

PhRMA Perspectives on Drug Substance Regulatory Filing Issues

Starting Material, Reprocessing, Retesting, and Critical Controls

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This article provides a PhRMA perspective and recommendations for several topics concerning active pharmaceutical ingredient development and manufacture that affect documentation provided in new drug applications. The PhRMA API Technical Group focused on starting-material definition, reprocessing, retest practices, and control of critical steps and intermediates as areas of particular importance. Further definition and clarity in these areas are needed with respect to existing drug substance regulatory guidance.

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FDA is currently revising its *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987). From an industry perspective, revision of this document is particularly timely for a variety of reasons, including

- the introduction of the common technical document (CTD) format for new drug application (NDA) submissions
- the changes in science and technology that have been introduced into all aspects of drug substance manufacture in the 15 years since the guideline was originally published
- the evolution of regulatory and industry practices that have superseded aspects of the 1987 guideline, particularly the issuance of *ICH Q3A(R) Impurities in New Drug Substances*, which now applies strict standards in the control of drug substance quality
- the opportunity to clarify current practice and expectations in cases in which these subjects are not adequately or consistently described elsewhere.

The PhRMA API Technical Group has identified four areas of particular importance to the new drug industry in hopes that these areas will be addressed in the revision of the 1987 guideline. These areas are as follows:

- starting materials
- reprocessing
- retesting
- control of critical steps and intermediates.

This article presents the PhRMA position on these four subjects. It represents the views of the PhRMA membership and includes the following recommendations:

- Broaden the current criteria for defining starting materials. This modification would represent a shift away from the traditional emphasis on commercial availability and literature precedence. A decision tree is proposed as an effective tool for defining starting material.
- Institute a standard definition of reprocessing to align with the definition currently in use in *ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. Clarification is proposed for scenarios in which reprocessing

should be reported in the NDA or drug master file (DMF) and instances when it need not be reported.

- Several specified clarifications related to the practical interpretations of the term *retest periods* for APIs should be provided in the new guidance to facilitate scientifically based decision making.
- Only those aspects of intermediate specifications that are used to control final drug substance quality should be considered as critical quality attributes (CQAs), and therefore, only these intermediate CQAs should require discussion in the CTD section currently labeled "Controls of Critical Steps and Intermediates."

Starting materials

Introduction. The concerns about drug substance starting-material definition can be classified into two categories:

- Concerns that exist in the current guideline, particularly with regard to the interpretation of the current starting-material criteria and also with regard to potentially problematic inconsistencies between the subject guideline and *ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*
- Opportunities for regulatory streamlining, consistent with the FDA Modernization Act of 1997, by an expansion of the current starting-material criteria. Beyond these opportunities for improved regulatory efficiency for both FDA and the industry, concurrent opportunities also exist for streamlining within technical drug development itself through the promotion of focused development of more-robust drug substance processes, and hence drug products.

This article attempts to identify the challenges and opportunities of a science-based approach to starting-material definition.

Reexamination of the current criteria. The FDA 1987 *Guideline For Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* addresses the question of starting-material definition and offers the following four criteria. Of these, one is clear and undeniably still appropriate:

- a. It is incorporated into the new drug substance as an important structural element.

PhRMA recommends that the remaining three criteria be re-examined. They are:

- b. It is commercially available.
- c. It is a compound whose name, chemical structure, chemical and physical characteristics and properties, and impurity profile are well defined in the chemical literature.
- d. It is obtained by commonly known procedures

Before addressing the three latter criteria, we first propose replacing the word *element* with *fragment* in the first criterion. Because the word *element* may also refer to the Periodic Table of Elements (e.g., carbon, hydrogen, oxygen, etc.), it may be confusing, particularly to chemists who do not speak English as a first language. The *ICH Q7A* definition uses the word *fragment* and we recommend following its example.

Although the three latter definitions may appear straightforward, they continue to be problematic with regard to interpretation and to their applicability to the concept of defining a starting material over which there is an adequate level of control.

The first concern is the commercial availability criterion, which is not further defined in the 1987 guideline. Inconsistencies occur in the interpretation of this criterion, particularly as it relates to the scale of availability and to the question of toll manufacturers. With an appropriate definition, this criterion certainly represents one of several criteria that may define the starting point for the NDA/DMF synthesis. However, it is not necessarily one that best serves the needs of the sponsor nor the agency with regard to control for each and every drug substance. It is undoubtedly clear that structures are becoming more complex for a variety of reasons, including the development of single stereoisomers and the search for ever more potent and selective drugs. Typically, more chemistry is being performed between commercially available feedstocks and the final target, and the starting-material criterion of commercial availability is, in itself, far too simplistic.

Second, the chemical-literature criterion has debatable significance in many cases. Although a literature precedent might provide reasonable support for proof of chemical structure, most literature references, particularly patents, provide limited data with regard to physical and chemical properties and far less, if any, information about impurity profile. Beyond the wording of the criterion itself, the guideline provides no clarification regarding the types of information that would be expected to appear in a literature reference. The criterion seems to apply more often to the question, "Is it known—period?" Therefore, the applicability of such literature information to the quality and control of a particular material in the proposed process is generally questionable. In spite of this, the regulators often seem to defer to this criterion when the commercial availability criterion cannot be met. Again, the real issue is whether this criterion contributes significantly to the specifications or control of the material in question. PhRMA will propose new criteria that will provide more-tangible value to product quality.

The third concern, although less critical, is uncertainty about how to apply the "commonly known procedures" criterion. Although the guideline indicates that the criterion "applies principally to starting materials extracted from plants and animals and to semisynthetic antibiotics," regulators sometimes have applied this criterion to chemistry with which they simply are not familiar. If other more-appropriate criteria for starting materials were to be established, one could reasonably argue that this particular criterion is irrelevant.

Admittedly, clear indications exist that the agency is moving toward a broader definition of starting materials, although there appears to be a range of expectations regarding this shift. For example, some cases of relatively complex intermediates have been redefined as starting materials in the traditional sense. In other cases, intermediates have been allowed to be designated as starting materials but with conditions associated with reporting (and sometimes prior approval) of changes in synthesis, vendors, sites, and vendor qualification procedures. The lack of a clearly publicized agency policy regarding its current expectations for starting materials often makes planning for drug substance regulatory filings and commercialization difficult.

PhRMA herein proposes that the criteria for starting-

material definition be reexamined and proposes a new hierarchy of modified criteria that will provide justifiable opportunities for a wider range of more-complex starting materials that will better serve the needs of both industry and the agency. In doing so, it would also provide consistency with the *ICH Q7A API Starting Material* definition, which provides for “material purchased from one or more suppliers under contract or commercial agreement or produced in house.” It is understood that *ICH Q7A* is a GMP-compliance document and is not intended to undermine the authority of the FDA reviewing division in the definition of starting materials from a regulatory perspective. Nonetheless, the inconsistencies in definitions between the two guidelines suggest a broader interpretation of starting materials under *ICH Q7A*, thus allowing for the possibility of different starting materials from the two different perspectives. Presumably this inconsistency is not the agency’s intent.

Opportunities for regulatory and development streamlining

Significant regulatory burden is incurred when lengthy syntheses are subject to regulatory review and GMP inspection. Considerable documentation regarding the synthetic process and the respective controls must be assembled, filed, and reviewed by means of either an NDA or a DMF. In general, the latter steps of the synthesis become the more critical ones with regard to ensuring the appropriate physical and chemical attributes for the drug substance. Therefore, more-stringent controls, consistent with current guidance, are put in place as the synthesis progresses. Analytical methodology has also improved dramatically during the past decade, so it is now realistic to expect that quality attributes for starting materials, intermediates, and reagents/solvents, which have the potential to affect the quality of the ultimate drug substance, can be identified and appropriately controlled such that the rigorous criteria set by *ICH Q3A(R)* for drug substances can be met. Selecting a certain process intermediate as a starting material with an appropriate level of analytical control will continue to provide appropriate quality assurance and process control. Concurrently, designating certain intermediates as starting materials would relieve manufacturers and agency reviewers as well as agency inspectors of a potentially significant burden in terms of managing early-step technical information that provides little value to overall drug substance quality, thereby allowing greater focus on steps of the process that have a higher potential to affect API quality. Similarly, rigorous adherence to

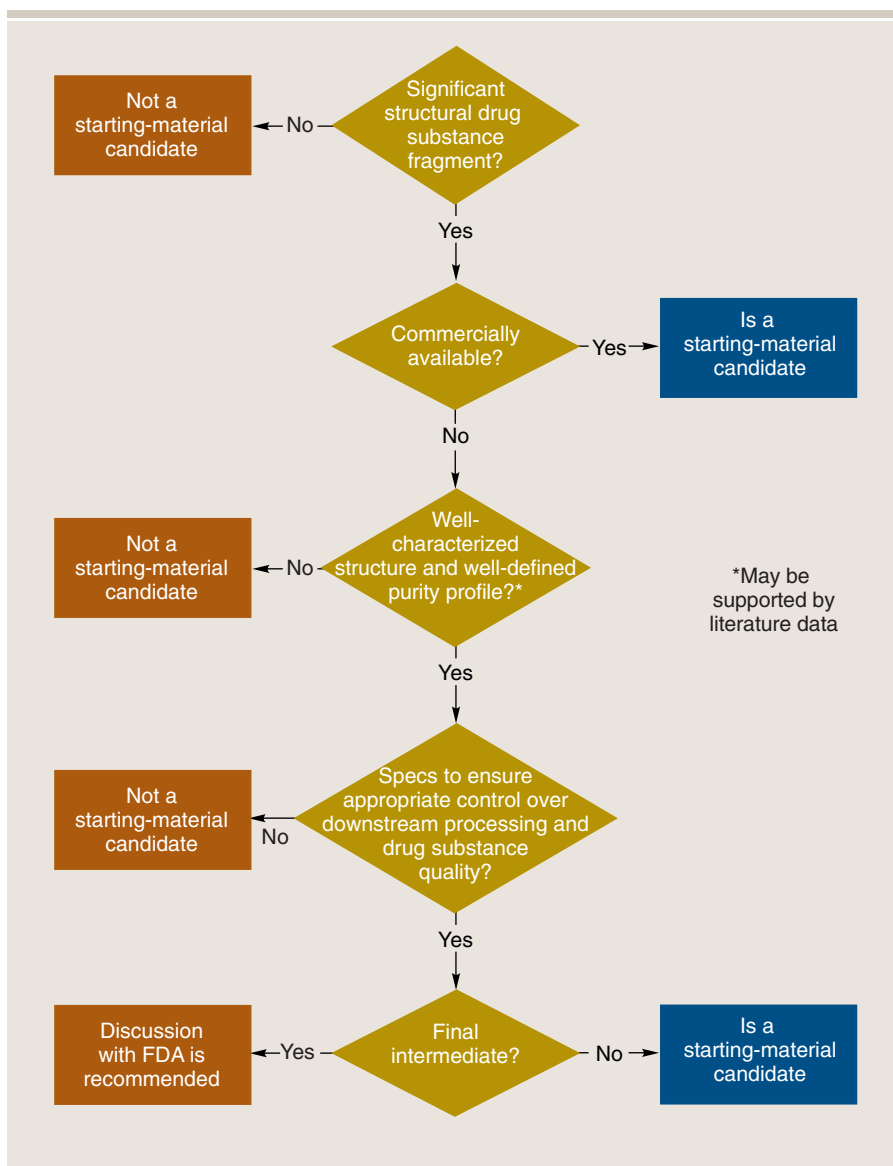


Figure 1: A decision tree for designation of starting materials.

GMPs should not be required before the starting material is designated in the NDA/DMF.

The development of clear, new standards for the definition of starting materials that may be independent of the commercial availability and literature precedent criteria would allow chemical development decisions related to starting materials (e.g., sourcing decisions) to be made earlier and with more predictability and certainty, which in many cases could help ensure the timely launch of a new product.

Decision-tree analysis

PhRMA proposes the development of a clear, consistent, scientifically sound policy regarding the definition of starting materials that would allow a broader range of opportunities for defining starting materials as well as redefine expectations regarding starting-material controls.

Defining a starting material according to a checklist of criteria will always be problematic without a clear logic or hierarchy for those criteria. One solution to this problem lies in the development of a decision tree, a concept that is used in the *Guidance for Industry BACPAC I: Intermediates in Drug Sub-*

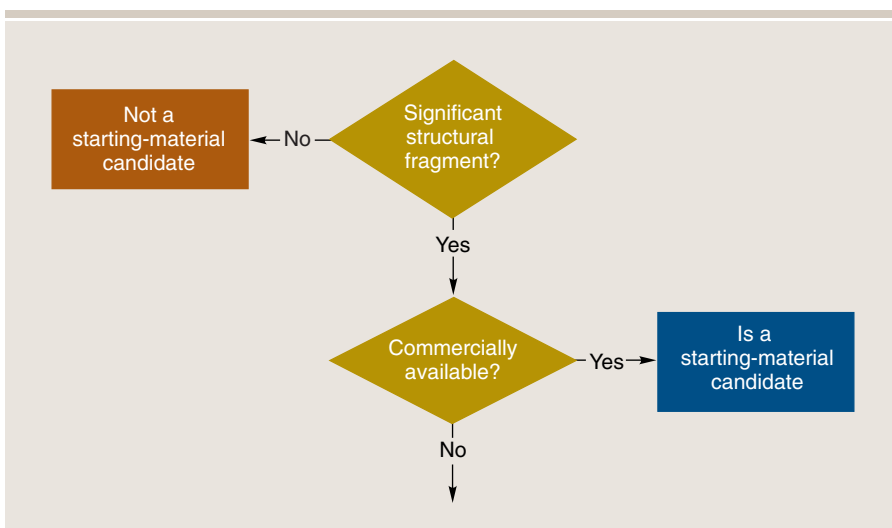


Figure 2: A decision tree to determine if a starting material is commercially available.

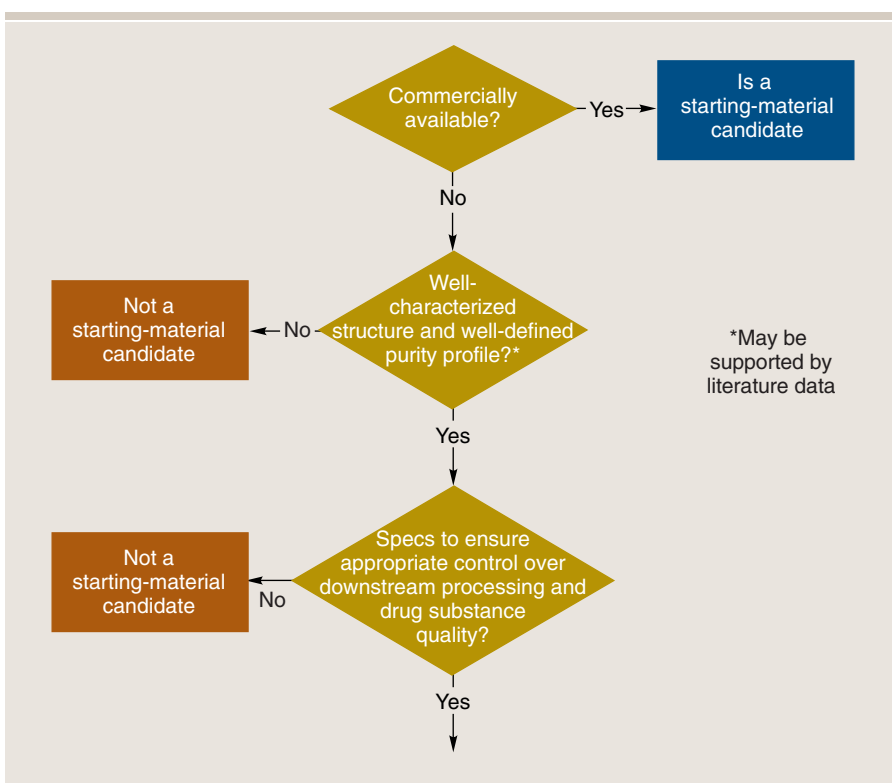


Figure 3: A decision tree that can be used to form the basis for a justification of the specifications of a proposed starting material.

stance Synthesis. Figure 1 shows a proposed decision tree for starting materials. The decision tree can be used to determine if a given intermediate is a viable candidate for a starting material. If the decision tree indicates that the intermediate is not a starting-material candidate, then an intermediate earlier in the synthesis should be similarly evaluated.

This decision tree would initially require that the starting-material candidate be incorporated into the new drug substance as a significant structural fragment. Thereafter, as shown in Figure 2, one must determine if the material is truly commercially available, which means that the material can be purchased on a scale that will support the commercial drug substance scale. Exclusive custom manufacturing by one or more contract vendors does not constitute commercial availability. Although a

vendor's specifications will serve as a starting point for material qualification, additional specifications may be required by the drug substance manufacturer to provide adequate process control.

If the material is not commercially available, that is, it represents a process intermediate, it may also be a viable starting-material candidate, as shown in Figure 3, if its chemical structure and purity profile are well characterized. Proof of structure may be based upon literature data and/or in-house data. The purity profile should be carefully developed with appropriate analytical methods and include an assessment of actual and potential impurities based on the chemistry leading to that material. Trace impurities, residual solvents, and chirality, as appropriate, should also be assessed. A careful assessment should be made with regard to the upper limits of these impurities and what effect they might have on downstream processes and on the drug substance quality specifications. This information about the fate of impurities originating in the starting material should form the basis for a justification of the specifications of the proposed starting material.

A final proposed criterion would be to assess whether the starting-material candidate is a final intermediate per the definition in FDA guidelines, e.g., *BACPAC I Glossary*. It is understood from *BACPAC I* that the final intermediate currently represents a break point in the categorization of risk. However, examples exist in which legitimate arguments have been successfully made for defining final intermediates as starting materials. Therefore, such arguments should be clearly discussed with the agency on

a case-by-case basis, as shown in Figure 4.

Although the criteria and decision tree previously discussed would apply to starting-material definitions in original NDAs/DMFs, it would also form the basis for changes in starting-material designation as the drug substance process continues to evolve. PhRMA believes that the provision for redefinition of starting materials (i.e., *CBE-30*) in the November 1999 *Guidance for Industry—Changes to an Approved NDA or ANDA* continues to be appropriate. Although this reporting category is also reflected in the *BACPAC I* guidance, the latter document should be revised to de-emphasize commercial availability and focus on appropriate analytical characterization and control. Inherent in a starting-material definition should be the premise that once a starting material has been defined (i.e., by means

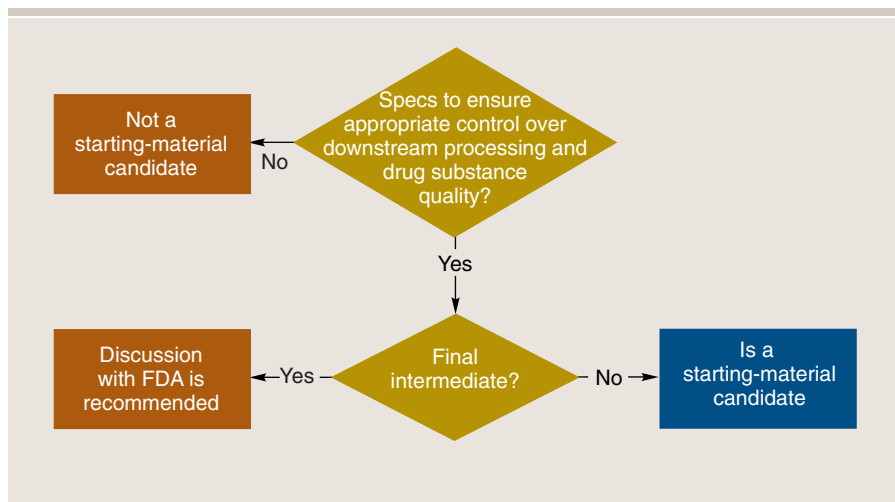


Figure 4: A decision tree to determine if a final intermediate can be defined as a starting material.

of an NDA, DMF, or NDA supplement), changes in vendor or manufacturing site for that starting material should have no regulatory (i.e., filing) impact. For changes in the synthetic route of the starting material, the adequacy of the existing specifications should be reassessed by the sponsor. If specification changes are warranted, they would be managed according to the *BACPAC I* guideline.

Recommendation. PhRMA recommends that the rewrite of the 1987 guideline include a new starting-material definition that will allow for clarification as well as broadening of existing criteria. The new basis for these criteria should shift away from the traditional paradigm of “commercial availability” and “known in the literature” to a new paradigm whereby criteria for starting materials would be based on scientifically sound and relevant controls. The decision tree proposed by PhRMA is recommended as an effective tool for implementing a common approach to starting-material selection.

The added benefits of these new policies would be to provide improved regulatory efficiency for both the agency and industry, to rectify existing inconsistencies in guidance and interpretation, and to meet PhRMA-company needs for streamlining R&D efforts. All these improvements could be accomplished at the same time that appropriate assurances are made that processes will perform as expected to provide high-quality pharmaceuticals with predictability and consistency.

Reprocessing

Introduction. The 1987 guideline for the manufacture of drug substances includes a section about reprocessing (i.e., II.E.2). This section implicitly recognizes that even the most tightly controlled processes occasionally produce material that does not meet the specifications set for the compound. Excursions or minor process deviations can and do occur despite the best of controls. Equipment failures or other minor deviations can occur that are unrelated to the process itself. For those situations and for out-of-specification (OOS) batches that can easily be rescued by reprocessing and that are expected to achieve the same specifications provided in the NDA, it is reasonable to reprocess. The agency clearly recognized this position by providing guidance on the reprocessing of intermediates and drug substances.

Although the 1987 guidance recognizes the value of reprocessing, it uses the terms *reprocessing* and *reworking* interchangeably, and it does not reflect the very clear distinction between the two terms that has evolved since the guidance was implemented. In addition, it does not make clear what reprocessing or reworking procedures are required to be filed in the NDA and what procedures can be used without being explicitly described in an NDA submission. This uncertainty can lead to the adoption of an

unnecessarily cautious approach to reprocessing and result in the costly and environmentally unfriendly destruction of material that could otherwise be recovered.

Therefore, from PhRMA’s perspective three relevant areas warrant close attention as the agency revises its 1987 guideline. These areas include

- a clear, concise definition of the reprocessing and reworking of intermediates and drug substances
- clarification of the scope of allowable reprocessing and the filing requirements
- a clearer definition of frequent reprocessing and the agency’s expectations for filing.

This article will discuss PhRMA’s perspective about each of these areas.

Defining reprocessing. Since the 1987 guideline was published, additional guidance documents were released that also address the topic of reprocessing. *ICH Q7A Section XIV-B* clearly defines *reprocessing* from a GMP perspective: “Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating appropriate chemical or physical manipulation steps that are part of the established manufacturing process.”

This definition focuses on the *repeating* of appropriate chemical- or physical-manipulation steps that are part of the “established manufacturing process.” In addition, it clearly provides for the reprocessing of both intermediates and drug substances. PhRMA finds this definition to be appropriately clear and recommends that it be adopted in the revised guideline.

Defining reworking. In contrast to reprocessing, *ICH Q7A Section XIV-C* defines *reworking* as follows: “Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established process to obtain acceptable quality intermediate or API.”

A rework procedure, or alternative procedures, should be described in the NDA/DMF to a similar level of detail as the routine manufacturing steps. If additional analytical controls are necessary to show that the reworked product is of equivalent quality to that produced by the original process, they should also be described in the NDA/DMF.

The scope of reprocessing and regulatory requirements. A frequent source of confusion that requires FDA clarification is whether or not reprocessing (i.e., repeating a step or steps) during the course of drug substance manufacture requires inclusion in the NDA/DMF. Inconsistencies exist not only between

companies and regulators, but also within companies with regard to what is expected by the agency.

As mentioned earlier in this article, infrequent process excursions that affect a batch of drug substance or intermediate occasionally occur beyond what is specifically allowed for in the NDA/DMF, thus prompting consideration of a reprocessing step. One example is the repetition of a filtration step when the first filtration didn't achieve its purpose—as in the case of a filtration to remove a filter aid such as Celite in which small amounts of the aid get past the filter. Another example is the removal of an inert foreign particulate substance (part of a filter, gasket, etc.) from a crystalline product. In this case, the intermediate or drug substance would be dissolved, filtered, and crystallized as before. Alternatively, an OOS failure may be linked to a process step that is known to be sensitive to minor variations such as a final crystallization that results in a particle-size distribution outside a specified range.

As with any process deviation or OOS result, an investigation should be conducted to determine the root cause of the problem, as required by cGMP. Depending on the outcome of this investigation, repeating certain process steps to rectify the problem and provide material of typical quality may be appropriate and should be allowed. This reprocessed material must meet the quality criteria for the step.

Many such excursions are unpredictable and therefore virtually impossible to anticipate, so requiring that a reprocessing procedure to correct them be included in the NDA/DMF seems unrealistic. Given the fact that the material is resubmitted to the same process and that the product must meet the same quality criteria, one could argue that adequate controls are already in place to ensure quality. For the same reason, even where an occasional failure could be predicted to arise from a process step, specifying the reprocessing provision in the NDA/DMF should not be a requirement.

The revised guideline should also make clear that certain nonchemical unit operations that are required to return the material to a particular point in the original process are also permitted. For example, in order to repeat a crystallization step, one might have to warm the solution to dissolve the solid. This dissolution step may not be in the original process because it was originally obtained as a solution by means of an extractive work-up. Similarly, to remove a failed gasket or seal it may be necessary to dissolve the solid and filter the solution before crystallization. However, filtration may not have been a routine part of the original process. In these cases it would be important to stipulate that the operations should be limited to simple unit operations as opposed to chemical operations. When additional steps to enable reprocessing are needed that go beyond simple unit operations (e.g., converting a salt back to a free base), then these enabling steps should be defined in the application.

Frequent reprocessing. PhRMA acknowledges that reprocessing should be an infrequent solution for failed intermediates or drug substances. When reprocessing is used frequently to correct a specific repetitive problem and obtain satisfactory bulk drug substance or intermediate, then it should become part of the normal process and be included as part of the NDA/DMF.

Confusion arises in the definition of *frequent*. Many companies recognize 10% as a threshold for this term. In other words, when a reprocessing step to address a specific problem is necessary in more than one out of 10 runs for a given process, then that process is not in satisfactory control, and the reprocessing step may need to be routinely incorporated into the process. But 10% is only meaningful when it is based on a large-enough population of runs. For high-volume processes with numerous annual batches, 10% is statistically meaningful. However, for a process that produces only three batches per year, a single failure may not be statistically meaningful if sufficient historical batches are not yet available. For this reason, PhRMA proposes that a 10% failure rate be used as a guideline only and that any failure rate be evaluated in the context of the particular process in question when one is assessing what course of action should be taken. It should also be made clear that any evaluation of failure rates refers to failures arising from a specific recurring cause. For example, in a sequence of 15 batches, one reprocessing due to a particle-size failure and one due to a filtration failure does not constitute an unacceptable reprocessing rate.

Reprocessing after release. The previously described examples address a situation in which the need for reprocessing is identified and implemented at the time of manufacturing. Circumstances exist in which reprocessing may be needed after the analysis and release of the drug substance. For example, two grades of drug substance may differ only in particle size, and the manufacturer may want to reprocess the drug substance to convert a surplus of one particular grade into another. Alternatively, a failure in packaging during storage may result in a drug substance absorbing unacceptable amounts of water. Another common occurrence is that in dispensing aliquots of batches to various suppliers, "heels" representing a few kilograms of material from individual batches or containers are left over. Rather than distribute multiple small batches to customers, a manufacturer may find it more convenient to combine and reprocess multiple heels to produce a single new batch. The guidelines should make it clear that reprocessing of released material is permitted in such circumstances even if it is not described in the application. Similarly, after release, the purification of degraded material by reprocessing should be permitted by this proposal, assuming that appropriate validation requirements are addressed.

Recommendations. In summary, PhRMA recommends that the following points concerning the reprocessing of intermediates and drug substances be addressed in the agency's rewrite of its 1987 guideline for drug substance submissions:

- First and foremost, a concise definition of *reprocessing* should be included that is consistent with that found in other guidance documents and preferably the same as that found in *ICH Q7A*.
- Reprocessing of intermediates/drug substances arising from occasional process excursions or OOS failures should be allowed without having been specifically mentioned in the application. This reprocessing procedure would generally involve repeating a simple chemical step or physical manipulation that is already described in the NDA/DMF.
- When a reprocessing step to correct a specific source of failure becomes a frequent occurrence, then it should become

part of the normal process and be filed either as part of the NDA/DMF or as a supplement. As a guideline, the term *frequent* would mean >10% failure rate for a specific cause. However, for any particular failure rate, including rates >10%, the course of action should be determined on the basis of the particular circumstances of the process in question.

- When certain additional unit operations are required to return a material to a particular point in the original process for reprocessing, these nonchemical steps should be permitted even if they are not described in the application. Chemical manipulations that are required to enable reprocessing should be described in the NDA/DMF.
- In general, reprocessing of released material also should be described in the reprocessing provision but need not be specifically mentioned in the NDA/DMF.

Retest period of drug substances

Introduction. The 1987 guideline does not specifically address the question of retest or expiration dating for drug substances. In the past 15 years, industry practice has evolved, and a need exists to codify the current understanding of expiry date and retest date as it applies to drug substances. This article identifies the problems and recommends a science-based approach to the retesting of drug substances to clarify the current uncertainty in this area.

Background. The subject 1987 guideline does not specifically address the question of retest or expiration dating for drug substances, but in Section II.B it references a second 1987 guideline, namely, *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*. This stability guideline refers only to “expiration dating where required” (p. 8, Section III.A). Since these documents were published, industry and the agency have developed a better understanding of the need for establishing appropriate shelf-life information for all drug substances.

The preference for retest dating over expiry dating was most recently reflected in *ICH Q7A*. “Expiry and Retest Dating” in Section XI.F (p. 30) states that “an API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.” *ICH Q7A* defines the terms as follows:

- Expiry date (or expiration date): The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.
- Retest date: The date when a material should be reexamined to ensure that it is still suitable for use.

The use of expiration dating is reserved for products that are less stable and a clear indication exists that the material is likely to fall outside of required specifications after a period of time or when there is a specific requirement (e.g., antibiotics).

Recertification period after retesting. Although any confusion about the need for and appropriate use of expiration dating versus retest dating seems to have been resolved, debate continues about how retest periods and retest dates are used. The two conflicting schools of thought are:

1. After an initial retest period as defined in the sponsor’s application, a drug substance may be tested to determine compliance with appropriate specification *and then used immediately*. Continued use of the batch of drug substance would be acceptable as long as the material is retested before each use.
2. After an initial retest period, a drug substance may be tested to determine compliance with appropriate specifications, and then *a new retest date is established* on the basis of available data about the stability of the material and sound scientific principles.

This debate has been further fueled by the fact that *ICH Q1A(R) Stability Testing of New Drug Substances and Products* (August 2001, p.18) defines the “retest period” as follows:

The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf-life than a retest period. The same may be true for certain antibiotics.

This definition, taken literally, fails to allow for the establishment of subsequent retest dates after the initial retest period and thus implies the restriction of immediate use after retesting.

The differences between the two schools of thought regarding the use of retesting may be explained by determining who generally performs a retest on drug substance materials. Usually drug substances are retested by either the drug substance manufacturer or the drug product manufacturer. The drug substance manufacturer generally tests material that has been stored within its control—under appropriate storage conditions and in original unopened containers. The drug product manufacturer also tests material that has been stored within its control and that has been stored appropriately. However, the product may or may not have been opened previously for use or sampling.

The first school of thought about retesting for immediate use accurately describes the practice of many drug product manufacturers: continuing to test and use drug substances immediately when they have passed the retest date established by the drug substance manufacturer. This is a rational approach to retesting drug substances given that drug product manufacturers’ experience with a drug substance may be less extensive than that of the original drug substance manufacturer. However, the immediate-use requirement does not address many drug substance manufacturers’ practice of retesting material and establishing a new retest date on the basis of both the available stability data and sound scientific principles. For example, the drug substance manufacturer may have additional real-time data from earlier lots, and the stability history of the drug sub-

stance may show it to be sufficiently stable when stored under the defined conditions. The material can continue to be used, and a new retest date can be scheduled for sometime in the future. This practice reflects the second school of thought.

Drug substances are generally stored as a single, very pure chemical and not as a complex matrix such as a finished product formulation. Many drug substances are extremely stable, and on the basis of real-time or extrapolated stability data they can be demonstrated to meet appropriate specifications for an indefinite period of time. For many other drug substances, the storage conditions and the integrity of the primary container closure system play the most significant role in the length of time a drug substance remains within specification. These factors can be better addressed by proper warehouse and materials management controls than by continuous retesting of the drug substance. In either case, the practice of resetting a retest date on the basis of data and sound scientific principles is highly justifiable.

Until now, the question of how often drug substances should be evaluated after the initial retest date has been viewed by both FDA and industry as a compliance question. As such, some inconsistencies have arisen about how retesting has been addressed. Although reviews of retesting procedures should continue to be addressed during site inspections, we propose that FDA offer clearer regulatory guidance about this topic, and establish a consistent approach to solving the problem.

Recommendation. To address the question of retesting, PhRMA recommends that the revised guideline adopt the following recommendations about the practical interpretation of the term *retest period* for APIs:

- If compliance with the currently filed specification is demonstrated at the end of a retest period, the batch may be used immediately, or a new date for retesting can be established.
- A new date for retesting should be documented internally and based on current retest results, stability data, sound scientific principles, the retest period filed in the NDA/DMF, and cGMP requirements.
- Successive retest periods may not be longer than the previous retest period.
- The retested batch may be used in the manufacture of drug product without further testing until that new retest date, provided that it has been stored under the defined conditions.
- A batch of drug substance may be retested multiple times and assigned successive retest dates if appropriate.
- The filing of a retest period for an API in an NDA or DMF allows for these successive retest dates without specific provision in the application.

Control of critical steps and intermediates

Introduction. The August 2001 *ICH M4Q: The CTD—Quality*, Section 3.2.S.2.4, “Controls of critical steps and intermediates,” contains a section that allows for a presentation of the tests and specifications that control quality for critical process steps. This section states:

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing

process to ensure that the process is controlled should be provided.

In contrast to virtually all other sections of the CTD, this information has not always been provided by sponsors in NDAs/DMFs and similarly has been inconsistently requested by FDA reviewers. Nevertheless, a common theme running through the original 1987 guideline, *ICH Q7A*, and the CTD guidance is the need for controls on the manufacturing process of a drug substance, not just quality testing of the final drug substance. In other words, checking quality at various points in the process helps ensure the quality of a final drug substance. PhRMA herein offers recommendations that provide clear direction for this section of the CTD and proposes that they be incorporated in the revision of the 1987 guideline.

In the broadest terms, section 3.2.S.2.4 addresses the question, “What intermediate controls in the process are critical for ensuring drug substance quality, and what is the justification for the specifications being proposed for these controls?” This query is complementary to the information provided about starting materials, in which impurities that can affect final drug substance quality are appropriately identified and controlled by starting-material specifications. Controls on intermediates ensure that key steps in the manufacturing process have been executed correctly, e.g., to ensure that formation of a particular impurity has been kept to an acceptably low level or that removal of an impurity to a required level has been accomplished. The difficulty perceived by PhRMA is ensuring a common set of expectations about what information should be discussed in this section. The ICH M4Q guideline references tests and acceptance criteria performed for critical steps, but the term *critical step* is open to individual interpretation.

Critical quality attributes (CQAs). It is important to recognize that not all intermediate specifications are established to control drug substance quality. Specifications for intermediates may also be set for economic or safety reasons. For example, the level of a precursor in an intermediate may have no bearing on the final drug substance quality because it is completely removed by downstream processing. Nevertheless, the sponsor could choose to control its level to prevent excessive losses in yield resulting from incomplete conversion. A moisture specification for an isolated intermediate could have no direct bearing on drug substance quality but may be set to avoid the hazardous decomposition of a reagent in the next step or to avoid unnecessary and wasteful solvent consumption during azeotropic drying before the next reaction.

PhRMA’s position is that only those aspects of the intermediate-quality attributes that are used to control final drug substance quality should be considered as CQAs, and therefore only those intermediate CQAs should be discussed in this section of the CTD. By definition, failure to meet the specification for a CQA significantly jeopardizes the ability of the process to meet ultimate drug substance specifications. The concept of CQAs with appropriate acceptance criteria as discussed later in this article sufficiently addresses the intent of this matter in the CTD. Beyond this, PhRMA considers the identification of particular steps as critical steps to be unnecessary.

Because they will affect drug substance quality, a logical ap-

proach to identifying CQAs for intermediates is to examine the specifications for the final drug substance. For example, in the case of impurities, it can be determined which process stages govern the observed levels of individual impurities in the final drug substance either through impurity formation at a particular stage or impurity removal at a subsequent stage. Limits to control the CQAs of appropri-

ate intermediates would be expected. Implicit in this analysis is the conclusion that the sponsor is not required to discuss any intermediate impurities or other quality attributes that do not give rise to impurities or other quality attributes in the final drug substance. Exceptions to this general statement may exist when process steps are controlled through CQAs to ensure that certain unspecified drug substance

impurities remain below the applicable *ICH Q3A(R)* threshold.

It is important to focus on the final drug substance quality in this analysis in addition to the intermediate quality. As mentioned earlier, the manufacturer may wish to control certain aspects of the intermediate quality for economic, safety, or other reasons. If variability in the intermediate quality attribute has no effect on the final drug substance quality, the intermediate quality attribute should not be considered critical and would not warrant discussion in this section of the CTD.

Acceptance criteria. Acknowledging that CQAs of intermediates are the focus of this CTD section, the next matter to address is the control limit or acceptance criteria for the attribute in question. For an impurity, the control limit may be determined by a direct analysis of historical data, an extrapolation of historical data, or by spiking experiments. Any of these and other approaches may be acceptable for determining the appropriate level of a CQA.

Circumstances sometimes occur in which the level of an impurity or other quality attribute far in excess of that typically observed in the process will still produce acceptable drug substance. Under these circumstances, this would not be a CQA and indeed, the sponsor may decide that no limit for this quality attribute is necessary.

It is expected that analytical methods governing CQAs of process intermediates should be validated. This validation should be appropriate to the purpose of the analysis and the stage of the process, as stated in *ICH Q7A*, Section XII.H, "Validation of Analytical Methods (12.8)." The analytical method validation should be available at the site for review during inspection but should not be included in the filing.

Drug substance process validation. The CQAs for intermediates provided in the CTD typically would be included as acceptance criteria for process validation. However, for certain parameters, the selection of appropriate validation acceptance criteria will to some extent be equipment dependent and will be based in part on all the results of experience before validation. Therefore it is not practical at the time of NDA filing for the sponsor to de-

fine all the validation acceptance criteria for the process. The process description, in-process tests with criteria, and CQA information that will be included in the filing provide adequate documentation of the process, and inclusion of a validation protocol in the filing would not provide substantive new information. Therefore, this section of the CTD should only address the CQAs of intermediates, and discussion of acceptance criteria in drug substance validation should be available at the site for review during inspection but should not be included in the filing.

Recommendations. PhRMA recommends that in the forthcoming revision of the 1987 guideline, the following points should be made clear regarding the content of CTD Section 3.2.S.2.4:

- Only those aspects of the intermediate specifications that are used to control final drug substance quality should be considered to be CQAs, and therefore only these intermediate CQAs should require discussion in this section of the CTD.
- With appropriate definition of CQAs, no need exists to define *critical steps*.
- Acceptance limits for the CQAs may be derived in several ways, but the sponsor should explain the rationale for the control limit selected for the CQA.
- Appropriate validation acceptance criteria will be determined at the time of validation, and although the CQAs defined in the NDA/DMF will typically also be acceptance criteria for

process validation, exceptions may be documented in the validation report.

- Inclusion of analytical method validation data for methods used to control the CQAs for process intermediates should not be required in the regulatory dossier.

Summary

This article represents PhRMA's position about matters of importance that relate to FDA's initiative to update the February 1987 *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*. Those matters are starting-material definition, reprocessing, retest dating, and CQAs. In each case, recommendations have been made that could eliminate ambiguity and confusion arising from current agency guidance and practice. The proposals also provide an opportunity for improved regulatory efficiency for new drug companies and for FDA. The recommendations are based on sound scientific principles that will provide equal, if not better, process control than currently exists. In addition, the proposals contained herein will provide consistency with other FDA guidelines (e.g., Q7A) and with long-held industry practices. PhRMA trusts that FDA will find these positions helpful in its considerations and offers its assistance to the agency to develop a consensus about these concerns. **PT**