Despite years of efforts toward developing common standards and testing policies for new drugs, pharmaceutical manufacturers continue to find significant differences between policy and practice among regulatory authorities. One example is the effort to establish global specifications for measuring the quality and consistency of new drug substances and products. Because these specifications evolve during product development and scale-up, manufacturers often revise initial criteria as a result of experience and data that indicate which test and analytical procedures best ensure the safety and efficacy of a product over time. Consequently, regulatory authorities have taken various approaches to the timing and scope of information required from manufacturers for setting specifications. These divergent policies and practices have been hard to change.

The International Conference on Harmonization (ICH) has tackled this issue as part of its ongoing effort to set common drug development standards and test procedures for manufacturers in the United States, Europe, and Japan. The result is the Guidance on Q6A Specifications, which FDA published in December 2000 (1). This guidance addresses how manufacturers should select and define tests, supplies references to analytical procedures, and provides appropriate acceptance criteria to establish a list of specifications. It also clarifies that setting specifications is just one part of a broader quality assurance system, which also includes product characterization and adherence to good manufacturing practices.

Various interpretations
Although the ICH definition of specification sounds fairly straightforward, it has generated considerable discussion about where, when, how, and who should set these specifications. A related issue is whether ICH standards establish a floor or a ceiling for regulators. Manufacturers seek a ceiling on demands from regulatory authorities, but FDA officials appear to regard the ICH policy more as a starting point from which they can request additional data.

How loose or tight initial drug specifications are can have a considerable effect on future manufacturing and regulatory processes. Drug development and production is not a static process; it responds to technological innovations, biomedical discoveries, and revisions in regulatory policies. If manufacturers are allowed to bring new drugs to market on the basis of fairly broad specifications, companies might experience considerable lot-to-lot variation and might be required to file manufacturing supplements as they refine products and processes. This places a substantial burden on regulators by adding to the thousands of supplement filings they already review.

Conversely, specifications that are too tight might yield many out-of-specification results and delay market approval. Identifying a reasonable and workable level of specificity remains a challenge for all parties involved.

These issues were discussed at a drug substance and drug product specifications workshop in March sponsored by the American Association of Pharmaceutical Scientists and FDA’s Center for Drug Evaluation and Research (CDER). Participants examined how manufacturers are responding to the ICH specifications guidance and how closely FDA is following the standards. The workshop also reviewed related ICH guidances about limiting impurities and residual solvents.

Now that the ICH policy has been available for more than a year and many issues remain unresolved, FDA officials are open to discussing the need for revision or additional guidance in a number of areas. Both FDA officials and manufacturers agree that this ICH initiative has fallen short of original hopes of establishing harmonized test and data standards for specifications.
Evaluating new approaches

The ICH guidance describes several important concepts for manufacturers to consider when setting specifications. FDA publishes ICH standards as guidances that reflect the agency’s current thinking about an issue. The agency does not require manufacturers to follow guidance recommendations, which makes it relatively easy for FDA to update and clarify its interpretation of these guidances without lengthy rule-making processes. While FDA officials develop guidances for implementing ICH standards, manufacturers are pressing for policies that mesh with European and Japanese interpretations. Some approaches have become more common in Europe than in the United States, reflecting divergent approaches in these regions. Various approaches include the following.

**Periodic or skip testing.** One idea is to perform specified tests on certain batches or at predetermined intervals rather than test every batch. For such an approach to work, ICH advises manufacturers to justify and gain regulatory approval before adopting a modified schedule of batch testing. The document notes that skip testing may be more applicable to certain tests such as identifying residual solvents and microbiological testing for solid oral dosage forms. Because manufacturers want to gather as much data as possible before their product is approved for market, this approach may be more appropriate for postapproval quality monitoring. Industry would like FDA to clarify which low-risk situations are most appropriate for skip testing and how manufacturers should justify this strategy. A tricky issue is how a manufacturer should respond to an out-of-specification result for a test that is conducted periodically.

**Release versus shelf-life specifications.** Although FDA and Japanese authorities ask manufacturers to submit only one set of acceptance criteria in applications that are relevant throughout a product’s shelf life, European Union authorities want to see distinct, more restrictive release specifications. Many manufacturers approach this discrepancy by setting...
their own in-house limits at the time of release. These limits usually are fairly tight and provide added assurance that a product will remain within established acceptance criteria throughout its shelf life. Even though FDA may seek release specifications for some biotech, radiopharmaceutical, ophthalmic, and inhalation products, CDER officials say they really don’t want release specifications included in most new drug applications (NDAs). Manufacturers acknowledge that tight release specifications can be useful, particularly for exports, but oppose changes in FDA policy for fear that required release specifications filing only would provide an additional possibility to fail a test.

Test sunsets. Another proposal is to allow manufacturers to discontinue conducting certain tests once enough data exist to demonstrate that a particular analysis is no longer needed to ensure product quality. Upon filing an NDA, a manufacturer would have to discuss with regulatory authorities a certain parameter that may not warrant ongoing monitoring. This would be most appropriate for measurements of low-risk attributes such as product weight loss or water content for a solid oral dosage form.

Interim specifications and postapproval commitments. When test data are limited at the time an NDA is filed, a manufacturer may want to establish interim specifications along with commitments to revise acceptance criteria during Phase IV. This strategy could apply to dissolution testing for highly water-soluble drug substances, microbiological testing for drugs shown not to support microbial viability, or tests for extractables on product containers with no unsafe levels. If product safety is not a major issue, such interim specifications could be loose initially, with the expectation that they would tighten in the future. This concept touches on the debate about loose or tight initial specifications and the potential effect on manufacturing supplement submissions. In any case, FDA officials want a fairly specific up-front agreement for setting final specifications to avoid an open-ended process.

Particle size. The ICH guidance states that particle size can have significant effects on dissolution rates, bioavailability, and stability of drug substances that warrant effective and appropriate testing for particle-size distribution and the establishment of acceptance criteria. Particle-size distribution is an increasingly critical issue for various dosage forms, including suspensions and inhalation products. However, this parameter may not be such an important measurement for highly soluble drug substances and may vary across these dosage forms. Sunset or skip testing may be an option when a manufacturer demonstrates that this measure is in control or has little effect on the substance. Manufacturers want FDA to clarify what it expects in this area.

Dissolution and disintegration. This topic is generating considerable debate between industry and FDA reviewers. Manufacturers complain that the agency fre-
More about impurities

Although purity and impurity issues are discussed in the specifications guidance, ICH also has developed separate standards about this subject. In February, ICH issued a revised version of its 1996 guidance (Q3A-R) about impurities in new drug substances. The revision is aimed at reducing inconsistencies. The group also is in the process of finalizing a revised guidance (Q3B) about impurities in new drug products. ICH participants are collecting data to determine whether they must update a 1997 guidance (Q3C) about residual solvents. The revised impurities guidance clarifies thresholds for reporting and identifying impurities and describes how to list impurities in specifications and in setting acceptance criteria. To review ICH guidelines, visit www.ifpma.org/ich1.html.

The guidance-update process is an attempt to expand on the limited information about impurities in the ICH specifications guidance (Q6A), which indicates how manufacturers can extrapolate meaningful limits on impurities from batch data when setting acceptance criteria. FDA officials are considering the need for additional guidance for interpreting and implementing policies involving impurities and residual solvents.

Reshaping policy

One reason CDER officials are reexamining the Q6A specifications guidance is evidence that manufacturers are not consistently following ICH recommendations. A fairly informal survey of team leaders in CDER’s Office of New Drug Chemistry (ONDC) indicated that manufacturers are implementing ICH standards unevenly and quite poorly in some areas, according to Charles Hoiberg, ONDC deputy director. Few manufacturers are trying approaches such as skip testing. FDA reviewers report that applicants frequently fail to provide adequate rationale and data for specifications.

An important factor that contributes to difficulties with harmonizing tests and setting standards for specifications is a trend toward increasingly compressed drug...
development strategies. Accelerated R&D programs frequently prevent manufacturing executives from obtaining sufficient data to fully assess process consistency at the time of filing, noted Pfizer vice-president John Berridge. Manufacturers gain more knowledge during the months when an application is under FDA review, a process that requires companies to revise initial submission criteria before setting a final specification.

This process reflects variations in the length of time it takes a company to fully understand its manufacturing capability, time frame, and scope of testing needed to determine which procedures will ensure long-run product quality. Manufacturers believe that the timing for setting specifications varies relative to the complexity of the production process and the type of raw materials being used. Some combinations take 3 batches to tell the story, others take 20 batches.

FDA officials want to resolve issues related to product testing and characterization at end-of-Phase-2 (EOP2) FDA-sponsored meetings that discuss chemical, manufacturing, and control (CMC) issues. However, manufacturers avoid these sessions for fear that they will get locked into specifications too early. FDA also is under pressure to evaluate NDAs in one review cycle, but often lacks full CMC data to review. This problem is even more acute for products that qualify for FDA’s fast-track review process. Manufacturers suggest that FDA develop a guidance for EOP2 meetings to clarify all parties’ expectations about discussions and negotiations.

Industry concerns about FDA demands for additional data and tests reflect a certain lack of trust on both sides, according to many participants in the March drug substance and drug product workshop. Increased testing is viewed as an increased possibility for failures or out-of-specification results. Manufacturers often don’t want to invest in extensive quality testing until basic safety and efficacy issues are resolved and a new product demonstrates some promise. By then, a manufacturer may have to rush into testing to set specifications and acceptance criteria, and data may be incomplete.

ONDC director Yuan-yuan Chiu promises to evaluate the summary report from the March workshop. FDA may incorporate some of the recommendations into CDER’s internal CMC review practices, which would help eliminate or reduce differences in how FDA reviewers approach data and test requirements. The agency also may publish additional guidances to better clarify its expectations for manufacturers. Although the goal of global specifications remains an attractive objective, it is still far away.

Reference