Commentary
Barbara Scott


Barbara Scott

The generic drug market has become increasingly competitive. The need for cheaper drugs in the American marketplace has driven the abbreviated new drug application (ANDA) submissions to staggering numbers, which in turn has lead to increasingly longer US Food and Drug Administration review and approval times. Section 3.2.S.2 of the Common Technical Document (CTD) is reviewed as part of the ANDA application and is intended to convey to the reviewer and field investigators all manufacturing process information, critical controls, and risk management related to the active pharmaceutical ingredient (API). In many instances, the ANDA applicant references a drug master file (DMF) that contains the API information. It is important to identify a high-quality API supplier, especially with regard to understanding the impact of starting material designation on the ANDA review time.

Presently, API starting material designation continues to be a troublesome issue. Historically, API suppliers (DMF holders) have relied on the 1987 Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacturers of Drug Substances, International Conference on Harmonisation (ICH) Q7A (good manufacturing practice starting material), and recommendations from 2004 and 2006 working groups for help in defining a starting material for the API manufacturing process (1). The draft ICH Q11: Development and Manufacture of Drug Substances provides recommendations with respect to API process controls and starting material considerations (2). The API supplier’s decision of how far back in the synthesis to go before designating the regulatory starting material is impacted by the cost of current good manufacturing practice (CGMP) compliance, publishing proprietary information, and the necessity of reporting any future changes to the process that might involve outsourcing. FDA uses a risk-based approach to determine where CGMPs should commence and defines the regulatory starting material accordingly (3). Increasingly, DMF holders define a key intermediate as the starting material and outsource the synthesis without due consideration to quality. In some cases, multiple suppliers of the outsourced starting material are provided, each with either a DMF or technical dossier requiring review. Inspections of

ABOUT THE AUTHOR
Barbara Scott is a chemistry and manufacturing reviewer (CMC) at the Office of Generic Drugs within the Office of Pharmaceutical Science, under the US Food and Drug Administration’s Center for Drug Evaluation and Research. All correspondence on this commentary should be addressed to Barbara Scott at Barbara.Scott@fda.hhs.gov.
these facilities or problems with the synthetic route for outsourced materials may significantly delay the ANDA review.

Furthermore, FDA does not formally approve DMFs. Technically only recommendations are made to the DMF holder. In the meantime, the ANDA applicant is notified that the DMF is currently under review. It follows that the lack of a timely response by the DMF holder or poor quality of the response increases the overall ANDA review time. Therefore, it is strongly recommended that the ANDA applicant make a judicious choice of the API supplier. High quality suppliers should be identified prior to commencing drug product development. Critical material attributes of the API need to be considered as part of the overall quality target product profile (QTPP) of the intended drug product.

The Office of Generic Drugs’ current thinking on the appropriate designation of API starting materials incorporate the recommendations described in detail in the following sections.

CHEMICAL SYNTHESIS

The starting material should be removed from the finished product by multiple synthetic steps with intermediates isolated and in-process controls specified. Salt interconversions, saponifications, esterifications, recrystallization steps, resolution of racemates, and in-situ reactions with no intermediate isolated do not count as synthetic steps. In Case I (Figure 1), the starting material selection is considered inappropriate because the synthesis is only one step removed from the finished product (salt interconversion is not a valid synthetic step). Furthermore, all of the key structural elements found in the API are already included in the proposed starting material.

For chiral molecules, how each stereocenter is introduced should be discussed in detail; proof of characterization using chiral methodologies should be provided; and appropriate in-process controls should be highlighted. In Case II (Figure 2), the starting material is inappropriate because all chiral centers A, B, and C are set in the proposed starting material with no indication of how they were put in place or resolved.

In Case III (Figure 3), the racemate is purchased, resolved, and purified. There are no reaction steps or isolated intermediates, and therefore, the racemate is not an acceptable starting material.

This also applies even in cases where the racemate is a drug substance in and of itself. For example, consider the case of the API dexmethylphenidate. The racemate, methylphenidate, which is also an API, cannot be declared a starting material, as there is only a resolution step involved in transforming it to dexmethylphenidate.

Molecules that contain potential genotoxic (4, 5) structural elements in intermediates anywhere along the synthetic route require extra care in managing impurity profiles and the corresponding risk associated with them. Designating a starting material too late in a synthetic route with no information regarding impurity carryover and purification methods is not acceptable. In Case IV (Figure 4), the DMF holder proposes the bis-anilino moiety as the starting material. A cyclization step and further purification leads to the finished product. Aryl aniline functionalities are known carcinogens and are quite frequently derived from aryl nitro groups, a well-known genotoxic functional group (4). From a risk-based point of view, controls of the impurities at the nitration step are critical in this manufacturing scheme. The proposed bis-anilino starting material gives no indication on how

---

**Figure 1:** Case I—unacceptable.

**Figure 2:** Case II—unacceptable.
the nitration step was controlled or how subsequent impurities were removed. Furthermore, the proposed starting material is only one step from the finished product with no intermediate isolated in between.

If a molecule is “well defined” in the literature, then the literature should be cited along with appropriate detailed comparative structural analysis from the DMF holder against the literature values (e.g., published papers and patents). It is recommended that data from multiple lots using the commercial process to demonstrate sameness be provided for review.

Commercially available starting materials need not be justified. In this context and per the draft ICH Q11, commercially available means “a chemical that is sold as a commodity in a pre-existing, non-pharmaceutical market” (2). In contrast, chemicals for which a contract manufacturer custom synthesizes a predefined amount of material specifically for the DMF holder are not considered “commercially available.” Primary DMF holders submitting syntheses defining non-commercially available starting materials will be asked a number of questions including the following:

The starting material for the manufacturing process does not comply with the Agency’s current definition of an appropriate regulatory starting material for an active pharmaceutical ingredient. Please declare appropriate starting material(s) from an earlier point in the process and provide complete information on the entire process in this Drug Master File. Alternatively you can provide the information shown below for the designated supplier:

A) The detailed synthetic route (including in-process controls, isolated intermediates, reagents/solvents, etc.) for the outsourced starting material OR a DMF # from the outsourced vendor should be provided.

NOTE: If a secondary DMF is referenced within a primary DMF, the ANDA review time will be impacted.

B) The full name and address of the manufacturing site, related phone/FAX, contact person, and email address should be provided.

NOTE: It is possible that the Office of Compliance will inspect the site. If issues are found then neither DMF will be in good standing with the FDA.

C) Extensive starting material specification requirements especially with regard to impurity carryover for both residual solvents and related compounds may be requested.

D) Updated Certificate of Analysis (COA) from the vendor and in-house COA for the starting material will be requested.

E) A commitment to notify the FDA if the starting material vendor changes or the process is modified in any way, and to provide again all the relevant information for any new vendor.

FERMENTATION-DERIVED STARTING MATERIALS

For those manufacturers using starting materials resulting from a fermentation process, it is necessary to pay close attention to the specifications for the well-characterized organic materials used in the fermentation (i.e., starch, glucose, lactose, corn steep liquor, and soybean meal) (6). Inorganic starting materials should meet the same requirements as for chemical...
Barbara Scott

synthesis. The microorganism cultured should be properly identified including morphological, cultural, and biochemical characteristics. More details regarding fermentation processes can be found in the draft guidance on fermentation (6).

PLANT-OR ANIMAL-BASED STARTING MATERIALS
Starting materials from plant (e.g., thebaine) or animal (e.g., low molecular weight heparins [7]) sources should provide source and location of plant or animal (i.e., species and organ tissue used), storage and transportation conditions, drying conditions, and grinding conditions. Full disclosure of how the starting material is isolated, purified, and characterized will be required. Pre-approval inspections of the source locations may be required on a case-by-case basis.

When choosing an API supplier, ANDA applicants must weigh the quality and commercial aspects judiciously. The choice will have a direct impact on the review and approval times of submitted ANDAs. The choice of a high quality API is also integral to building quality into a proposed drug product as part of a quality-by-design approach. API quality is essential to development of a quality drug product, and API attributes should be considered as part of the QTPP (8). While the author has highlighted a number of points with respect to API starting material designation and process controls, this is by no means an exhaustive list of considerations when selecting a potential API supplier.

REFERENCES
3. ICH Q9, Quality Risk Management, ICH, June 2006. This is directly applicable to the drug product manufacture but also applies the risk-based thinking with regard to the drug substance.
8. ICH, Q8(R2) “Quality Target Product Profile” definition; see also Spring 2011 GPHA Meeting Slides by R. Lionberger; Yu, Pharm. Res. 25:781-791, 2008. JVT

DISCLAIMER
The views and opinions in this article are only those of the author and do not necessarily reflect the views or policies of the US Food and Drug Administration.

ACKNOWLEDGEMENTS
The author thanks Naiqi Ya, Dave Skanchy, Bob Iser, and Aloka Srinivasan for their scientific input.

ARTICLE ACRONYM LISTING
ANDA Abbreviated New Drug Application
API Active Pharmaceutical Ingredient
CGMP Current Good Manufacturing Practice
CTD Common Technical Document
DMF Drug Master File
ICH International Conference on Harmonisation
QTPP Quality Target Product Profile