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FDA is Driving the Manufacture of Drug Products Outside the United States

March 1, 2018By David C. Gibbons & Dara Katcher Levy —

While likely not FDA's intent, the net effect of FDA's requirements surrounding importation of active pharmaceutical ingredients is driving manufacturing of investigational finished drug products outside the United States. In its most egregious implementation, FDA's current interpretation sets up a Catch-22 in which a batch of investigational API cannot be imported for manufacture of finished drug product without an IND, but an IND cannot be obtained without analyses and stability data on that drug product. As a result, investigational API and drug product, from a practical perspective, must be made entirely within or entirely outside the US. Because API manufacturing is largely done outside the U.S., FDA's requirements have the effect of encouraging sponsors to manufacture outside the U.S. to the detriment of pharmaceutical developers, U.S. contract manufacturers and patients.

An active pharmaceutical ingredient (API), or bulk drug substance, is "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body," but does not include intermediates used in the synthesis of the API. 21 C.F.R. § 207.1. Because API is intended to diagnose, cure, mitigate, treat, or prevent disease, or to affect the structure or function of the body according to this regulation, it meets the definition of a drug under the Federal Food, Drug, and Cosmetic Act (FD&C Act). See 21 U.S.C. § 321(p). Generally, API undergoes further manufacturing into a drug product, or finished dosage form, that contains the API and excipients (see, e.g., 21 C.F.R. § 210.3(b)(4) for a definition of drug product). Recent estimates from FDA indicate that approximately 80 percent of APIs used in the U.S. drug supply are manufactured in more than 150 countries. United States Government Accountability Office, *Drug Safety: FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices*, at 1 (Dec. 2016). Like all FDA-regulated products, API is subject to examination when it is imported or offered for import into the United States and must meet applicable statutory and regulatory requirements. FDA has the authority, under the FD&C Act, to refuse admission to any drug that "appears" to be misbranded or in violation of the requirements for new drugs, such as the need for an approved marketing application. 21 U.S.C § 381(a)(3). In general, the FD&C Act requires that any drug must have labeling that provides adequate directions for use or be subject to a regulatory exemption from this requirement. Id. § 352(f). API, because it is not yet a finished drug

product, is unavoidably misbranded within the meaning of the FD&C Act as its labeling cannot bear such adequate directions for use. Therefore, any API imported into the United States must be subject to a regulatory exemption from the labeling requirements, such as existence of an active IND, and comply with all regulatory exemption requirements.

To see this in operation, one can examine the impact of regulatory exemption requirements at certain points in the drug development cycle. Early in the drug development cycle, manufacturers may utilize a single lot of API to conduct preclinical testing, manufacture drug product for analytical and stability testing and for use in initial clinical trials. Certain preclinical testing, as well as the manufacture and testing of drug product must be completed prior to filing an investigational new drug application (IND) to initiate human testing of a drug. See 21 C.F.R. § 312.23(a)(7). Initial U.S. clinical trials, on the other hand, can only occur after an IND is opened and in effect. Before the IND is opened and in effect, the importing pharmaceutical company can bring the API into the country for laboratory research so long as it complies with an exemption for API not intended for clinical use. The importer must provide information on this intended use to FDA at the time of import.

A separate import shipment that complies with a different exemption must be made in order to lawfully manufacture clinical trial material from the API. Under this exemption, the API must be labeled with the statement "Caution: For manufacturing, processing, or repacking in the preparation of a new drug limited by Federal law to investigational use." In addition, the API must be used only in the manufacture of such new drug limited to investigational use as provided under the IND regulations. 21 C.F.R. § 201.122(b). The importer must provide information on this intended use to FDA at the time of import and, if the clinical trial is to be conducted under an IND, the IND number must be provided. The practical effect is that pharmaceutical firms who wish to import API from outside the U.S. but manufacture drug product in the U.S. must undertake at least two separate imports prior to initiation of clinical trials. Even then, however, there are more hurdles. Because imported API for clinical drug product can enter the U.S. no earlier than the day the IND becomes effective (no sooner than 30 days after submission of the IND), drug product for use in clinical trials can not be available for use on day 30, when the clinical trial would otherwise be able to begin enrolling subjects. Instead, the clinical trial cannot begin until that API is manufactured into drug product and subjected to sufficient testing for release. Thus, the use of imported API to manufacture clinical trial material in the United States will result in a delay to beginning the clinical trial—a delay imposed by FDA's overly rigid interpretation of its regulations. On the other hand, the manufacturer could produce clinical trial material outside the U.S. in time to import it into the U.S. and ship it to investigators on day 30, without delaying the start of clinical trials.

Once all necessary clinical and nonclinical studies have been completed to support an NDA, the manufacturer will want to begin producing finished drug product—the final dosage form in finished packaging "suitable for distribution to pharmacies, hospitals, or other sellers or dispensers of the drug product to patients or consumers" (21 C.F.R. § 207.1)—in anticipation of marketing the product upon FDA approval of the NDA. Because the finished drug product is not for investigational use, the API used in its manufacture cannot be imported under the previously described exemption. A separate

exemption covers API intended for use in the manufacture of a finished drug product that is subject to a pending NDA. See 21 C.F.R. § 201.122(c). FDA regulations state that API can be subject to this exemption if an NDA has been "submitted but not yet approved, disapproved, granted, or denied, the bulk drug is not exported, and the finished drug product is not further distributed after it is manufactured until after the new drug application . . . is approved." Id. Alternatively, manufacturers could produce commercial scale batches of finished drug product outside the U.S. and import them into the U.S. once the NDA is approved or utilize FDA's Pre-Launch Activities Importation Request to stage finished product in advance of approval.

FDA has significant concerns about API imports, as is reflected in its Import Alert 66-66, requiring detention without physical examination for APIs that appear to be misbranded because they do not meet one of the exemptions provided in the regulations. FDA, Import Alert 66-66(Dec. 1, 2017). Import Alerts are issued when FDA identifies a potentially recurring problem with imported articles. A drug placed on import alert shifts the burden to the importer to prove that its drug does not violate the FD&C Act. FDA issued the Import Alert for APIs because of concerns that importers obtained entry of their APIs by supplying legitimate NDA or IND numbers when the number did not cover the source of the API or when the importer had no right of reference to the NDA or IND number.

In essence, FDA's current interpretation of its regulations may delay the importation of API at critical times during the development cycle and thus result in an overall delay to drug development. It may also present substantially increased costs involved with manufacturing the same finished drug product twice, but for different uses. Manufacturing drug product outside the U.S. may be a viable strategy for eliminating certain delays imposed by regulatory requirements. Therefore, the unintended consequence of FDA regulations covering the importation of APIs may be to drive the manufacturing of drug product outside the United States.

FDA should interpret and enforce the law and regulations to allow for the intended use of imported API to "evolve" through the drug development cycle.

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