may suggest potential tampering of that material, than now you have reasonable doubts regarding the quality of that material, in which case I would say that you should probably not resell it as it and it should be reprocessed, reworked or destroyed.

Q. What is required in order for the manufacturer to be able to do the rework and sell the batch? For example, validation protocol, prior approval from FDA, annual report filing, supplement, etc.?

Aside from the filing issues, what you would rely on is extensive sampling and testing of that reworked batch to assure that the rework batch is of equivalent quality. The rework would then be conducted under concurrent validation under Q7A.

Q. Section 14, from a QA perspective, what is the difference between designating reprocessing versus rework? If the difference is nil, than why is it so important to make this distinction between reprocessing versus rework?

It's very important to make this distinction because, first of all, there are very stark differences between these two activities in the API arena. In reprocessing, you can reprocess conforming and non-conforming material. You can only rework non-conforming material. Reprocessing involves taking the material, introducing it back into a batch and basically repeating a step or steps that are part of the established process. Reworking involves taking material, putting it back into the process and doing something to that batch that is different from the established process. The reprocessing of APIs is typical; reworking is non-typical. So there are clearly very distinct differences between the two. It's important that you clearly understand what these distinctions are because when you have these kind of problems, what you do and how you handle the situation is, in general, going to depend on how it's classified, whether it's a reprocessing or a rework.

Q. Do your recovered materials, second crop…need specifications if there are established procedures to purify this material and this purified second crop always passes finished API specifications?

You should have specifications no matter whether it's first crop, second crop, or third crop. If you're producing it for release, it should have specifications. The fact that it always passes and you may be doing this all the time, maybe it should be part of your normally filed process.

Q. Is it possible to reprocess or rework a batch after the expiry and retest dates are reached?

From a GMP perspective, yes,

Q. This is rather interesting, if you rework something and rework procedure becomes part of your established procedure or in other words, the rework procedure became routine, it was incorporated as part of the established procedure and it was validated. If you have to do the same rework again, would that be reprocessing?

If the rework was incorporated into the process, it's no longer a rework procedure. It's now your established process. If you had to repeat a step of that now established process, it's a reprocessing procedure.

Q. Is there a distinction between a validated processing step and a validated process?

Yes.

Q. Assuming a validated process will normally contain both validated steps, critical and unvalidated steps, would it not be correct to define reprocessing in terms of the validated process?

No. We did not define reprocessing or even reworking within the context of a validated process because sometimes companies may want to reprocess or revalidate material produced by a non-critical process step, which Q7A doesn't expect validation. That's why we had to define both terms within the context of established process.

Q. You have an API, you've discharged it, it passes all specifications, but it's highly colored so you decide to repeat the crystallization. However, in repeating the crystallization, you this time add activated carbon. The inference is that activated carbon was not part of the original process and the carbon is added to remove the color bodies or impurities. Then the question goes on to ask is this rework or reprocess? The solvent remains the same. If it is a rework, is it a CBE or an annual report?

It's a rework because, as indicated in the question, the use of the activated carbon is not part of the original process. So here you're doing something different from the established process. So that's rework.

Q7A is silent on the question of filing. Filing issues should be discussed with the regulatory agency.

Q. The reason for non-conformance should be investigated if for a reworking, but it is not mentioned for reprocessing. Does it mean that in the case of an OOS reprocessing could be done without investigating the cause of the OOS? For example, OOS endotoxin of an intermediate could simply be resolved by reprocessing in a chromatographic step that was part of an earlier step in the process.

The fact that we do not mention it in reprocessing doesn't mean that you would not need to do an investigation. The investigation is driven by another section, whether it's a critical step, a critical parameter, etc., and at least documenting it is also defined in other sections

Q. If all of the equipment in a room is dedicated to a unique operation, is it enough to label the room or should we indicate the individual status of each piece of equipment?

It depends. Q7A is not explicit to that level, and you need to use judgment based on your exact operation for that.

Q. You mentioned that reprocessing for biotech applications might require higher scrutiny than as outlined in Section 14.2. What criteria should be considered as unique to biotech applications to allow reprocessing? Is validation required prior to lot release?

The general answer there would be yes. There have been a few reprocessing examples where they've come in either as one time exceptions or they've come in as part of a larger reprocessing scheme. The problem is by running a product from a biotech process back through the same process you can have minor changes in the process that would affect the product quality, so it may need to be validated. There's going to be a separate CBER guidance document on reprocessing and reworking, especially for the biotech products, and some of the other biological products.

Q. I'm processing an API batch and one of the operators mentions to a supervisor that foreign object has fallen into the batch. Our tech ops group has evaluated the situation and feels that it could be removed by repeating a filtration step. If we are confident that there is no solubility or extractable issues, can this be considered reprocessing rather than rework?

Now, there could be other circumstances involved here, but reading this question, and since there is no concern about extractables or solubility issues, and if they use the filed process and they don't make a change in the file process, than that is reprocessing.

Q. In the event of raw material supply shortfall, can the API producer reprocess or rework a raw material?

If you're not producing the raw material, then how are you going to reprocess or rework it because you'd have to have the established process?

By definition, reprocessing and reworking is doing something to a batch that's either within the established process or outside the established process, which implies that you have to have some familiarity with the established process for producing that raw material. If you're doing something to purify your raw materials, that's really outside the scope of Q7A.

Q. Does material reprocessed by the filed process get a new manufacturing date under Q7A? There is a school of thought that understands original manufacturing date must be kept.

Manufacturing dates always reflect the actual processing dates. This includes the date a reprocessing took place. Original manufacturing records should to be kept as per Q7A.

Q. If an OOS API is reprocessed and then passes all final release tests, can tailings of this batch be blended?

Yes. It's a new material.

Q. If prior to the finished purification we add to the batch second crops from previous batches or residues from the dryer process of a previous batch, is it not blending? Is it reprocessing? So are we allowed to do this type of reprocessing?

It is reprocessing and yes, you are allowed under Q7A. Any filing issues should be discussed with your regulatory agency.

Q. The guideline applies to reprocessing of both conforming and non-conforming materials, what is an example of when you might reprocess in a conforming batch?

You may just have a small quantity left over of a lot and it's not worth testing.

Q. Do recovered solvents need to be reused/returned at the same steps from which they were recovered?

If you look at Section 14.4, it says that solvents can be recovered and reused in the same process or in a different process provided that the recovery procedures are controlled and monitored.

Q. How frequently can a rework step be performed before it is considered routine?

This is not addressed in Q7A. Reworks would normally not repeat since they occur for unusual situations. There's language with respect to reprocessing where it says if the majority of the batches are reprocessed, than you might want to consider incorporating that into your normal or established process, but there is no similar language for reworks.

Q. We had an FDA auditor objecting to a remilling of an API because the remilling was not included in the registration as an option. Based on the information provided here, I would understand that this is an acceptable reprocess.

It is an acceptable reprocess under Q7A. However, if the are other regulatory issues, you should consult your regulatory agency.

Q. If the rework batch is only done to eliminate a specific problem, how can it be released because it would not have come from a validated process?

Look at Section 14.3, where it talks about concurrent validation.

Q. During a rework, the product is subjected to a different process step. Does this mean that each rework batch must be characterized and validated?

Refer to Section 14.3.

Q. Please comment about minimum testing requirements for returned material that will be reworked. What will be the minimum testing requirements before reworking?

It depends. The first question you need to ask yourself is why was the material returned? Was it returned because they simply purchased too much or was it returned because there was something that did not meet your specification? The second question you've got to ask yourself is even if it was perfectly good material that met all specifications, was it opened in your customer's facility, and under what conditions was it opened? Has it been subjected to other contaminations while it's been outside of your hands? Unfortunately, there is no one simple answer because there are a lot of circumstances that have to be taken into account. Another important issue is whether reprocessing or reworking needed? There is a difference between the two.

Q. Can you reprocess or rework the same material more than one time?

Basically, yes. Again, you're going to have to do a very good investigation on this. You need to look at why did your reprocessing or reworking not work the first time. There is no limit in Q7A to the number of times that something can be reprocessed or reworked

The key is to have an adequate investigation of why you're repeating a rework or reprocess because it does bring into question some of your other GMP issues at the plant as to whether you have adequate control. Reworking or reprocessing would usually improve final quality.

Q. Why does Q7A not prohibit the use of recovered solvents from process A or process B? What is absence of process impurities? Not detected does not seem to be reasonable acceptance criteria. Not detected is up to what level of accuracy?

In Q7A, we try to provide guidance as to what is expected or what is not expected. It is up to the industry to establish appropriate acceptance criteria.

Q. Is it acceptable to reprocess non-conforming batches without an investigation? This presentation implies that investigation is only expected for batches to be reworked. Does reprocessing that involves a critical step need to be validated?

By definition, if it's a critical step, it needs to be validated. The Q7A document explicitly requires an investigation for anything that needs to be reworked.

Q. For batches reprocessed or reworked because of non-conformance, do all analytical tests need to be performed again?

Probably the best section to reference is Section 14.3 where it says that appropriate evaluation testing, stability testing, if warranted, and documentation should be performed to show that the rework product is of equivalent quality to that produced by the original process. We're specifically addressing rework. Reprocessing should follow normal production controls and specifications.

In section 11.2, for each batch of intermediate and API appropriate laboratory tests should be conducted to determine conformance to specifications.

Q. Is it necessary to validate the solvent recovery?

Section 14.4 requires control and monitoring - not validation.

Q. If during a reprocessing, two lots are dissolved prior to crystallization and one has an unknown impurity level, can a reprocessed lot be reprocessed, dissolved, crystallized to remove the impurity, provided that the impurity is a common one for the product?

If it's an unknown impurity and you've failed specifications, you can reprocess using the normal process.

Q. Although Q7A covers biotech compounds, the descriptions of reprocessing practices mainly represent small molecule operations.

That's correct.

Q. Did the working group discuss that rework/reprocessing in biotech is typically not allowed or allowed after consultation with the agency?

Yes, we did.

Section 15: Complaints and Recalls

Q. Are complaint records required between different sites/operations of a single company, i.e. a drug product manufacturer at Site A and the API supplier at Site B? And, I will take

this one step further. The API supplier actually might have two facilities that feed that drug product situation, because a lot of us have that situation in our plants. So, basically, the question becomes, where should the complaint records be kept and what are required.

It doesn't matter. We don't mandate that in Q7A. You should communicate with all the affected sites and all the affected facilities. The requirement is that you make the communication, get closure according to what's required. But, it really makes no difference if it's plant A of the manufacturing company or plant B of the manufacturing company. If your procedure is in writing and you show that you've gotten a close on the loop.

Those records should be readily available at the point of inspection or visit by the regulatory body, or can be retrieved to demonstrate the closure.

Q. Can you define examples of quality-related complaints? Are they "out of spec" issues only, or what other examples fall under this heading?

An example would be a wrong label on a drum. Something in the drum that shouldn't be there, for example, the glove the operator was wearing when he was packing off.

Particle size. For example, the customer had a very narrow spec and you shipped your general product, which did not meet their requirements. It's a complaint.

Q. The first bullet point in Section 15 deals with quality related complaints. What about non-quality related complaints? Do they have to be investigated?

Q7A is specific to quality related issues. There is nothing to prevent a firm from doing investigations, which are outside the scope of Q7A.

Q. Is there an expected function from marketing or senior management in responding to complaints or recalls according to Q7A?

It's a notification requirement. Q7A does not get into defining responsibilities for general functions and management. We do define what is expected for quality management, we do define what's expected for the quality unit and the production operation, but no, there is no explicit requirement established in Q7A for marketing or senior management.

Q. When would a retest date be used as opposed to an expiry date?

Generally you would only see a retest date. The only time you would see an expiry date is when a regulatory authority mandated such a thing. See the Q7A glossary and document for additional discussion.

Q. If product fails its retest, can you recrystallize it to bring it back into spec and then start the clock all over again?

Yes

Q. Do you think a recall procedure is really needed at the API manufacturer considering that it will be the API customer accepting or rejecting that API, and in case of rejection, sending the material back to the manufacturer? The real recall will be in charge of the pharma transformer that will put the drug product into the market.

You may uncover some day, a very low-level trace impurity that didn't fail anything that has caused major health problems, and you have to have a recall. You do need to have a recall procedure.

Q. In Q7A it states that all quality related complaints be recorded. Is there an expectation to record and investigate non-quality related complaints?

No.

Q. If an API is supplied from one location to another within the same company for manufacture of dosage form at the other location and quality complaints are received from the dosage form manufacturing location, are these considered complaints as defined in Q7A?

Yes.

Section 16: Contract Manufacturing

Q. Is it all right to use contract warehouse space for storage of APIs?

Yes. Recognizing that the contract warehouse now becomes an extension of the manufacturing facility. If the APIs require special storage conditions, you still have the responsibility for ensuring that they are, in fact, stored under those conditions.

Q. For contract manufacturing, is an audit required if the firm has on-site representatives during all the manufacturing at the contractor's site?

Although not addressed in Q7A, an audit of a contractor is normally used to "qualify" them for specific operations. Section 2.2 of Q7A discusses the responsibilities of the Quality Units, which include "approving intermediate and API contract manufacturers." Individual companies should determine what is necessary to support contract manufacturing.

Q. Under QA responsibilities not to be delegated, approval of contract manufacturers was listed. The question is, what does this mean? What specific responsibilities does QA have to approve a contract manufacturer?

The API manufacturer's Quality Unit is responsible for ensuring that the contracted facility is in compliance with cGMPs for performing whatever activities have been contracted to them. If they are performing, laboratory operations, they should be in compliance with the laboratory records section and documentation of Q7A. If they are performing some kind o manufacturing activity, they should be in compliance with cGMPs for that particular activity. A contractor becomes an extension of the manufacturer's facility and would be expected to comply with the appropriate sections of Q7A.

Q. Reference standards are extensively characterized in house. When we send these standards to our contract manufacturer, what tests should they conduct on the material received?

A contract manufacturer is an extension of your own operations. There's nothing that says they have to do any testing on those reference standards that you are sending them as long as they

are being shipped and stored in conformance with labeled instructions. So unless there's something unusual that's going by a circuitous route and some very adverse conditions, a company doesn't necessarily have to have a contract manufacturer do any acceptance testing on your reference standards that you are sending to them.

Q. In the situation where the contract giver officially releases the API, is it acceptable to delegate review of batch records to the contract acceptor?

Yes. The important thing is that it is done. It is also important is that the responsibilities be described in the contract.

Q. If a contract manufacturer needs to change the raw material supplier, may the contract manufacturer make the change and simply notify the contract giver?

No, section 16.16 reads: "Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes."

Q. Can you expand on the requirement that contract manufacturer should permit a company to audit its contractor facility? What recourse does a company have when the contract manufacturer is not allowing audits?

Section 16.13 says it very clearly: "The contract should permit a company to audit its contractor's facilities for compliance with GMP." In cases where the contract manufacturer refuses to be audited, he cannot be your partner anymore.
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Q. Company A owns the DMF for an API; company B buys the API for making their drug product. Is company A a contract manufacturer or supplier?

It's clearly a supplier.

Q. Does the quality unit have to be the point of contact for a complaint with the contract manufacturer? Can the production person be the gatekeeper for that?

The Quality Unit is responsible for reviewing all complaints and making sure that these complaints are effectively resolved. Often times, the initial complaint can come in through multiple ways and this is not necessarily the quality unit initially. What is critical is that the quality unit review and insure that all complaints are resolved.

Q. If an API is manufactured by a contractor and not yet released by their QA, can this be shipped by the contractor, to the original company with the intention of then shipping on to another contractor for manufacturing the drug product?

There's no prohibition in Q7A about that. The expectations are that you have a system in place including proper documentation and that you have adequate control over it to prevent the material from ultimately getting into trade before release by the Quality Unit. One may very well question the wisdom of having it shipped all over the place still awaiting a release, but there's nothing that would prohibit it.

Section 17: Agents

Q. Given these new requirements for agents, who will enforce these? The API manufacturer may not even know his product is being repacked and redistributed, so the API manufacturer cannot police. Is the burden then on the finished product manufacturer who purchases this? If the repacker is clever, and they are, you may never know. Will the FDA be more active in this area? Many of these distributors don't even register with the FDA.

The intent of Q7A is to clearly establish the expectations for agents, distributors, brokers, traders, repackers, and relabelers and to be sure these expectations are understood and applied by them. Only regulatory agencies could provide enforcement.

Q. Is an agent who imports or sells an API without doing any other operation responsible for determining the GMP status of the overseas manufacturer?

Section 17 indicates that agents should comply with Section 2 "Quality Systems". In addition< the actual manufacturer has the primary responsibility for GMP compliance. Where a firm is purchasing a critical component, that firm would have ultimate responsibility in addition to the primary manufacturer.

Q. Who would have the right or the responsibility to audit or assure GMPs are adequate at the repackaging or relabeling company?

If the repackager or relabeler is a contractor, it becomes an extension of the manufacturer. The manufacturer is still responsible for assuring compliance of GMPs of that contractor for whatever activities they have contracted out. If you have a contract lab or a contract micronizer, it is still your responsibility to assure that your contract micronizer or lab, or repackager or relabeler is operating within compliance for GMPs for those activities that they are performing. If they're referenced in a drug application, a regulatory agency also may do an audit or inspection of those contracted activities. If it's a contractor, it's quite clear who has the responsibility; it's still your responsibility as the manufacturer.

Q. Why did Q7A not include a requirement to have a written contract that covers GMP responsibilities?

If you're asking about a written contract for contractors, that is in Q7A. Q7A does talk about having a written contract for contract activities.

Q. How do you know if an agent is authorized?

Most representatives of offshore manufacturers in the United States have a letter of authorization by that supplier to give them the right to market that material. In some cases, some manufacturers may even have two or three agents. You should ask the supplier for a letter authorizing him as the legal representative for the material.

Q. What you suggest in Section 17 may be appropriate, but how can we appropriately

regulate nations that seem to freely operate outside the sphere of accepted regulatory practice? Can it truly be effective or is it easily circumvented?

The best approach is not to purchase materials from these sources. You put at risk your own product by purchasing from such firms.

Q. Will the FDA inspect the ABTDR to ensure compliance with GMPs?

FDA can conduct a "For Cause" or directed inspection from headquarters of such firms.

Q. Why was Section 17.5 included?

The FDA has had a compliance program dealing with re-packers and re-labelers of drug products. This is a similar issue in that when the container contact surface or package is changed, data must be provided to assure that the stability is not affected.

Q. I believe that most at this meeting would agree that it would a mistake for a body to attempt to write guidelines for the API industry without having representatives from the API industry involved. Other than the ability to provide comments on step two, did the industry participate in writing of Section 17?

To one degree or another, the answer is yes. The document was open for comment during its entire development.

Q. Staying with out favorite subject, does this section apply to customs brokers and shippers? The definition seems to apply.

Yes.

Q. Are there FDA filing requirements for agents? (It seems like a DMF is needed.)

Yes. Contact FDA for details.

Q. Given the high level of concern over the Haitian incident, why doesn't Q7A require approval of incoming materials prior to use rather than allow use when systems are in place prior to completion of testing?

Your own internal procedures should prevent the risk.

Q. Is an API manufacturer responsible for insuring compliance of his agents that purchase material from the API manufacturer?

The agents themselves have responsibility under this guidance, and the API manufacturer is responsible to be sure that they are receiving what's mandated under this guidance.

Q. If an agent or user of an API requests a retest date extension, can the API manufacturer based upon analysis stability samples retained by the manufacturer provide the extension?

If the data exists that justifies an extension or a new retest date, there should be no reason why that shouldn't be allowable under Q7A.

Q. Could you comment on the responsibilities of an agent as opposed to a contract manufacturer?

Agents and Contract manufacturers each have their own responsibilities under Q7A. Please review the document for details.

Q. Section 17 very explicitly, in the opening paragraph, says that it applies to APIs or intermediates. Is that written for raw materials?

Yes, but its application is driven by the individual country.

Q. How is Section 17…enforceable when Q7A is a guidance document?

Generally, guidance is enforced by linkage to the country's laws. Also, you're going to make it enforceable by your purchasing power. FDA can do for cause inspections just about anywhere in the food, drug and cosmetic chain. In light of counterfeiting issues that are going on around the world, the bottom line is the real enforcement issue here is going to happen when the users of these materials are going to demand compliance with Q7A.

Q. Will the FDA audit agents for compliance in Q7A?

Only FDA can answer what they will do in the future. They can and have audited such firms in the past.

Q. For supplier approval, it's stated that there should be full analyses at appropriate intervals versus the Certificate of Analysis. What does a company do when they don't have the ability to do such testing?

You should consider submitting the material to a contract laboratory for verification.

Q. Is it okay to state that the company has audited the supplier and therefore full analysis of a lot is not required?

What the section says is that you can use an identification test as long as you're periodically verifying the results.

Q. Who is going to monitor that agents comply with GMP regulations? Are health authorities like FDA involved or is this part of the purchaser or manufacturers' responsibilities just as it is now with suppliers of raw materials or contract manufacturers?

Correct. All of the above! I think you need to place the emphasis on you taking a look as a user of materials.

Q. If an FDA inspector comes to audit our API plant, could we tell him or her that we are following the Q7A guidelines?

Yes.

Q. We are a generic pharmaceutical manufacturer and we use APIs. Most APIs are purchased through vendors, and the questioner actually mentions a couple companies, some purchased directly from manufactures. Are these vendors considered agents and are they bound to Section 17 even though we are drug product manufacturers?

You, as a generic pharmaceutical manufacturer, should use Q7A as your guide for your API suppliers. And if, indeed, you're purchasing it from an agent, then you need to make sure the CA's and everything else that we talk about in Section 17 are met. It's your protection that's involved here.

Q. If I understood well, the Haiti incident, the problem was caused by a raw material, how does Section 17 prevent this from re-occurring? Should the requirements be part of the material section?

Well quite frankly, it doesn't matter what section it was a part of. Nothing can, with a 100% assurance, prevent everything. What Section 17 was trying to do in implementing the recommendations of the workshop that was made to World Health, is to be able to open up all the doors and the information so that if it were to happen again, and it probably will, you would be able to trace it back to a possible cause and at least have a shot at preventing it.

Section 18: Specific Guidance for APIS by Cell/Culture Fermentation

Q. It was stated that Section 18 should not be used as a stand-a-lone, what parts of other sections don't apply? For example, process validation for drugs has different completion data than biologics.

What we're trying to say here is that there are other sections of Q7A that may be applicable to APIs produced by biotech and fermentation. That is, Section 18 provided specific information related to the manufacture and control of these processes but that in reviewing Section 18 you should not just focus on and read Section 18 and leave it at that. You probably need to look at other sections of the document that could also have an impact on or be applicable to APIs produced by biotech and fermentation. In other words, don't look at Section 18 on its own and ignore the rest of the document because there are other parts of Q7A that may apply to APIs produced by biotech and fermentation processes.

Section 18 is very clear about this and states that it is not intended to stand by itself and that all the other relevant sections of the Guideline apply.

Q. Do you think Q7A will affect current guidelines on biologics and biopharmaceuticals when current regulations are already ten times more stringent than anybody else's?

It's my understanding of the ICH process that the United States Government is a signatory to an agreement along with the EU and the Japanese Government, which says that once ICH documents achieve step five, none of the signatories are will have national regulations, legislation or guidance which contravenes the ICH guidance. So to the extent that the question is a presumption about the rigidity of U.S. regulations, it is true.

Q. If there is a biologics regulation that is more comprehensive and more specific than Q7A, why was Section 18 included in Q7A in the first place?

Section 18 covers both classical fermentation and biotech. So Section 18 was designed to provide principles that applied to both. Where possible we tried to highlight the differences between classical and biotech, and in general, the controls needed for biotech are higher than classical fermentation. However, there isn't another GMP guidance that addresses classical fermentation or biotech at least to the extent that Q7A does. Does it cover all possible aspects? No. But it is an attempt to highlight the important aspects for these processes, and we were able to reach agreement between the three ICH regions, which is also another really important point. We do have that regulation in the U.S., but Q7A is applicable to all three of the ICH regions. Also bear in mind that the filing requirements for biotech in classical fermentation are somewhat different. The information submitted for the biotech processes exceeds what is submitted for classical fermentation. This will be addressed further in the CTD, which is the common technical document, which will also probably have higher expectations for biotech.

Q. Regarding the table indicating application of Q7A to biotech processes (Section 1.3 Scope, page 4), and the arrow indicating increasing GMP, does this indicate a change in CBER's attitude toward GMP levels from early process steps to late process steps, or is the attitude still in place that GMP levels should be consistent through the entire process?

It hasn't really changed the CBER perspective. We have been applying the GMPs from start to finish of a process. Not only is it necessary to control the process, but also CBER regulations make a direct link to the Code of Federal Regulations Part 211. Moreover, since we license bulk facilities, we felt it necessary to have these levels of control. In a general sense, as you move through the process, requirements get tighter, and that is consistent with the arrow in saying increasing GMP requirements. However, we would expect to see these controls in place from start to finish. There are certain early steps that are not really covered here (in ICH Q7A) but would normally be part of an application (for product authorization), where we would certainly expect the GMPs to be applied. These issues were just a little bit beyond the scope of this document, because we didn't really want to get into the source cell issues. This may be dealt with in another ICH guidance document to come later.

Q. As per the presentation, Q7A isn't intended to raise the GMP expectations for classical fermentation. It was mentioned that cell culture fermentation was one of the two differences between Q7A and the FDA's previous draft guidance. Confirm or clarify that the main difference is the moving of the line from isolation/purification back to the introduction of cells into the fermentation.

The distinction made in the presentation was that FDA's March 1998 draft industry guide for manufacturing, processing and holding APIs was essentially biased toward chemical synthesis activities or operations. It did not provide guidance for APIs produced by biotech or fermentation. It has always been the expectation that APIs produced by biotech or fermentation be manufactured under cGMPs. So this is not a new expectation. The difference is that these APIs were not specifically addressed in the FDA 1998 draft guide.

Q. On the definition of fermentation, can a protein isolated from a microorganism, which occurs in nature, be considered as being derived from a classical fermentation if the protein is well characterized?

That probably is an approach that could be tried. I think there would be an expectation that you would, in fact, be able to generate data that would confirm the "well characterized" part.

Q. Does a recombinant protein produced for use as a vaccine, either therapeutic or prophylactic, fall under Q7A?

No.

Q. Why are human plasma-derived protein products specifically excluded from the Q7 guidelines?

There were a number of issues with both how the products were regulated and source material issues. There are differences in the regulations. Some of the testing requirements are different. So, they were not included and they were specifically excluded from the scope of the document. That is not to say that most of the principles in Q7A would not apply. Certainly record keeping, validation issues, facility equipment, are general issues that would certainly apply to these materials. However the specific manufacturing issues that relate to those products could not be included in this document hence they were excluded.

Q. Is it anticipated that these products would eventually be covered by this guideline?

No. There has been some discussion about possible subsequent guidance documents produced for either biologics, or perhaps source materials or excipients. But there are no plans to reintroduce those products into Q7A.

Q. A biotech intermediate is chemically modified. This modification is maintained throughout the API and drug product. A biotech intermediate is chemically modified, but this modification is removed prior to the completion of the API. Is either or both of the chemicals used for the modification considered an API starting material?

Q7A does not require identification of an API starting material for every process. Q7A tells us in the introduction that the company should designate and document the rationale for the point in the process at which production of the API begins and hence the point at which increasing GMP expectations as described in the Guideline should start to be applied. For synthetic processes, this is known at the point which API starting materials are entered into the process. For other processes, e.g., fermentation, extraction, purification, this rationale should be established on a case-by-case basis. In other words Q7A gives you the responsibility to identify the point in your process where you consider the API process starts. However there is no requirement for you to define an API starting material but you need to be clear about the starting point for applying GMP according to Q7A guidance, and also get regulatory concurrence, because this will be used as basis of inspections.

Q. If an API is extracted for a mammalian tissue, does Q7A apply? At what stage?

If you turn to slide number 12 in Section 1, it shows fairly clearly in the second row of that table that materials extracted from animal tissues are covered by Q7A after the tissue preparation is completed.

Q. Please provide some examples of blood or plasma as a raw material where Q7A applies versus blood derivatives where Q7A does not apply?

I think perhaps the clearest example of this would be transferrin, which is not currently a licensed plasma derivative. However human transferrin is in some cases purified from human plasma to be used as a raw material in serum free cell culture.

Q. Adenoviruses. Are they considered whole cell and thus excluded from Q7A?

Well adenoviruses are viruses, they're not cells. It seems that Q7A is silent on the question of viral product and in any case vaccines are not included in Q7A. Adenovirus used for gene therapy products are probably more like vaccines than anything else, so they are probably not covered under Q7A.

Q. For semi-synthetic APIs where the fermentation and is registered as an API Starting Material, does Q7A cover maintenance of the working cell bank, etc.?

My understanding (see Table 1 in Section 1) is that the main cell bank would not be covered.

Q. Can all starting materials be considered equal?

The simple answer is no. For example, polyethylene glycol is more commonly being used in the manufacture of bulk or recombinant proteins in essence becoming a part of the API. Should this be considered a more critical starting material? Yes, when it is covalently linked with the protein or other macromolecule. It is certainly no longer an excipient. In fact it is now part of the API and is certainly critical with a fairly high priority.

Q. Could you clarify the distinction between the starting material for chemical synthesis of an API and a source material? For example, a component of a fermentation medium used in the manufacturer or biological API. In the latter case, is audit and qualification of a supplier expected?

The definition of an API Starting Material in Part 1, Section 1 of Q7A requires that it is a significant structural component of the API. I do not believe that source materials are defined in Q7A, but my experience has been that typically they are materials where substantial control is exercised over the origin and properties of material in order to achieve the desired result. In some cases, source materials are actually licensed products in their own right such as blood derivatives. Would an audit and qualification of the supply be expected? Well yes, and the more complex the material becomes, the more important that qualification becomes.

Q. For components of fermentation media, such as Casein Digests, what constitutes a specific identity test and, is it necessary if you have an appropriately qualified supplier?

This gets into a fairly grey area and there are perhaps a couple of ways to approach it. One is to attempt a "finger print" method that will give a profile that will point out some peaks that are connected with the characteristics of the material that are required for the growth of the organism in question. There are some kinds of media where immunological assays have been done to assure the medium, in fact, contains, for example, bovine-derived casein as opposed to some other kind of casein. So, depending upon what the issue might be, there might be different ways of assessing identity, depending upon whether the concern is the correct origin, or correct processing, or the use of the right kinds of (media) ingredients.

It is really an issue not so much for Q7A (GMPs) as it is for filing. This something you would work out during your original filings. If, indeed, it is an issue connected with a new process, it will come up during registration. If it's defined there (in the regulatory submission), it is academic as far as Q7A is concerned, because it will be pre-determined what you need to do.

Q. What is the appropriate level of control for materials used to increase biomass and prepare inoculum?

In general they need to be traceable, that is you need to know what you have and where you got it from. Furthermore, these materials need to be released as a controlled raw material on the basis of at least an approved raw material specification.

Q. Could you address the subject of water quality? Would it be acceptable to use "softened" water versus Purified Water for fermentation/cell culture activities, with Water For Injections used for subsequent purification steps? What types of testing data would be expected on this soft water, i.e., if it meets the lot criteria for Purified Water but was not processed as Purified Water? The use of water, USP, which meets all the test requirements of WFI or Purified Water, but which is produced in a different fashion acceptable for biotech APIs?

We've seen a number of different systems used to generate the water and there is no one easy answer. Certainly the water quality for, let's say, an E. coli fermentation can be different, probably a lower quality than you'd need for a mammalian cell culture. However, having said that, you won't find that Q7A specifically requires Purified Water, as defined in USP, or WFI, as defined in USP. Certainly, the question about "softened" water, depending upon the cell line that's being used and the process, if that would meet the Purified Water requirements that could be acceptable. Again, you'd have to take a look at the process, at the intended use of the product, and at what point in the process you use a higher-grade of water. The same is true for WFI. Some firms use, essentially, ultra filtration to produce water that goes into fermenters. Technically, that doesn't meet the requirements for USP quality water. However, if you look at the specifications, the testing that's done, it certainly could meet the USP specs. Certainly for early process stages, if it's WFI-quality water that's being produced by UF, there should not be an objection to it.

The other way to look at this is to look at the product and look at the process, and see how effectively you can remove Endotoxin from the product by downstream processing. For example, if you're going to make a recombinant product using E. coli, (which is the organism in which most microbially produced products are made), E. coli is four percent Endotoxin by weight. So, it's pointless to start off an E. coli fermentation with WFI. That is not necessary, and, in general, deionized water works just fine for most E. coli fermentations.

The general rule is to use WFI for all cell culture fermentations. But, if you're talking about cell culture, especially serum-free cell culture, and you're talking about relatively large molecules with complex structures; you may not be able to remove Endotoxin from those kinds of products if they creep into the process. The other consideration is that Endotoxin, itself, also can upset the metabolism of mammalian cells in culture in ways that are unpredictable, which is another reason to keep it away. Yet another reason is that serum-free cell culture leaves the cells without the protection that serum proteins, like transferon, would normally provide it. The only way that you can be reasonably certain that you're going to be able to provide water of a high enough quality to get consistently good results, in my experience, is to use WFI.

Q. Regarding contamination, if incomplete discharge of fluids in a biotech process occurs

upon transfer of the material to the next step in the process, microbiological contamination could be a risk. Therefore, this type of contamination could be unacceptable, yes or no?

That depends on what process step you're talking about. If it's an early process step where you're doing some of the harvesting and maybe in some of the initial purification steps, it may not be an issue. You would have to look and see where you've got control points, where bio-burden is an issue for your process.

Q. If microbiological standards have been established (this refers back to Section 4.1) where should the specifications be established? Please provide some examples of where microorganisms have affected a product's suitability for its intended use and micro specs may have prevented the incident.

There are a couple of issues here. The microbiological specifications, themselves, are intended to establish limits of your product capability. That is, you would be looking at certain stages of the manufacture - again, I am talking about cell culture and fermentation. You would be looking at some decision points in fermentation and looking at the culture purity. You would have a decision point at various points for continuous processing. You would also try to establish these decision points perhaps after major modifications or perhaps after long-term storage. It is not necessarily a question for just the suitability for intended use, though there is a component of that. The microbiological specifications are really there to ensure that your process can handle any contamination in subsequent steps. Suitability for intended use goes to one of the points - just to give you an example, there was a topical product that was being used for ulcers and burn patients. When pseudomonas was detected as one of the organisms that were present, that was not acceptable because it would have a direct impact on the suitability of the final product because there were no assurances that it would be removed at subsequent processing steps. Part of the issue for microbiological specifications, and especially for biologics and biotech processes, if you have a high level of microbial contamination (including moulds) it is somewhat difficult to know what impact it's going to have. Contamination with molds in particular, has been an issue for some of processes. In particular you need to consider the metabolites of the (mould) contaminants that could be potentially in your product and how you can assure yourself that you won't get something that carries through the entire process and that would be sensitizing. Those are some examples of issues where, setting the appropriate microbiological specifications are useful provided that you know that, subsequent processes that could remove contamination and you can detect contaminants that would have direct impact on API or drug product quality.

Q. Can the periodic monitoring of the cell banks be performed via successful thaw/runs, meaning if the vials from the bank are frequently thawed and expanded, what is meant by determining suitability for use? Full characterization?

I think that the intention of this part of Section 18 is that instead of creating another cell bank, or another working cell bank was to say, okay, take a look at the performance of the cell bank that you are currently using in production. So periodically take a look at it, and that could be just the end of production cells that you're running as part of your normal production and say do an assessment. You need to ask yourself I've stored this cell bank for X number of years, this vial 87 of 225, is it still performing adequately? Certainly you should be taking a look periodically to make sure that the cell growth characteristics and the quality of product are still being maintained.

For biotech products, if you're in reasonably frequent or constant production, there's no need to make additional checks, just the normal controls and checks that are part of manufacturing are adequate, but if you're in an infrequent manufacturing situation, ICH Q5D actually gives some specific guidance. I think it's if you're making less than one batch every two years, every two

years, you're supposed to check the viability of the working cell bank. That's my recollection of the guidance. I don't think though that that was intended to apply to conventional microbial products but just to biotech.

Q. How does one define actual yield at appropriate phases or times for a fermentation-based product?

The actual yield is much broader for these types of processes than you would find in a final dosage-form manufacturing situation. You should have some idea of what the cell viability is and what your yield should be, but there will be a much wider range available to you. You should also have enough historical information to have an idea of what that range is and define some parameters to assess the process quality.

This is typically something that the process development scientists need to work out during product scale-up, that is the appropriate ways to control yields. It will be different for different kinds of processes. In some cases, there's a need to control the amount of protein coming from the cells, and sometimes it's control of the amount of protein in a certain volume, because it depends upon how robust the purification process is. The goal is to be able to ferment consistently so that you can purify consistently, but the way you actually control it will vary from process to process, and that needs to be worked out during development and the manufacture of clinical material.

For classical fermentation in most cases it is an economic issue. The yield generally is not a problem other than economics, because you usually have a purification process that follows the classic fermentation, and the kind of compounds that can occur are likely to be removed by the processes that are used.

It is important, though, when you do this work, to distinguish clearly between controls that are being imposed to control product quality by GMP, as opposed to controls that are being imposed for economic reasons, which are not GMP matters, in general.

Q. Section 8.4 implies that combining several lots of an Intermediate for further processing is not blending, and therefore the individual lots need not be tested for conformance to specifications. Would this hold true for fermentation processes where several lots are harvested and pooled for purification? Does only the pool need to be tested, or must we still we test each harvest to ensure that they are not blending into compliance?

Typically, each one of the batches is tested prior to putting it into the pool. It also can depend on the nature of the process and use of the Intermediate. If you are talking about Intermediates that are going to be prepared, and then blended after a period of storage, that might lead you to a test and pool control system. But, if you are running multiple aliquots of a harvest across a purification column sequentially within a small period of time, and then pooling all of these aliquots, individual testing of aliquots that may not require individual testing of each aliquot. But, it might also be a good idea to have a look at each of the individual aliquots, at least once or so, to make sure that they're more or less the same. But, that would not require individual testing and confirmation each time.

One of the issues that you get into, and this sort of drifts over into the filing issue, is what defines a lot or batch. Certainly, if you've got a fermentation process that is relatively short, and you can do three in a week and then pool them. This might however be different than, say, one of the batch re-feed systems that goes on for up to six months. The batch dynamic is going to be

different, and how you would test and how you would characterize each individual harvest as opposed to each individual "pool" might be different.

Q. The guidance requires that API manufacturers establish and monitor impurity profiles. Can the panel explain how this will be done in practice, and especially for APIs where impurities are difficult to characterize, such as biologics?

There is no substitute for doing your "homework", and the regulatory community can't help you, they can only assure you that you've done it properly. This begins in early development, or one has to combine process development with product characterization, and begin to understand your product and your process and know what belongs there. Get a handle on what it's supposed to look like and if you have a decent level of experience and analytical capability, it gives you the maximum ability to generate an appropriate profile from which you can then monitor. It is necessary to do your homework during development, so that when you file a license application or a product approval application, you have the basis to, in fact, be able to do this. Staying current with the analytical state-of-the-art is also very important in order to maximally assure that you can do this to the extent that science will permit.

Q. Do you think that shared or divided manufacturing will be possible in biotech? Would this require the ability to file a DMF for a biological?

Shared or divided manufacturing is certainly possible. Be aware that under our regulations those have specific meanings. Divided manufacturing to regulators means both manufacturers are capable of doing the entire process, that is, A to Z. A shared manufacturing arrangement means that you would be licensed for part of the manufacturing process. Say, a manufacturer would be doing the initial inoculation and fermentation, maybe even up through purification, and then sending the API perhaps to another company for additional processing, and then fill and finish activities. So, yes, and if you take a look at one of CBER's guidance documents that came out in August 1999, that talked about the Center's [i.e., CBER] policies on shared manufacturing arrangements.

The other possibility is contract manufacturing. A number of years ago, we changed the definition of applicant. It used to be that an applicant had to be a manufacturer, that is, doing some of the manufacturing steps. We realized, with the way the technology was going, it wasn't possible in a lot of cases for one manufacturer to be doing all the significant manufacturing steps. So, we redefined the license holder to be an applicant. Essentially, at this point, you could have a virtual company, with all the manufacturing steps contracted out. That may be another possibility if you're looking for a licensing scenario. You could be the applicant and contract out all the manufacturing steps. With respect to Drug Master Files, our Center handles and reviews Drug Master Files, as well. I think the caution we have with Master Files is, Master Files, while they can be used to submit a lot of supporting information, when it comes to some of the process-specific information, I would tend to shy away from those. Those should be in the application. I'll step over into the application world for a minute and talk about some of the problems we've had with Drug Master Files. We had one for a product, it was a contract manufacturer that had a Drug Master File, and they submitted some of the information for the container closure system and some of the sterilization. The information that they submitted wasn't what was in the application. The application was for a 5 ml vial and what was in the DMF was for a 100 ml vial. I think you have to be careful on how you're relying on the Drug Master File. I think there's going to be additional discussion on this, but the Drug Master File is really appropriate for general things: procedures, facility overview, and those sorts of things. But, when it comes to specifics of container closures, sterilization parameters, those are things that are best left for the application.

Q. For classical fermentations that have been around for 30 plus years the practice has been to validate the sterilization of the fermentation vessel and the feeds. Do you think this is adequate?

That should be appropriate. Normally what one would expect to see, and again, my background is more in the biotech processes, so if I err for classical fermentation, someone else please step in, but what we typically see is all the media, all the transfers performed in aseptic fashion. Essentially, the early stage manufacturing, that is the subculture and fermentation for biotech process is done in aseptic fashion. Once you've got to the harvesting stage, it really is a bioburden control situation. So if you are sterilizing the material that's going in and running the fermenter and then harvesting, that would seem to be an appropriate level of control.

The normal procedure in classical fermentation would be to steam it, sterilize it in place, and then introduce the cell, and that's been practiced for probably more than 35 years. It goes back to the original production of liquor. Concerning the feeds, the question is whether or not the feed materials, whether they're nutrients or pH adjustment buffers need to be sterilized and whether the lines leading from those vessels into the fermenter need to be sterilized. Look for a practical solution here. If a system is set up in such a way that it's running trouble free, than maybe it's not necessary, but if there are problems associated with those materials, if they've not been sterilized, then it is clearly an issue that needs to be addressed.

Q. How is the API source material for fermentation process defined? Can you provide an example as was provided for the chemical process?

The EWG had a lot of debate about this particular subject and really didn't come up with a particularly good analogy for fermentation. Is it really the cell lines used in production? Is it the media and media components that make up the source material? What exactly is it? We also had this discussion with the CTD working group because they were trying to define the same thing, and I don't think there was ever a plausible resolution to this. So what we came up with is nicely illustrated as part of the chart, and we thought it was a more workable solution, was instead of trying to define something as a source material, what we would do is try to show the processes in parallel. And that is one of the reasons we chose to start with fermentation because that seemed like a good starting point for the process for both biotech and classical fermentation. So the answer is we realized that trying to define the source material for these processes was a difficult task and it was one that ultimately we did not resolve.

Q Are there specific CBER expectations for classification of rooms in which biotech fermentations take place? For example, 10,000 and 100,000.

Typically, Class 100,000 or European Class D, which is Class 100,000 at rest, is expected. Typically, biotech fermentations take place in closed systems, they're pressurized; you wouldn't expect ingress. However, you have to look at how additions are made, how frequently additions are made, how you're taking samples, and the nature of the process.

These comments revolve around biotech-related activities. I'm not aware of any classical fermentation operations that are conducted in classified areas.

Q. What type of controls/room classifications/gowning, etc., would you expect for a media prep area of a dedicated biotech facility, especially if the media raw materials have a known but unpredictable level of bioburden?

The room classifications typically seen for the media areas have been Class 100,000. Most manufacturing areas in a facility are Class 100,000, at least for the purposes of this guidance document. Q7A addresses API drug substance. It is a different animal altogether when you go towards the drug product end of things. I think the level of gowning that you would see may vary a little bit. Some of the manufacturers may be using plant uniforms, but most of them are using Tyvek gowns of some sort.

Q. How stringent must the environmental monitoring program be for the biotech API facility? Do you expect to see the same level of monitoring that is done in a filling facility? Is passive monitoring sufficient?

I wouldn't expect to see the same level of monitoring that you'd see in a filling facility, but I don't know that I would agree that a passive monitoring system is sufficient, assuming that you're talking about settling plates there That wouldn't be the recommended practice, at least not in all cases. More active monitoring is preferred.

Q. Please comment on the environmental monitoring and air space classification in facilities generating API from MMC (assuming that mammalian cell culture, and fermentation processes). There is a breadth of practice and inspectional findings in the industry.

We could write a separate guidance document just on environmental monitoring. The locations where monitoring will be performed should be defined; the action and alert limits need to be established; and monitoring should be performed using varying frequencies depending on the level of control necessary for a particular manufacturing area. The need for environmental monitoring doesn't necessarily rise to the level of the aseptic processing area where you'd be monitoring every fill, but certainly there should be some correlation between the activities in the room and the environmental monitoring. That is, you would want it to be active monitoring. The level of control, whether you're talking about a class 10,000 or a class 100,000 room, is really going to depend on the type of process you've got, the types of equipment and systems that are used. Are you talking about an open system? Are you talking about a closed system? What is the impact of the environment in the process? How robust is the process? And how many manipulations are you talking about within the defined area? There are a lot of things that factor into that. It's going to be difficult to define it for all cases. Typically, a fermenter is going to be placed in either a controlled environment or it's going to placed in a Class 100,000 area. Typical process areas range from Class 100,000 to Class 10,000. So again, it's not quite the same level of control that you would see for an aseptic fill.

If you're able to complete the vast majority of your batches without contamination due to environmental organisms, it's pretty good evidence that whatever your system is adequate, but if you're losing a substantial fraction of your batches to environmental contaminants, than you probably need to be doing more than you're doing.

Q. In classical fermentation, history would be, the fermentation operation itself is obviously in a closed vessel and the environment around that vessel is non-controlled, quite frankly. I hear you saying, in the biotech area, or the cell culture area, that you're suggesting or saying that you need at least a 100,000 classification. Can you explain to the people here as to why, number one, that has evolved, and two, are you suggesting that you need that kind of environment than classical fermentation too?

I think it's easier to address the second question first. No, we're not implying that that's something that would have to be in place for classical fermentation. My presentation showed that a relatively high percentage of non-host organisms could be in the fermenter and yet ultimately not affect the product quality. So it's not necessarily the same level of control that you'd expect to see in a classical fermentation area. Typically a biotech fermentation area is going to look somewhat like a clean room, albeit, you're going to have associated piping, etc., so it's not intended to be a sterile area. By and large, they are relatively clean. Part of the problem you run into, especially with the mammalian cultures, is that they are sensitive to contamination, and so from an economic standpoint, you need to protect them as well as you can. Whether you need to go to the extra level of control and raising the air classification, it's going to depend, again, on the types of manipulations. Arguably, you know, if you had a E. coli fermenter that's running for 20 hours, you might consider a less rigorous set of controls than you would for a mammalian culture that's going to be running over six months.

My recollection is that the Class 100,000 notion for contained or enclosed fermentation areas was never a written requirement, but rather may have arisen over time as a compromise position acceptable all parties. It is sort of arbitrary. But one also has to remember that it's hard to really define what a closed system is. There are a lot of avenues for things to enter, even into a fermenter, you're drawing samples off, you're doing a lot of manipulations, and so I think the thought was to keep the environment as controlled as possible without being too onerous. Most manufacturers, at one point, were putting fermenters into Class 100,000 areas. Some still are. Some are choosing to say it is controlled but not classified. I am also aware of some fermenters, especially the larger ones, where it's impossible, you've got a two-story fermenter, you're not going to have the thing in a controlled environment. So basically what you have is all the controls and all the interferences in a controlled environment, and the rest of the fermenter is essentially in an unclassified gray space, which is probably more similar to what you'd see for the classical fermentation.

The thing that's really important is to have good controls wherever you have open operations, and where you've got closed or contained operations; it's far less important what those controls might be.

Q. Would it be expected that the sterilization process of fermenters be validated for a classical fermentation operation?

Q7A is silent on that point. In many cases, companies doing classical fermentations do not claim that the fermenters are sterile. They may be sanitized, and have reduced bio-burden. But there should be procedures to make sure batches do not get contaminated.

You have to understand that in fermentation processes, the reactors are not typically sterilized empty. What is really sterilized is the culture media. The culture media is prepared and transferred to the fermenter and sterilized in situ inside the fermenter before you transfer the inoculum into the fermenter.

Q. In a classical fermentation, is it necessary to validate the process no matter if we consider the step a non-critical one? The other one is what guidance can you give for validation of classical fermentation processes? What type of factors should be considered for validation?

If a factor has been identified as non-critical, there is probably no need to validate it. The second part, how do you determine which factors need to be validated. If you're developing a process in the modern era, it's probably fairly straightforward to look at standard fermentation variables and see which ones affect product quality and which ones don't. The ones that do affect product

quality are the ones that ought to be validated. For a process that's already been running for 30 or 40 years some types of retrospective analysis under the right conditions is probably appropriate?

Q. Should process validation be performed on classical fermentation? For classical fermentation, should the sterilization operation be validated?

It was never the intention of Q7A to even suggest that all classical fermentation processes have to be validated.

I think if product quality demands that the fermenter be sterilized, than it's probably wise to sterilize the fermenter and to validate it as such, but if you have a long history of being able to operate the process successfully and maintain product quality in the absence of sterilizing the fermenter, but rather just merely sanitizing it, than that's probably okay.

Let me just say that in the classical arena, when you're talking about fermenters that could be five stories tall, the whole issue of validating a fermenter of that size becomes almost an impossibility from a product quality perspective and given what you're doing is normal classical fermentation, it becomes, as you said, an economic issue more that a quality issue. In fact, unless you're generating a whole broth of material, the fermentation is just the start of the process, and you're going to go from there into true purification, chemical purification and extraction and clean-up. So from the classical perspective, while it's a very nice, theoretical concept to want to validate that sterilization, what is going to happen is if you fail to really sterilize, your yields are going to go way down, you probably may even throw away your entire fermentation run if it goes bad, and in reality, will have almost no ill effect on the real product that you're generating in the classical sense. Some of these fermenters can get very, very large and the sum cost of a batch can become very, very large, and no company wants to lose substantial chunks of a million dollars or more because the fermenter isn't sterilized. So there can be multiple reasons for wanting to have good quality on the machinery, and product quality is one of them. There can also be valid economic reasons that really have nothing to do with product quality, but do reflect the economics of the situation.

My understanding is that you wanted to file a market application for a product prepared by classical fermentation, there would be the expectation that the critical parameters would have been identified and subjected to whatever level of validation was justifiable. I think it's important to understand that validation of fermentation is not the same as validation of terminal sterilization autoclaves. Some parts of it certainly may resemble it such as determining whether or not the fermenter can be reliably sterilized, but the parts of the process are just not approachable with the same level of rigor, and even to determine which variables are critical is not always easy. So it's an area, frankly, where there is not a lot of standardization, there is not a lot of useful guidance and it tends to be case by case. I think in many cases though, the processes are still so complex that it's really difficult to make progress because the tools of science are just not there.

I would go on record as an FDA rep to acknowledge, that validation of sterilization, in situ sterilization, culture media and the fermentation process is a different animal as compared to a terminal sterilization process for a sterile drug product. Again, you have to consider what are we trying to accomplish here? The real purpose of sterilizing culture in situ, in place, is not so much to achieve total sterility for the downstream, but to try to minimize contaminants in the process in the fermentation broth that may affect your process later on. The intention for drug products is different in that it is to kill all living organisms in the product.

Q. What are the expectations when validating the in situ sterilization of culture media in a fermentation process? Is this done in the traditional way when validating an autoclave, for instance using temperature monitoring with thermocouples and biological indicators, or can the sterilized broth be sampled and tested for sterility?

Let's look at that as two different parts of the process. You would certainly want to have an operational qualification of the equipment. Then as part of the performance aspect, you would be looking at the sterilization of the media, and any associated hold times. So the whole aspect of the sterilization (lack of contamination, I guess, is a better phrase) for the media is another consideration.

There's a family of issues here that are related, but they probably need to be distinguished. Sometimes the easiest way to resolve a complex problem is to attack it in parts. The first is, can you sterilize the fermenter? The second is, can you sterilize the medium in the fermenter? And, thirdly, can you operate the fermenter after the medium has been sterilized to grow the organism you want to grow? The first part, you can address by typical thermocouple monitoring methods, and even biological indicators, if necessary. The second part you can address by putting the medium in, running the sterilization cycle, doing some temperature monitoring, perhaps also doing some sampling. But, if you're going to sample and test, it's important to be careful how you sample, because if you don't sample in an aseptic manner, it may not be a valid test. One also has the issue of whether or not you can find anything in the test article; in other words, can the test medium actually grow organisms that might have been "in the environment" and, therefore, inadvertently not sterilized by the sterilization operation So the fact that you get a negative test result doesn't necessarily mean anything and there needs to be some background laboratory work to show that you could have, in fact, found expected contaminants if they were present. Then, finally there is the question of aseptic operation of the fermenter, which one can address by running some batches and seeing if you get results that are in line with your expectations and your control limits. It's best to approach it in parts rather than trying to do it in a single approach and a single experiment.

In the case of a classical fermentation, there is a fourth issue and that is a foreign organism that may enter or survive the original sterilization of the fermenter and the media, itself. It may or may not be an issue. It could be purely an economic issue if a foreign organism were to be there. That's probably not true in the biotech area, but it can very certainly be true in the classical fermentation area where a foreign organism could have an effect on the productivity of the organism of the drug you are producing. For example you may get 3 grams per liter throughput instead of 4 grams. So, your productivity may go down but it really may have no adverse effect on the material in your fermenter. There are other issues, and based on industry experience, foreign organisms, especially on long-term fermentations are not uncommon. When you talk about hundreds of hours of fermentation, having foreign organisms all of a sudden show up is not unusual, and many firms will have experienced the situation of having them show up in the late logs. Just to answer the question about Log 0, Log 0 is the start of the fermentation. Those are the kinds of things you have to examine. In some cases, it may be a big issue; in other cases, it may not be.

Another detail to watch out for is, if you're running recombinant bacterial fermentations, where you might use antibiotics to maintain selective pressure. That may be how you have to run the fermentation to make your product, but, as you might imagine, if you have tetracycline in the medium, you're not going to find too many organisms when you go to sample it. There, it's best to remove those kinds of agents from the test, just so that you can have a reasonably valid result.

In conclusion, validating a fermenter and a fermentation process is quite different from validating an autoclave and a terminal sterilization cycle for a finished drug product, or from validating equipment or materials that would be used in an aseptic filling operation for a drug product. Obviously, terminal sterilization of a drug product is your last opportunity to kill any

microorganisms in the product before it gets to the consumer. In the fermentation process even if you had some contamination it may or may not be significant. If you have some contamination and it can be "cleaned up" in further processing steps, fine; if it cannot be "cleaned up", what happens is that batch is dumped down the drain, so it never reaches consumer. So these are very different things, you are trying to accomplish one thing when you're dealing with terminal sterilization of drug products; and you're trying to accomplish something else, or something slightly different when dealing with a fermentation process.

Q. Is the expectation for process validation being completed before commercial distribution of the final drug the same for CDER and for CBER regulated products?

Certainly the answer from the CBER side is yes. Process validation must be completed before distribution of the final drug. Moreover, not only would the validation be complete, but also the validation data would be reviewed as part of the filing. In CDER, the validation information doesn't necessarily get submitted as part of the NDA, but that is something that would get reviewed by the field inspection, and then the field would say that the process is validated and would recommend or not recommend approval based on their inspection.

The only time validation for CDER products would be expected in the filing is with sterile products, sterile processes, and sterilization processes, that type of data would be submitted in the filing. Generally, CDER does not expect a completion of validation for purposes of a pre-approval inspection. CDER like to see is at least one validation batch completed at the time of the PAI so that the field investigator can see technology transfer. But completion of validation is not an expectation for purposes of the PAI or approval of an application.

Q. Slide 5-15 - representative intermediates or APIs can be used for cleaning validation: does this mean a placebo API might be substituted in the case of very high active or very high value protein production? And, what would be considered representative, only those properties that affect cleaning?

If you've got a number of products that are using the same cleaning procedure, the representative intermediate or API could be a worst-case product. In defining the "worst case" product you need to take into account difficulty in cleaning, toxicity, and potency. Validation may need to include more that one product in order to fully address "worst case." It really depends upon what type of product matrix you've got running through that piece of equipment.

I'm taking a different approach on this question because I hear that your concern is about using a very expensive product for cleaning and substituting a placebo instead. Why would you consider that wasting product? What you're trying to do is remove residues of the product from equipment after that product has been processed in the equipment, so you're not wasting product. You produce a batch of what you consider to be the most difficult material to remove from the equipment, and then you validate that you can remove any residues of that from the equipment surfaces. What's possible with using a placebo for cleaning validation purposes is that you only prove that you can effectively remove a placebo, not the product.

Q. What type of qualification would be expected for steam used to sterilize media in a classical fermentation process?

For classical fermentation, most plants that make conventional products don't use clean steam. Most use processed steam or said another way, plant steam.

Q. For biotech cleaning validation, is it sufficient to validate the cleaning from rinse samples? What additional tests might be considered from swab samples?

The validation process typically includes swabs. You may get to the point where you can correlate swab results that with rinse water for normal cleaning between batches, between lots. But, certainly, the validation should include swab samples.

A lot will depend on what it is you're trying to clean. In other words, what might the residues be and what is the equipment? Some are easier to develop by looking first at rinse water and then later just using swabs to confirm that you're getting adequate cleaning. Also, don't overlook the value of visual inspection or other alternative tests like challenge with riboflavin because these, in some environments, can be very useful aids in cycle development.

Q. At what stage of process development is the validation of viral clearance required?

For viral clearance studies where chromatography is used for virus removal CBER expects small-scale models to be used, but these models need to be representative of manufacturing scale. A good reference on this topic is the January 2001 "Gold Sheet" report on a PDA/FDA meeting in September 2000.

Q. Section 18.5 refers to viral removal and viral inactivation steps, and refers to Q5A. Has FDA determined if validation of inactivation of mammalian model viruses is required for insect cell culture processes, since the growth temperature of insect cells would not allow replication of mammalian viruses, it is not appropriate though Q5A seems to imply it is?

Q5A states that insect cells are included. The issue would be identifying the potential virus in the insect cell line, then developing the appropriate methods to validate the removal and/or inactivation of those viruses. The tables that are provided as part of Q5A list the model viruses, and perhaps are a little bit biased in that they refer to the mammalian viruses, but they only serve to list those that would potentially be used for those production systems. So, your viral clearance steps and demonstration of the capability to remove the viruses in your process would really be dependent upon the cells that are used in production.

Q. Is there still a requirement for virus removal and activation when there are no animal derived components in the manufacturing process? That is no bovine serum albumin in the media. That's the first part of the question. Is there ever a requirement for redundant virus removal in an inactivation step?

Regardless of whether you've got a serum free or an animal source free media, you still have the potential for adventitious agents as part of the cell line. And so, my understanding of the viral removal requirements would be that you would need two different methods for viral removal. Part of the reason for that is you want to have the back up, and part of it is using different means. Often you don't have one single method that achieves the level of viral removal that you're looking for. So you may have one step that's using a low pH, you may have another one that's a solvent- detergent treatment step. There are some instances where the column chromatography is used, as removal can be achieved by physical means. There's a lot of good background and explanation of this entire concept in ICH Q5A.

Q. If a biologics (API) batch for clinical study use was already manufactured, does the FDA

still require sterility test if it wasn't tested before it was used in the manufacturing process of the drug product? If yes, the risk of drug contamination increases. Would they still require a sterility test, or is a passing a test of zero bioburden conducted prior to (drug product) manufacturing sufficient? Drug contamination can occur when taking the drug through the sterility testing room because the package will go through vigorous cleaning processes using harsh chemicals. Then, when the drug is ready for packaging, these harsh chemicals may break through and contaminate the drug product.

The first part is the easy part. Any product for parenteral use should be sterile, whether it's in clinical trials or not.

Yes, under an IND, the first concern would be safety, so yes, the sterility test would be required for that. The other concern when talking about the manufacturing steps is that it wasn't clear where they wanted to apply the sterility test. Was it at various points along the manufacturing or was it for the final product? The biologics regulations are very specific. If you have a discrete bulk, prior to filling that bulk product there should be a separate sterility test, and then an additional sterility test after it's filled in the final container. For the biologics product, it's two parts.

There seems to be an implication in the question that passing a sterility test means the product is sterile. That's not necessarily true or the best way to look at it. The best way to look at it, whether you're making clinical products or marketed products, is that they're supposed to be handled in a manner that keeps them from becoming contaminated; processed, especially near the end, by methods that have been validated, such that you have a high degree of assurance that the product in the vial is sterile and the test merely confirms that. To think that passing the sterility test is the only thing that's necessary to assure that the product is sterile is oversimplifying the problems.

For some small volume parenteral operations, when the solution is sterilized and put into a sterile tank, that whole process is validated in order to assure the sterility of the sterile bulk solution. Often, once that has been validated, during routine manufacturing it is highly possible that the manufacturer may not sample the bulk solution because they always run the risk of contaminating it. That's perfectly acceptable, as long as they have adequately validated that process. That is a common thing in small volume and other parenteral manufacturing.

The situation in CBER drug products is a little bit different because of the two-part sterility test. One is the requirement to do a sterility test on the final product. But, again, if there is a discrete bulk, that would have to undergo a sterility test, as well. That is something that is required under the regulations.

Q. For fermentations that are long, 300 plus hours, complicated and produce products with no anti-microbial activity, a foreign growth bacterial contamination level of 10 to 15% is difficult to impossible to maintain. Can you comment on this level of foreign growth and your recommendations?

Based on the question this was classical fermentation? However for biotech that would certainly not be the case.

It sounds like that was addressed by the previous discussions. I don't know that it comes down to so much an absolute percentage as it does one of economic issues and one of ultimate product quality. If you can demonstrate that you've got the product quality, albeit, with contaminating foreign organisms, I don't think it would be that much of an issue.

Q. Was the combining of chromatography fractions to meet a specific percent of purity discussed in regards to blending, and if so, what was the outcome of the discussion? It is a blending question, that is correct, but in this particular case, instead of talking about tailings or yields out of our normal API chemical processes, this happened to involve chromatography.

My understanding is for blending of batches you typically need to be certain that all the batches that you're going to blend will all meet the quality criteria that are appropriate for that material. And then you're allowed to blend them. You can't, if you will, blend away a certain level of impurity by averaging. With pooling of chromatography fractions though, the fractions aren't equal to begin with; they're not supposed to be equal. They are different as they are different cuts of the material as it comes off of the column, and the fractions that meet the criteria are allowed to be pooled but they would all have to be tested.

The central issue is reproducibly meeting prospectively defined cutting criteria to fully meet the purpose of that particular step where it's a polishing step at the end or a capture step at the beginning or things like this. Often in development, we'll take fractions, characterize the process and never take fractions again, but do in-line cutting based on OD or on other criteria, and the central issue here is setting prospectively defined cutting criteria that allow you to reproducibly meet the purpose of that step and then to continue to do that over and over and over in a consistently monitored setting. Again, sometimes you take fractions, sometimes you don't. Sometimes you cut by OD based on concentrations, sometimes there's a different co-eluting chromaphor. That is really the essence of reproducibly controlled chromatography.

I t is important to establish the relationship between the OD profile and whatever else you're actually going to be measuring during processing and product quality. That is usually figured out in development, and if not, then you usually end up collecting a bunch of fractions in manufacturing and trying to figure out how to pool them. If you've been able to establish these relationships, then it's usually much easier to use OD or some very simple surrogate to give you a product that will consistently meet quality attributes.

Q. We currently manufacture a non-sterile bulk active biological product derived from the fermentation of a non-recombinant microorganism for the European markets. If we sought registration for the U.S. market, would FDA inspect under Q7A or 211 CFR? It goes on to say that our UK partner's license holders formulate and finish the product.

You certainly would be inspected and reviewed according to the principles of the 211, and Q7Aprovides additional guidance. Part of the issue would be - is the product that is intended to be marketed in the U.S. going to be a licensed biological product or something that's regulated by the Center for Drugs? The other consideration for a licensed biological is have we licensed the product from start to finish?

Q. Assuming quality systems are operational, please comment on the fate of product when PQ requires actual API processing. Can it be sold provided successful validation follows and specs are met? Examples would be chromatography and those types of steps.

The real question is can it be sold? And the answer is yes. Changes in the process are routinely handled as supplements to applications and you should look at the biologics regulations, CFR21 601.12. So if your PQ that required the API to be processed, you have successfully validated and you have a number of lots that have been manufactured as part of the conformance to your

protocol, then yes, there isn't any reason that those batches couldn't be sold after approval of the supplement.

Q. During the purification process of some recombinant proteins, affinity chromatography techniques with monoclonal antibodies are used. It's well known that leakage of antibodies frequently expected that would contaminate the API. How can this possible contamination with another biologically active entity be considered under control in order to validate the process? Is this procedure regarded by the Q7A as an appropriate procedure since it incorporates contaminants into the API production process?

I wouldn't consider this to be inappropriate under Q7A. It's certainly a process contaminant, but it would be expected and, as part of your monitoring program, you would evaluate the API for the monoclonal antibody that potentially could be coming off your affinity column. Moreover, as part of the column cycle, you should evaluate the lifespan of the column. That is, you should be periodically monitoring and know the lifespan of the column. You would be monitoring its use, and therefore, you will minimize the potential for what would be viewed as cross-contamination with the monoclonal antibody coming off the column.

I agree with that completely, and I would add that typically, phase III studies sort of define the level of antibody contaminant that is tolerable because these studies showed that the product was safe and effective. So as long as you don't exceed these levels in the marketed material, that's typical an acceptable level of contaminant, then the trick is to make sure that the process does not exceed these levels. It could be validated as Jay mentioned always not to exceed those levels throughout the intended life of the column.

Column lifespan is something that would be looked at on inspection. So if you have got a number of different columns in addition to an affinity column that is something that would be key for inspection because we often find it is lacking in the validation or prospective validation of the facilities.

Q. Biotech API (manufacturing, fermentation, primary recovery, and purification) where closed unit operations are used could be manufactured in facilities with lower environmental classifications than many of the facilities currently found in the biotech industry. Many biotech API facilities with closed unit operations have been built to ensure drug product environmental standards. Comments?

Well it's an interesting thesis. The problem with systems that are described as being closed (assuming that they really are closed - meaning gas-tight) is not what happens to the product or the API when the systems are closed, it is what happens when you have to either put the product or API into the system or take it out at the end. When this happens the system, by definition, can no longer be considered to be "closed" and it is in fact "open". There are a variety of approaches that are possible to deal with this that include engineering controls, environmental controls, procedural controls. However there is no single right answer and whatever the solution it has to protect the process and product. I have to add however that it is difficult to say more in the absence of details about the individual facility and process.

Q. For APIs that are small molecules, as long as your reactor is closed and what is outside the reactor does not really matter, what you really care about is what the API sees (if you pretend you are the API). With biological processes, it tends to be a little tighter specification, is that what you're getting at?

Well conceivably: for example, in the example that you described, does "closed" mean the lid is on the entrance to the tank or does it mean the lid is in place and sealed so it's gas-tight?

No, we are talking about contained systems, totally contained where the API, the intermediate or even the raw materials or API starting materials are not exposed to the environment.

It is the same for biotech, however most contained biotech procedures that I have seen are typically done in a Class 100,000 environment and as you know there are a lot of things that are not controlled in this Class of environment. For example the operators will typically wear some sort of a uniform but there is no attempt to cover all body surfaces. So I would agree that there are probably some similarities between biotech and small chemical entities.

An example is where we needed to add a tank to do a refolding step and the tank was going to be located in a room adjacent to the facility that wasn't in a classified area. Since the material would be pumped into the tank, where the refolding took place, and then pumped back out into the facility, would you really need to have the strict environmental classification for that room? The question is what happens if you have to open up the system?

A typical problem in purification is column chromatography where people argue that the column is certainly not a closed system, but that is operated as a contained system. That is fine as long as you're talking about routine operation of the column, however you have to think about how you add and take the load off the column and also how you pack the column because typically the column has to be physically open when you're packing it. But it is not that these situations are impossible to deal with it is just that you may need other kinds of controls whenever a part of the system has to be opened.

I would like to clarify that under no circumstances would a guidance document that is not legally binding supersede a regulation and especially an established regulation that is legally binding. If that were the case with Q7A, FDA would have never signed off on this document. We were very conscious that Q7A, particularly the section on APIs produced by biotech fermentation, should not be in conflict with the biological regulations.

Q. In the case of mammalian cell culture where inherent viruses must be removed during purification, to what extent does the equipment suites, etc. need to be segregated?

It's important when you plan this kind of a facility to think about how you are going to segregate the equipment and the HVAC systems such that you do not get forward flow of any potential contaminants as a result. Many of the facilities that do this work, in fact, are designed with multiple separate HVAC systems to provide this level of insurance.

Q. Is systemic autoclaving part of routing materials into a Class 100,000 facility?

Well it can be, especially whenever autoclaving is required to provide sterilized small equipment. It certainly can be part of it, but it's typically not imposed just so you can operate a Class 100,000 facility, it is imposed because that is what the particular equipment or material requires.

Q. Can the product of a classical microbial fermentation be classified as a starting material in the preparation of an API? It kind of gets to both the small molecule as well as fermentation.

Yes.

Q. The integrity test on the final sterilizing filter for parental products is required to be implemented in situ. However, it is hard to do because they're a big facility consisting of many cartridges. Is an off line test instead of an in situ test acceptable?

Q7A does not address sterile APIs.

Once the API has been sterilized, then all the aseptic manipulation downstream would be covered under drug product GMPs.

Q. Who regulates classical fermentation? Is it CBER or CDER?

Sometimes that's hard to say because many times, we have what's often called a shared responsibility for regulating such products in which case it's possible that both CBER and CDER may regulate a particular type of product of this nature, but one of the centers will take the lead in any regulation or enforcement issues. CBER has taken the lead, and of course, they're probably looking at the biologics regulations, the nature of biologics and the need to have tighter controls, more stringent controls because of the nature of the process. You're dealing with cell culture; you're dealing with processes where contamination becomes an issue right from step one. These are some of the main differences between these types of processes and chemical synthesis. In chemical synthesis of APIs, generally contamination with microorganisms is not an issue in the early steps. It only becomes an issue generally when you're producing an API for sterile drug production. So again, we're trying to recognize the differences in the manufacturing processes.

Q. If a process is out of the scope of Q7A, i.e., master cell bank establishment, will those processes be or that process not be covered in FDA inspections?

There is a separate guidance on master cell banks.

Which is not Q7A.

Even when we did not have Q7A and when we didn't have other ICH guidance documents dealing with the establishment of the master cell bank, I remember when I was in the field many years ago, whenever I did an inspection of a fermentation process, I always thought of the inspection in the laboratory and actually observed when they take stock culture and they incubate that in Erlenmeyer flasks and they start the fermentation process in the laboratory. And I would ask questions about the establishment of the master cell bank. So, again, I don't think that's going to change the way FDA does inspections, it might change somewhat our focus that we may not focus so much those initial steps versus the later, but again, I think at the point where we initiate the inspection that's not going to change.

Section 19: APIs for Clinical Trials

Q. It is good to see in ICH guidelines a set of requirements for APIs that ought to be used in clinical trials. It is noted in Section 19.1 that process and test procedures should be flexible. Would the panel please comment on the interpretation of flexibility?

During development of the process, flexibility is needed because you are monitoring changes, adjusting parameters and making improvements to the process. This process evolution is

essential in deriving the final manufacturing process. Similarly, flexibility in analytical method development is also needed. However, you must fully document your changes along the way. A complete history is required for each batch.

Q. When will the Agency start inspections of clinical trial manufacturers using these guidelines?

The agency has the authority to inspect clinical trial manufacturers generally following the provisions of 211. Q7A provides further guidance specific to API's in addition to the general guidance found in the March 1991 Guideline on the Preparation of Investigational New Drug Products for Humans and Animals. This document provides guidance to the industry on how to apply 211 to the manufacture of drug products for clinical trial use. Section 19 provides additional clarification - it does not grant new inspectional authority.

Q. For multi-use or multi-product equipment used to make clinical trial materials, would you expect the analytical methods used to verify removal of the previous API to be fully validated, and would you expect reference standards to be fully characterized?

Because of the nature of the manufacturing process for APIs for clinical trials, cleaning validation per se is not expected. What is expected is cleaning verification. Verification can be done on a single batch where validation involves multiple batches to demonstrate consistency. Visual inspection is often suitable.

Reference standards (particularly impurities) of API used in early clinical studies may not be fully characterized depending on how fully developed your process is. Full characterization is expected later in development, once the process is more fully understood.

Q. Should there be second party review of batch records and lab data by QA for clinical materials?

Quality review is not specifically mandated in Section 19. What is specifically mandated is that the quality unit should approve or reject each batch of API for use in clinical trials. Use good common sense. If this is a really sophisticated process using some sort of really intricate chemistry, your normal quality people may not be qualified to do the review of those records, and you may be using someone in the research group to review the records. Q7A does not specify who has to review records for API used in clinicals. You have the flexibility to make that decision yourself, based upon your organization.

Q. Please clarify the wording under documentation (19.9), where it says, "Ensure information gained during development and manufacturing is documented and available." What is the difference between development and manufacturing? The way I would understand manufacturing is when I make the batches. What is development then? Making the clinical batches? What does the word development refer to here where it says the development must be documented? (Reference is slide 19-18.)

Section 19.9 refers to documentation for the development and manufacture of APIs for clinical trials. For the purposes of documentation, it is not important that we draw a distinction between development and manufacturing. What is important is that you to keep complete records and that these records be available.

Q. I think what we may be confusing here is, I might do development batches - process

development - and never intend to put those into a clinical trial. Then, after I've developed the process somewhat, I will manufacture batches to put into a clinical trial. So the concern is that, is ICH Q7A saying here that there will be some GMPs applied to that development work? Clearly, I think the answer's no.

You have the flexibility in development to make changes to the process, but suffice it to say that the information you obtain during development needs to be documented and available. Lab studies carried out to define critical process parameters also need to be fully documented. (Section 19.2)

Q. Early clinical batches may be produced in laboratory equipment as opposed to plant facilities because of limited batch size requirements. What are the expectations for environmental controls in laboratory facilities versus pilot plant? (Section 19.3)

Section 19.3 states that "procedures for the use of facilities should ensure the materials are handled in a manner that minimizes the risk of contamination and cross-contamination." There are no absolute requirements for room classification or other environmental controls. Regardless of whether the API is made in a laboratory, pilot plant or commercial manufacturing facility, appropriate controls should be in place to minimize the risk of contamination.

Q. Does the out of spec procedure as required by Q7A also require OOE or out of expectation investigations? If so, what is the definition of OOE?

First of all, there is no requirement in Q7A. It is guidance, not a regulation. There is no guidance in Q7a with respect to OOE.

Q. Can development batches produced prior to validation be used for validation of the drug product or commercially?

Assuming that the process is now validated and if there have been no changes between those development batches and what you validated, then that would make perfect sense. If you have changed the process, or if you have not yet validated the API process then, while Q7A doesn't prohibit it, you're putting a lot of drug product dollars on validating something that you have not yet shown to be consistent.

Q. APIs in clinical trial material - I fail to see the logic of employing a use test to release raw materials. If you use a material without some form of analysis and it turns out to be contaminated, the yield of your reaction may be what you expect, but the contaminant may still be present and go undetected by your analytical method for the API or Intermediate.

What was said in the presentation is that in some cases a use test may be most appropriate. You may also do traditional analytical testing, but often with a new process, a use test can be more meaningful. For example, you have a new raw material. The supplier sends you a Certificate of Analysis. You don't know what the appropriate limits are; you don't know whether it's going to work or not. You're using it; that's part of the development work, part of the information. Certainly nothing in Q7A would ever prohibit a person from doing whatever analytical work they thought was appropriate. (Section 19.4)

Q. Can you comment on why there are so few specifics in Section 19 and it's so general in nature?

Section 19.1 states, "the controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development." This statement recognized that during development a synthetic process is often not finalized and the dose form is certainly still under development. With this broad backdrop, in order to adequately cover GMP issues, the EWG provided very general guidelines so that they could be applied across a poorly defined development timeframe for an API. Our attempt here was to identify the exceptions. If you look at the opening paragraph Section 19, we basically say that. We did not try to make it an all-inclusive chapter; we tried to explain where flexibility or where certain sections were not applicable. We were not writing a "how to" document. Good judgment had to apply.

Q. Assume a 13-step process, in which step 8 is registered as the point where API starting material is introduced. Between steps 8 and 12, there are materials, including critical Intermediates, used. If the Intermediates are obtained from suppliers or manufacturers known not to have GMP facilities, applying Q7A's sliding scale of GMP-ness, will this be interpreted as non-compliant or contrary to the spirit of Q7A?

Yes, Q7A would apply to any step after you have applied the API starting material.

Q. If you take the same scenario from the previous question back into development, talk a little bit about how Q7A GMP guidance would be applied there.

Exactly the same way. If a contract manufacture is used during development, then it is the responsibility of the contractor who has chosen that contract manufacturer, to ensure that the contract manufacturer either already is in compliance with cGMPs or, between the two of them, they agree how that will be reached.

Q. Do all lots of APIs used in clinical trials need to be put in a stability study?

Typically, the expectations will change as you are going through the developmental phases. In the early phases, the API that you're making for use in the trials, you're also using to start establishing the stability. By the time you get into Phase II and Phase III, where you may be making a sizeable number of lots, if your process remains essentially unchanged, then having stability on a representative lot may be sufficient.

Q. What level of equipment qualification is recommended for clinical APIs?

The qualification concepts would apply, but maybe the magnitude of that documentation would be less than you would see on a commercial scale. But, the concepts would apply because you want to make sure that the equipment is properly installed and that it's operating correctly, according to the manufacturer's specifications.

Q. What are the GMP expectations for a development facility or an API supplier who manufactures a lot of API in that facility to be used for an exhibit batch for an ANDA submission? Would the concepts for API clinical trials be used here?

The GMP expectations for an exhibit batch for an ANDA submission are likely to be the same those of the commercially manufactured API. By the time you are filing the NDA, you would have a better idea of what your critical process parameters were, for example, than you would in the early phases of development. Again, think of that increasing scale, and by the time are ready to

start putting your NDA together, you're starting Phase III, and so you should have more data than early on.

Q. Earlier, it was stated that QA approval was not required for manufacturing procedures for clinical trial material. What is the justification for this difference between commercial and clinical materials? And, at what point in the development process is it expected that master procedures be generated? Once they exist, should an independent QA unit approve them?

Just to clarify the question, is the person talking about QA approval of completed records or QA approval of the instructions, because it really is two different things? QA always approves the release of materials, and that would be review of completed records.

Q. The question was related to the instructions, the manufacturing instructions.

Section 19.9 states, "A system should be in place to ensure that information gained during the development and manufacture of APIs for use in clinical trials is documented and available." Often, the very first clinical batches are being done in a laboratory and being recorded in a lab notebook, as opposed to having manufacturing instructions written out where you fill in the blanks. Frequently, your PhD chemists are running the process on a lab scale, at this point, and they are recording - hopefully, in a lot of detail - what they're doing and what they're observing.

What we were trying to do here was, again, to recognize the real world of development. Section 19.2 states, "a quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials." It is pretty clear that you need to have a separate quality unit for the approval or rejection of each batch of API for use in clinical trials. But, it goes on to say that some of the testing functions commonly performed by the Quality unit under the rest of this document, could be done in the clinical API area by other functions. In other words, it's very common for the R&D function in a firm to be doing the testing and releasing, or review and releasing, use testing and releasing of raw materials that they're buying to use to make the synthetic material. And, it recognized that. It wasn't going to be a violation, and it shouldn't be a violation if that were happening.

Q. For clinical APIs, should vendor test results on the Certificate of Analysis be confirmed by in house testing? (Section 19.4)

Regarding raw material testing, Section 19.4 states "Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice." In early phases of development there may be minimal testing in addition to identity. As the process becomes better defined during development, it is typical to identify critical raw material factors and test for them.

Q. In a commercial process, can a non-conforming Intermediate be used if lab use tests show the drug substance is within specifications? Sometimes, even in production, you set the specs for Intermediates. Sometimes the Intermediate batch did not meet the specs for Intermediates. But then you do another few tests, and the drug substance derived from that batch looks good. It passes all the specifications for the drug substance. Can you consider that compliant to a GMP or is it not?

Under GMPs, deviations can be justified and things can go ahead. There may be filing issues, if you're outside of a filing or a registration. But, in terms of GMPs, there's nothing inherently wrong.

Q. In Section 19.6 does the applicant need three different batches of the API to make their demonstration lots?

No, generally you don't need three batches because in many cases you're not going to be producing three batches.

Q. Q7A is the only ICH guidance that provides input on development of ICH for registration. What was the thinking of the EWG that led to inclusion of Section 19?

As clearly indicated in the opening paragraph in section 19.1, the purpose of this section is convey that not all controls in the other guidance sections are appropriate for the manufacture of a new API for investigational use during its development.

Q. Section 19 doesn't seem to address the need for master production instructions, Section 6.5. These don't make much sense for processes that are admittedly carried out only once and can be documented in lab notebooks.

That's the reason it is not mentioned in section 19. It's recognized that you are developing the process, you can keep your records or your production instructions in various ways including written, or handwritten in a laboratory notebook. This needs to be a flexible situation.

Q. How does one determine which parameters, intermediates, etc., are critical in early phase processes where not much is known about the process?

Because a company is still developing an API process during early clinical phases, it is not expected that critical parameters and intermediates be defined.

Q. Does one need to do ID tests on all non-hazardous raw materials for early phase production for solvents, reagents and processing aids?

As stated in 19.4 it is a normal expectation that one do an ID test on all non-hazardous raw materials. An alternate approach, e.g. use test, may be acceptable.
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Q. Clearly while development is underway and early phase clinical batches are being prepared, there is little experience for setting a pre-approval of specifications for intermediate starting materials and process parameters. This can lead to an unreasonable number of OOS investigations especially for the first batch. During this stage, would it be instead acceptable to the regulatory authority to gather information that can be used to assist future specification setting rather than require a hard pass/fail quantification of the materials used?

That's typically exactly what's done in the first batches. You are gathering the data to set the specifications that you will be testing against later on. (See sections 19.1 and 19.2)

Q. I asked that question because within our organization there's a lot of debate about when they can actually transfer the method and when, especially for stability studies, and the stability studies for the clinical materials not being conducted per the stability

program, within the stability database. One of the defenses to that was saying that the QC group unit wouldn't be conducting that method until it was validated and appropriately transferred over to QC, so it's residing within the analytical group.

That could be a requirement within your own company, but that is not so stated in Q7A.

Q. By which clinical phase should API methods be validated? And two, would you recommend the same guidance for drug product method validation for clinical phase?

Q7A does not specify when validation of methods is expected, i.e. during which clinical phase. But section 19.8 states that methods used should be scientifically sound. Your question on the drug product is outside the scope of Q7A.

Q. Following the logic of cGMP applying to APIs and drug products including drugs and clinical phase, one would have to apply and comply with sections of CFR 211 regarding laboratory controls. CFR 211 specifies analytical procedures requiring to be validated. Isn't Q7A Section 19.8 in conflict with CFR 211?

No. It's not in conflict. While Q7A applies only to APIs, CFR 211.165 deals with drug products. .

Q. Do clinical trial APIs require expiry date and retest date? What if it's not known or on concurrent stability?

Clinical trial APIs do not require expiry or retest dates. You should refer to Section 19.8. Expiry and retest dating, as defined in Section 11.6, applies to existing APIs used in clinical trials. So if you have a currently marketed one that someone's using in a new dosage form, than, yes, obviously your API at that point is an established one, it will have it. For new APIs, Section 11.6 does not normally apply to early stages of clinical trials.

Q. Section 19, For Phase I contract manufacturers, are OOS investigations required? At this stage, all methods are non-validated so how can you have specifications?

Section 19.2 does not require investigations (e.g. OOS investigations), but says that process and quality problems be evaluated. In fact, you probably would be further down the development process before you got definitive enough specifications for an OOS investigation to have significant value.

Q. Is it required to use qualified suppliers audited by the company in clinical trial batches? All suppliers including solvents, etc., or just critical materials?

No, it's not required. What is meant by "appropriate equipment qualification" for clinical trials in section 19.6? It is not the intent of Q7A to imply that there is a different type of equipment qualification during clinical manufacturing. Section 19.6 says that equipment qualification should be done "where appropriate."

Q. What is the FDA expectation for process validation of clinical trial materials after an NDA is approved? Example, for a product line extension using pilot batches of APIs?

Once the application has been approved, even if the API is still produced in a pilot scale facility or a small-scale facility, then process validation is an expectation (19.6).

Q. For early clinical material, if reprocessing occurs during a batch, but this reprocessing step is not yet validated, can the batch be released if it is found, during an investigation, that there is not product impact?

Yes, the batch should be releasable if in agreement with your filing. Validation of the process for clinical trial APIs is not expected. So, if we don't expect it for the original process, we would not expect it for reprocessing either. (19.6)

Q. Is it an expectation for analytical methods used to test APIs in clinical trials to be validated?

Section 19.8 states that analytical methods performed to evaluate API for clinical trials may not need to be validated, they should be scientifically sound.

Q. For clinical trial APIs, does manufacturer of material versus supplier have to be identified?

It is often difficult to get the supplier to identify the manufacturer. The intention of the EWG was not to require this level of detail early in the drug development process. Section 19.4 on control of raw materials does not specifically mention having the manufacturer identified.

Q. Please discuss differences between commercial API and clinical trials on approval by the quality unit, at what stage of the product?

Slides 19-6 and 19-7 provide comparison of quality unit functions for the commercial and clinical APIs.

Q. Please discuss the expectations to have specifications in place for clinical trials, at what stage?

Section 19.1 indicates that the controls used in the manufacture of APIs for clinical trials should be consistent with the stage of development. Process and test procedures should be flexible to provide for changes as knowledge of the process increases. During development, sound judgment and good scientific decision-making must play a role.

Q. Please discuss the expectations for equipment qualification for clinical APIs, at what stage of production?

The degree of documentation that you would need in a development facility may not have to be as comprehensive, but you should at least have it installed and operating correctly. Section 19.3 states an expectation that equipment is calibrated, clean, and suitable for its intended use. Whether or not you need a comprehensive package covering that, I don't think you need to make a lot of work, but you should have checked it.

Q. Please discuss the expectations for records of deviation for clinical APIs.

Section 19.2 expects that process and quality problems be evaluated for clinical API's. In addition, Section 19.5 states that productions of the clinical APIs should be documented. It is up to the company procedures as to how this is documented.

Q. How do you assure that the material that will ultimately be used in product for human use is safe considering many exemptions such as discussed about validation?

Section 19.1 indicates once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API. Q7A EWG did not believe that any of the exemptions would make a product unsafe.

Q. Does Section 19 mean, in the manufacturing for APIs for clinical trials, it is not required to conduct formal DQ, IQ, OQ, PQ for equipment?

Sections 19.3 states that during all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use. Your company procedures should direct the particular approach that is taken.

Q. When commercial production in a pilot plant occurs, do you expect this to happen in dedicated equipment apart from equipment used for development?

Q7A does not expect dedicated equipment, except for those materials included in Section 4.4 (e.g., sensitizing materials, etc.) Since you're in the pilot plant, you're probably using equipment that's also used for development or has been and will be. You've got to make sure it's clean, you're not creating cross contamination, and that you've established acceptable levels for any kind of carry over if you were going to have it.

Q. Please elaborate on the need for equipment cleaning, verification versus cleaning validation for clinical trial products.

Q7A EWG members believed that you would want to test, in an appropriate way, to show that the residues from your previous material are removed to an acceptable level based upon some tox or pharmacological acceptable level, and that's a scientific-based decision that you should make. Section 19.3 expects that you have procedures to ensure that equipment is clean. .

Q. Is Section 19 applicable for generic in process development phase for ANDAs?

Chapter 19 would probably apply only if there is a new twist on an API that is beyond what the innovator originally had.

Q. Phase I clinical manufacturing. In a multi-step synthesis, after the quality unit releases our equipment before the start of the project, what is required/expected for equipment cleaning verification for the next step? Is the quality unit required to release the equipment or can the R&D team perform the project input and release the equipment?

In this case cleaning verification may only require visual inspection, versus analytical testing. There is also no specific expectation that the quality unit release the cleaned equipment.

Q. Slide 19.2 states that R&D frequently performs testing. If so, is the lab subject to inspection and expected to be GMP compliant. Should QC still be responsible for review and approval of data and the resulting C of A or just QA disposition based on R&D?

During an FDA audit, a company can reasonably expect that any labs used to generate test data for clinical materials could be inspected. With respect to the second point, the quality unit (as defined in Q7A) is still responsible for review and approval of the clinical lot, which may include review of data and the resulting C of A.

Q. Would it be sufficient to assure equipment is clean and validation not executed for the cleaning procedure when clinical trial lots are manufactured in facilities used for commercial API production where other cleaning procedures were validated?

For clinical use APIs, you may not have the number of batches or the number of campaigns to show the consistency of that cleaning. However, it would be expected that you have each of the other aspects of cleaning validation for the new compound. While not asking for validation for the clinical compound, Q7A would expect a thorough verification each time you clean to supplement your commercial product cleaning validation. (Sections 5.2 & 19.3)

Q. This is follow-up on cleaning for clinical trials. For phase I facilities, what is considered satisfactory equipment verification? How much validation is required for swabbing? What is the GMP expectation for cleaning residue limit, i.e., is .05% of the batch size considered to be adequate?

Q7A does not include any guidance regarding limits for residual level following cleaning. Early in Development you will be using verification, not validation, because you don't have the multiple campaigns to show that your cleaning process is consistent. Nonetheless, it's still important that you sample appropriately and test to show that your equipment has been thoroughly cleaned.

Q. If you have a validated process using commercial scale equipment, but have material manufactured in small scale or pilot scale equipment following the same process, can you use this material for commercial drug product?

If the only difference between what you made in the pilot or small scale and the commercial validated process is the scale, your material meets all your specifications, and is consistent with your filing, then based on a review by your quality unit and their decision, that material could be released for sale.

Q. For equipment infrequently used to manufacture materials for research, toxicity studies, or Phase I clinical trials materials, how detailed should the cleaning validation be or is visual examination sufficient when toxicity is often unknown?

Section 19.3 says "During all phases of clinical development, . . . procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use." APIs for clinical trials are usually produced in laboratory glassware and small-scale equipment that is easily disassembled, cleaned and inspected. In such situations, visual examination may suffice. Cleaning validation is really not an expectation at that level but, obviously, cleaning verification would be appropriate.