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Toxicology Studies- GMP *or* non-GMP?

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"If you don't have time to do it right, when will you have time to do it over?" -John Wooden

This white paper provides an overview of your GLP test article characterization requirements for an IND. A cost vs. risk analysis is also provided for use of non-GMP or GMP drug substance and/or formulated drug product (test article) in your GLP studies. Three different batch options are compared vs. cost and risk. Key words are CFR 58.105, test article, GLP, non-GMP, GMP, stability, impurity tracking, drug substance, drug product, and vendor IND-deliverables for drug substance and/or drug product used in your GLP and proposed clinical studies.

GLP Test Article Regulations

The primary regulation governing test articles in GLP studies comes from 21 CFR Part 58.105 "Test and Control Article Characterization". The central concepts from this section are summarized below.

i) *The identity, strength, purity, and composition or other characteristics (of the test article) shall be documented.*
ii) *Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented.*
iii) *The stability of each test article shall be determined either before study initiation and upon completion, or by a stability study covering the study period*

Item (i) "Identity" refers to a chemical "proof of structure" / formula using techniques such as NMR, Mass Spectral analysis, Elemental Analysis. A physical identity (polymorphism) may also be relevant when dosing solids or suspensions. "Purity" refers to impurities that might be present which can be organic related substances "Impurities" per ICH Q3A/B, volatile organic impurities (solvents) per ICH Q3C, elemental (inorganic) impurities per ICH Q3 D[1], and potential genotoxic impurities (PGIs) introduced in the synthesis process per ICH Q7[2]. "Strength" refers to the weight-weight percent content of the active drug substance, usually by HPLC using a reference standard of assigned purity. The strength may be required to adjust for salt counter-ions, water, solvents, or other impurities. These attributes per (i) are then summarized in your IND in Module 3.2.S.3.1 "Characterization" ("identity"), 3.2.S.3.2 "Impurities" ("Purity"), as well as 3.2.S.4.4 "Batch Analysis" (comparing the GLP batch to clinical). The report deliverables from your CDMO to populate the IND sections would be a Characterization Report, a Certificate of Analysis (COA) for the test article, and all supporting source data. Per the GLPs the COA should also have an assigned expiry or retest date and should confirm a GLP testing quality- more on this later.

Item (ii) addresses how the drug substance used in the test article is synthesized and how the test article is formulated (made) for dosing in animals. While no requirement besides "documentation" are indicated, it should be understood one needs to compare the synthesis route/process used to make the drug substance used in GLP studies to that used to make the clinical GMP drug substance, i.e., justifying any process changes used for the clinical batch manufacture vs. the process used in the toxicology batch that might impact safety. The IND deliverables to support the drug substance requirement for your test article per (ii) are then summarized in Module 3.2.S.2.6 "Process Development" (to address route/process changes in drug substance used in GLP vs. clinical studies) as well as 3.2.S.4.4 "Batch Analysis" (to compare analytically the drug substance used in the GLP vs. clinical study). The deliverables from your CDMO to populate the IND sections to document the synthesis, raw materials, process would be a chemical development report.

Item (iii) addresses test article stability such that one must demonstrate there were no changes in purity between study start and end. This is a frequent gap found in virtual biotechs since in order to test at study end it assumes the appropriate analytical development and initial testing at study start to address (i) "identity, strength, and purity" have been properly completed and documented. Obviously if the initial characterization and testing have not been completed before study start then step (iii) is not possible since one can not "go back in time" to test article at beginning of study[3].

In summary, the GLPs governing the test article require one to compare/link key attributes of drug substance used in the GLP and the proposed clinical studies by documenting in real time, the i) identity, strength, and purity, ii) the synthesis process and any changes that could affect safety in clinical batch, and iii) the stability of the drug substance used in the studies. While this addresses the "what" part, the GLPs are very clear that the "how" part be compliant to GLP standard, meaning the analytical testing and documentations must conform to a GLP or GMP standard.[5] It should also be noted that the importance of complying with CFR Part 58.105 becomes most critical for the chronic (pivotal) "longer-term" 2-species GLP studies where stability of the test article is most at risk.

Impurity Tracking and Control

Impurities must be documented for each batch used in pivotal GLP or clinical studies at study initiation and completion and these profiles, of same or different batches, must be compared to the clinical lots to ensure the clinical lots do not contain any "new" impurities. The limits allowed for any *new* impurities in the clinical trial materials, that were not present in the GLP batches, is addressed by ICH Q3A (Drug Substance) and ICHQ3B (Drug Product) to be no more than 0.15% in drug substance and 0.50% in drug product, assuming a maximum dose of ≤ 2g/day. Any impurities at or above these limits in your GMP clinical batches of drug substance and drug product must be justified. Impurities reported per ICH Q3A/B may be identified or may be tracked by relative retention times (RRTs) if unidentified.

In summary, since impurities in drug substance can change between lots due to differences in the manufacture, process impurities, degradants, and in drug product by degradant growth, the selection of *which* lots of drug substance to use, *and* the level of manufacture control (non GMP vs. GMP) to use in the pivotal chronic toxicology studies vs. your planned clinical studies is critical.

Non-GMP vs. GMP Drug Substance and Drug Product

Before we present different batch matrix options for both drug substance and (formulated) drug product to be used in GLP studies, let us revisit the meaning of these terms.

- GMP quality is required for drug substance and drug product intended for human use in a commercial INDs.[4]
- Drug Substance test articles *manufactured* under non-GMP conditions may be used in a GLP study so long as the *testing* and documentation compliance level is either GLP[5] or GMP.
- If GMP-grade drug substance (or formulated drug product) is used it is always accepted by GLP study directors and CROs as complying with the GLPs.
- While a non-GMP manufactured drug substance batch may be formulated and used in a GLP study, it is understood that a second (GMP) drug substance batch for use in humans must be made.

The different matrix options and risk – benefit considerations of using either a non-GMP or GMP drug substance or formulated drug product as your test article in your GLP studies is presented below.

Option A: Use of non-GMP Drug Substance & non-GMP Drug Product in your GLP Studies

This is the fastest route to opening an IND and accordingly "most" sponsors end up on this path, whether planned or unplanned. The risk-benefit considerations for this approach are summarized below.

- Use of a non-GMP lot of drug substance to make your finished GLP dosage form drug product (test article) in GLP studies still requires you conform to the aforementioned GLPs Part 58.105 Sections i-iii, i.e., testing and documentation is done per GLPs.
- Use of a non-GMP lot of drug substance in GLP studies allows the sponsor to start GLP studies earlier but requires that a second GMP drug substance batch for the clinic be made at later date.
- Since a different lot of Drug Substance will be used in the Clinical study, the Sponsor must ensure that the proposed clinical drug substance and drug product batch contain no *new* impurities as previously defined under ICH Q3A/B.
- In this case it is understood the GLP lab performs the drug substance formulation into non-GMP drug product test article and demonstrates no change in purity or strength in the test article vs. input drug substance as required under Part 58.105, iii. If the GLP test article is made at a different site and shipped to the GLP lab then the burden is on the sponsor to manage the GLP documentation and testing requirements i-iii for the *formulated* mixture as this mixture is now your test article.
- This two batch approach is risky when drug substance or drug product impurities are difficult to control *or* unknown (not yet studied). In such cases the likelihood of a new impurity appearing above ICH Q3A/B limits in either drug substance and (formulated) drug product test article may be great requiring bridging toxicology studies.

Option B: Use of GMP Drug Substance & non-GMP Drug Product in your GLP Studies

Considerations for using the same lot of GMP drug substance in both toxicology and later to manufacture clinical supplies are as follows.

- This approach *requires* that the drug substance be manufactured under GMP conditions since only GMP drug substance can be used in human studies. As noted earlier, the GMP status will also meet the GLP test article requirements.
- Impurities are "automatically" controlled since "the same lot" is used thus risks of any "new" impurities being introduced in the production of a second GMP clinical batch through process changes, inability to reproduce initial process, is avoided.
- This approach requires a stable drug substance since the batch will need to stay stable for use in the entire GLP and clinical program.
- This approach requires that the process and analytical test method development have been completed to allow for a scalable GMP synthesis and analytical testing to meet GMPs. Depending on dose this batch size can range from 50 g to 15 kg to support both toxicology and clinical through Phase 2a.
- This approach is less risk and overall cost ("one" COA, "one" stability study") but requires more up-front investment in time and money (development) to be able to make and test at GMP standards.
- As in approach A, this strategy assumes the GLP lab is responsible for formulating the GMP drug substance on-site into the non-GMP drug product test article and thus conforming with GLPs. If the GLP test article is made at a different site and shipped to the GLP lab the burden is on the sponsor to manage and ensure GLP documentation and testing status for the drug product part.
- This approach is less risk and overall cost, i.e., one batch COA, stability study, but requires more up-front investment in time and money (development) to be able to make and test a drug substance at GMP standards.

The approach with the least risk and overall cost but requiring far more up front development is the use of clinical quality (GMP) formulated drug product in both your pivotal GLP as well as clinical studies. This approach is discussed below.

Option C: Use of "one" batch of GMP Drug Product in your GLP Studies

So far we have assumed the drug substance, whether non-GMP or GMP, is formulated into the test article and controlled at the GLP facility at time of use.[6] The lowest risk option is the case where finished GMP product suitable for human use is also used in the pivotal chronic toxicology studies, i.e, animals are dosed with the same formulation (IV, topical, oral drink, capsules, or tablets) to be used in the clinic. In this case cGMP

drug substance is formulated into a range of drug strengths under cGMP which are then used in BOTH the GLP and the clinical studies. For example a single GMP batch of capsules is made which supports both GLP and IND human studies. This approach is the lowest overall cost and least risk but requires more time and up-front spending. Additional considerations for this approach are summarized below.

- Since GMP drug product requires GMP Drug Substance, GLP Labs accept GMP drug product supplies as 'GLP compliant'.
- This is an excellent strategy for poorly-controlled / variable impurity profile Drug Substances such as peptides or small molecules with long syntheses subject to complex impurity profiles that may be hard to reproduce.
- Analytical demands for this approach are lower since you are dosing humans with the exact same lot(s) used in the pivotal 2-specie toxicology studies so even impurities you might not have tested for are qualified.
- The overall cost is the least from all approaches.
- Excellent approach when i) sufficient GMP Drug Substance is available, ii) clinical strengths are known before chronic toxicology studies conducted, and iii) stability drug product is documented for duration of proposed GLP + clinical studies.
- Less common for oral products where tablet and capsule dosing is challenging for some species such as rodents. More common for solution dosage forms such as injectables, topicals / ophthalmics, where one "bulk" sterile solution can be used in the GLP and in clinical.

Summary

The three matrix options presented for the use of non-GMP/GMP drug substance/drug product in your GLP studies and the associated IND risk-cost-time analysis is summarized in **Table 1**. Option A where one starts early using non-GMP research drug substance and formulated drug product in pivotal GLP studies can be considered the fastest track to an IND with the lowest initial spend but has the highest overall cost and risk due to its step-wise approach. At the other end of the spectrum is Option C, where GMP quality is used for both drug substance and product. This is the lowest overall cost and risk but the highest initial spend and time to open an IND. Option B, where GMP drug substance is used to formulate non-GMP supplies (test article) for the GLP studies and GMP drug product for the clinical supplies is the best balance of risk, cost, and timing to the IND.

Table 1: Cost-Benefit Analysis of Batch Strategies for your GLP Studies

Option	Drug Substance	Drug Product	Cost		Time	Risk
			Overall	Initial		
A	Non-GMP	Non-GMP	▲	▼	▼	▲
B	GMP	Non-GMP	▼	▲	▲	▼▼
C	GMP	GMP	▼▼	▲▲	▲▲	▼▼▼

Over 12 years managing some 50 NCEs for virtual biotechs I find at least half failed to properly manage this phase. In best of cases issues were recognized early enough to correct before the IND submission, in other cases these deficiencies are dealt with after a clinical hold. If you are planning or already doing your GLP studies please contact us for a free console on your development strategy. If you are doing things right it will cost you nothing. If you are not, we can manage this for you. In the end this investment will more than pay for itself. We have many references and case histories to support this position.

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[1] For Elemental Impurities, see TRIPHASE® white paper titled "ICH Q3D Elemental Impurities"

[2] For potential genotoxic impurities, see TRIPHASE® white paper titled "Addressing Genotoxic Impurities in Drug Development"

[3] Prior to all GLP studies I recommend storing a portion of the test article at -70 °C freezer. It is "accepted" this slows and/or stops all changes and degradation in the test article thus allowing testing after study completion to document starting profiles long after study completion.

[4] For resources covering quality, CMC, cGMPs, and required and documentation in IND Module 3 for Phase 1-2 studies, see:
Guidance for Industry- CGMP for Phase I Investigational Drugs
Guidance for Industry- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
Guidance for Industry Q & A- Content and Format of INDs for Phase 1 Studies of Drugs
Guidance for Industry- INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls Information

[5] A drug substance used in a test article if manufactured under non-GMP conditions must still be tested to a GLP (or GMP) compliance level and you must "document" per CFR 58.105, part ii the manufacturing process meaning a synthesis report from your GLP batch. Also note a common misnomer that something is "manufactured under GLP" or the material is "GLP". These statements can not be true since the GLPs do not address methods of test article manufacture. Only the GMPs do that.

[6] Another common gap found at virtual biotechs is the management of the formulation step of drug substance into the test article for animal dosing. For simplicity I have "assumed" the GLP lab will "formulate" for you. In reality the required data to formulate by the GLP lab or anyone else for that matter is rarely known. Common questions from GLP labs are, "what should I dissolve it in?" "What is it's maximum solubility? Is it stable in water? At pH ? How do we store it? For how long are solutions stable? Again your GLP CDMO will not have this information so it is imperative to properly plan for any GLP studies to ensure you are ready.