Spotlight

COVID-19 Update

Analytics

Development

Downstream Processing

Manufacturing

Outsourcing

Quality/GMPs

Upstream Processing

Topic See All >

Analytical Methods

BioBusiness

Cell Culture/Fermentation

Continuous Processing

Drug Delivery

Fill/Finish

Formulation

Process Chromatography

Process Control/PAT

Process Development

QA/QC

Separation and Purification

Single-Use Systems

Supply Chain

A Rational Approach for Setting and Maintaining Specifications for Biological and Biotechnology–Derived Products—Part 1

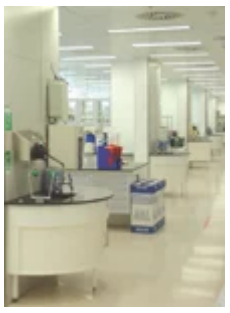
May 31, 2008
BioPharm International, BioPharm International-06-01-2008, Volume 21, Issue 6
Pages: 40–45

A staged approach to limits should embrace future capabilities.

ABSTRACT

This paper discusses an approach for the establishment and lifecycle management of biological and biotechnology-derived product specifications. The views presented are consistent with the concept of Quality by Design (QbD), in which critical quality attributes (CQAs) are distinguished from parameters used to monitor process consistency. Specifications and the corresponding limits as applied to CQAs serve to ensure that the product is fit for use, whereas control limits are a manufacturer's tool to monitor shifts and trends in the manufacturing process. In the current paradigm, inappropriate use of specifications creates a disincentive for continuous process understanding; more suitable approaches to analyzing development and manufacturing data are discussed. Statistical methods are presented for deriving and interpreting data against specifications that better manage the risk to the customer of receiving product with diminished safety or efficacy, as well as the risk to the manufacturer of earmarking a satisfactory lot as unacceptable. The recommendations are presented as a rational approach to setting and maintaining specifications, while recognizing that their applicability may not be suitable in all cases, given the heterogeneity of types of regulated biological and biotechnology-derived products and their unique challenges.

The purpose of this paper, which has been developed by the Working Group on Specifications and Formulations of the Pharmaceutical Research and Manufacturers of America (PhRMA) Biologics and Biotechnology Leadership Committee, is to provide guidance on a lifecycle approach to setting global specifications for biological and biotechnology-derived products. In the pharmaceutical industry, specifications are legally binding criteria that a product must meet in order to be marketed. They ensure the consistency and quality of the product and help ensure that it is safe and efficacious over the shelf life of the product. Specifications evolve during product development and ideally should embrace future process capability. This is true for biological and biotechnology-derived products for which there may be limited experience at the time of regulatory filings (including the marketing application), and for which early commercial production often is necessary to gain a better understanding of product quality attributes, methods, and limits.



Wyeth

Currently, there is no industry-wide guideline about the process for establishing specifications for biological and biotechnology-derived products at different stages of the product lifecycle. The International Conference on Harmonization (ICH) Q6B document provides detailed guidance for commercial products and refers to specifications as a list of tests, references to analytical procedures, and appropriate acceptance criteria with numerical limits, ranges, or other criteria to describe the result of the test. Specifications establish a set of criteria to which a drug substance (DS), drug product (DP), or materials at other stages of manufacture should conform to be considered acceptable for use. *Conformance to specifications* means that the drug substance or drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. However, this definition may be too restrictive for some applications, such as stability testing or process validation, for which more appropriate means of establishing product quality might be considered.

This paper is laid out in five sections. We will first provide some terminology and definitions. This terminology is not necessarily common throughout the industry, but we hope it will cover all aspects of setting specifications and provide a basis for discussion throughout the paper. The second section of the paper outlines the stages of the lifecycle of a biological or biotechnology-derived product, with emphasis on the level of product information at each stage. The third section describes the components of a product specification, including parameters and components that are unique to this class of products. The fourth section highlights some unresolved issues that must be addressed before setting specifications. The last section proposes a strategy for developing a quality system for biologicals and biotechnology-derived products that helps ensure safety and efficacy to the customer throughout the shelf life of the product, and provides the manufacturer with a powerful set of tools to monitor the manufacturing process.

Sections 1 to 3, covering terminology; the stages of the lifecycle of a product; and components of a biological and biotechnology product specification, appear below, as Part 1 of this article. Section 4 (current issues related to the development of specifications) and section 5 (the suggested approach for developing and maintaining a total quality system), will be published as Parts 2 and 3, in the next two issues of *BioPharm International.*

TERMINOLOGY

A *quality attribute* is a property that is either demonstrated or predicted to be related to the clinical safety or efficacy of the final product. Among these are purity and potency, which are linked to preclinical and clinical experience during product development. Other properties such as pH and osmolality might be measured to demonstrate the consistency of the manufacturing process.

The *reportable value* of a quality attribute is the result that is held to appropriate limits. For release testing, this is the value that is reported in the certificate of analysis (COA) for the lot, and may be

the average from replicate independent determinations of multiple samples from a lot.

For the purpose of this paper, *specification limits* will refer to the limits on a quality attribute that predict that the product is fit for use. This is the same as the *acceptance criteria* set forth in ICH Q6B. Product that does not meet a specification limit for a quality attribute is said to be *out-of-specification* (OOS).

Control limits, sometimes called *process capability limits* or *alert limits,* are limits on a parameter that have been empirically derived from measurements made on product produced in the manufacturing facility, and are used by the manufacturer to monitor a process for shifts or trends during routine manufacture. Product that does not meet its control limits for a parameter is said to be *out-of-expectation* (OOE) or *out-of-trend* (OOT). The specification limits for a quality attribute need not be the same as the control limits for that attribute, as the purposes and risks associated with each are different.

It is important to distinguish *characterization testing* from *conformance testing.* A significant level of physicochemical product characterization must be performed before establishing specification or control limits. Detailed product characterization may take several years of investigation. Some of these characterization tests will become conformance tests with specification limits, once it has been established that the test measures a property that is related to product quality. Primary among these are tests that may be associated with product safety and efficacy, while others may forecast performance throughout product shelf life. Other characterization tests will be eliminated or reserved for characterization after a process change.

Limits used at release may be different from those used throughout the shelf life of the product. *Release limits* on a quality attribute are internal or registered limits that forecast that a lot will be fit for use throughout its labeled shelf life. An *expiry limit* is a limit on the predicted or measured value of the quality attribute beyond which a lot is no longer fit for use.

Preclinical studies are performed in animals or in cell culture, and are undertaken to predict outcomes in the target clinical population. *Nonclinical studies* are performed to investigate the factors that affect product performance and quality. These include process and product optimization studies, assay development and validation studies, and process intermediate and final product stability studies. Some studies are performed to provide information that guide company business decisions, whereas other studies are used to help ensure quality and support regulatory requirements.

STAGES OF THE LIFECYCLE OF A PRODUCT

An evolutionary approach to specification setting should reflect the fact that at early stages of development, manufacturers have limited knowledge of the product and limited clinical experience. During late stage development, there is limited manufacturing information to develop meaningful monitoring tools. Therefore, a staged approach to establishing limits should be considered.

Early-Stage Development

Early-stage development involves predicting relevant quality attributes (and their parameters), methods, and acceptance criteria for the class of molecules based on preclinical characterization, industry experience, published scientific literature, and guidance from regulatory agencies. At early stages of development, selected quality attributes and corresponding limits (acceptance criteria) should be focused on well defined expectations related to product safety (e.g., DNA, *Limulus* amebocyte assay (LAL), and host cell proteins), and allow clinical experience to define other quality attributes such as product-related substances and impurities. The predicted specifications may be able to take advantage of the knowledge base of other well characterized products and prior research experience.

Specifications are ultimately used to protect the patient from receiving product that is not fit for use. The basis for defining *fit for use* derives from the preclinical and clinical development experience with drug product, which ultimately is tied to specifications in the product license application. Unless quality attributes can be linked to preclinical and clinical experience, there is no rational basis for establishing specifications. Thus, in early development, measurements of product quality should be made to reliably identify potential quality attributes of the product. The relationship between the level of a quality attribute (such as potency) and its clinical impact is best understood when the attribute is allowed to vary rather than be constrained by narrow limits. This information can then be used to determine which attributes forecast clinical outcomes, and to set limits that ultimately (i.e., during commercial manufacture) predict fitness for use.

Because of this, it is unreasonable to set restrictive specifications for quality attributes that are not directly linked to product safety. Early development data should be unrestricted and thereby scientifically informative. Fit-for-use specifications may be set from these data, and verified in late-stage development.

Late-Stage Development

In late-stage development, selected quality attributes should be based on a biochemical and biophysical understanding of the product that is linked to manufacturing experience and clinical relevance. The selection of analytical methods and corresponding acceptance criteria should be based on sound scientific judgment and an appropriate statistical analysis using knowledge coming from clinical, preclinical, and nonclinical development experiences.

Attributes that are not related to product quality may be either eliminated or reserved for characterization after a manufacturing process change. Such process changes are frequently associated with the preparation for commercialization. Attributes that are redundant with other quality attributes may be eliminated. In principle, the test with the greatest sensitivity and/or reliability should be reserved for conformance testing.

Early-Stage Manufacturing

Process performance attributes that are used to monitor consistency rather than fitness for use require adequate experience to reveal the process distribution. This involves a sufficient number of lots manufactured across a representative range of process conditions. Because this is not the primary objective of product development, specifications that are developed to monitor product

consistency require data acquired during full-scale manufacture, under normal operating conditions, over a range of changes in process parameters.

Continued Manufacturing

Limits related to process consistency may evolve with extended experience in manufacturing. Process control limits should reflect the current state of the process. Thus, if an improvement has been made that has no impact on quality attributes related to safety or efficacy, but results in a shift or change in the distribution of a consistency parameter, process monitoring limits should be amended to reflect the change.

COMPONENTS OF A BIOLOGICAL AND BIOTECHNOLOGY PRODUCT SPECIFICATION

As described in ICH Q6B,[1] specifications are the list of quality attributes, methods, and limits. However, for biological and biotechnology-derived products, some quality attributes may have several parameters. For example, purity of a monoclonal antibody (MAb) typically has three parameters related to its size, charge, and molecular integrity. Consequently, specifications for the purity of protein products have four components:

1. Quality attribute (e.g., purity)

2. Parameter (e.g., size, charge, molecular integrity)

3. Analytical method (e.g., size-exclusion chromatography [SEC], ion exchange chromatography, capillary electrophoresis–sodium dodecyl sulfate [CE-SDS])

4. Limit or acceptance criteria (e.g., main peak relative purity for SEC).

It is important to stress that protein products are not structurally homogeneous, such that a single peak on a chromatogram, electropherogram, or in a spectrum may not represent a single molecular entity (as is typically seen with small molecules). No single analytical method can define product purity; therefore, a combination of orthogonal analytical methods typically is used to properly describe a single quality attribute such as purity.

Another quality attribute that is unique to biological and biotechnology-derived products is potency. Potency reflects activity in a biologically relevant system, usually expressed as relative potency to a standard or specific activity. While there is scientific debate regarding the relevance of potency to clinical effectiveness, potency assays typically are considered a link to the mechanism of action of a biological or biotechnology-derived product, which potentially can bridge changes in biophysical characteristics to biological activity.

Specifications can be divided into two categories, product-specific specifications and compendial or regulatory specifications:

- Product-specific specifications are those for which components of quality attributes, methods, and limits are unique to the product (e.g., molecular weight by SEC, potency, charge distribution by ion exchange, pH, color).

- Compendial or regulatory specifications are those for which attributes and limits are well defined by regulatory agencies[2] (e.g., DNA, endotoxins, particles). For these

specifications, the application of an evolutionary approach will be limited.

Although the focus of most discussions about specifications is about acceptance criteria, a certain clarification about types of specifications, quality attributes, and methods would benefit the industry.

ICH guidelines specify quality attributes for DS and DP, acknowledging that in some cases in-process testing may be more appropriate than DS or DP specifications. Nevertheless, the guidelines specify desirable quality attributes for DS and DP, including the following:

- DS: appearance and description, identity, purity and impurities, potency, and quantity.
- DP: appearance and description, identity, purity and impurities, potency, quantity, general tests, and additional testing unique to the dosage form.

For the most part, the quality attributes for DS and DP are similar. Additional testing specified for DP is associated with changes related to the formulation, vials, or devices. At early stages of development (corresponding to Phase 1–2 clinical trails), many manufacturers do not use the final commercial formulation; instead, they may use a frozen liquid DS or other simple dosage form. Therefore, at this early stage of development, many tests performed on DS and DP may be redundant without adding value for patients or the manufacturer.

Another difference between conformance testing for DS and DP is the treatment of impurities. In testing the DS, the term *impurities* refers to product and process impurities, whereas in testing the DP, the focus of impurity testing is on degradation products. The purpose of testing for process-related impurities (e.g., DNA, host cell proteins, solvent and buffer components) may not change during drug development. Whether or not expectations regarding impurity testing are well defined in a given regulation, such testing should not be relaxed at any stage of development because impurities are directly related to patient safety. However, robust process validation that demonstrates the removal of impurities (e.g., adventitious agents) may alleviate the need for such stringency. The issue of product-related impurities and product-related substances may merit different considerations. At early stages of development, understanding the presence and chemical structure of product-related impurities may be limited, making a distinction between product-related impurities and product-related substances difficult. Frequently, we refer to them as isoforms, structural variants, or posttranslational modifications. Many of these "modifications" are well known to scientists, but their quantification and physiological significance sometimes remains elusive. In addition, existing literature does not provide unequivocal or uniform evidence about their physiological relevance.[3–4] This category includes several well known posttranslational modifications, such as methionine oxidation, deamidation of asparagine residues, and N- and O-glycosylation. Therefore, at the early stage of product development, specifications may not need to focus on product-related impurities. At the later stages, when the understanding of the product increases, and the clinical relevance of product-related impurities and substances can be elucidated, the specifications can be amended to include additional testing for product-related impurities and degradants.

Analytical Methods

Analytical methods associated with specifications define how a particular attribute will be tested. Therefore, any change in an analytical method may affect the numerical limits and statistical considerations applied in establishing this limit. Because of the continuous progression of analytical technologies, the industry and regulators will need to continuously develop strategies to address the issue of the difference between old and new methods. Modern, more efficient technologies will appear on the market, while old technologies (instruments and consumables) will no longer be supported by current vendors. For example, an evaluation of the history of separation methods suggests that separation technologies have doubled in capabilities in approximately 11 years.[5]

As analytical methods evolve over time, these new methods frequently provide additional information that was not previously available. In such cases, the relevance of this new information to specifications needs to be evaluated including attributes, methods, and limits.

A hypothetical example follows. At the early stage of product development, an anion-exchange chromatography method was developed to evaluate the charge distribution of a MAb. The chromatogram showed a single main peak and two minor peaks. Based on extensive product characterization and clinical experience, a specification was developed around the relative purity of the main peak, with an understanding that the main peak contains multiple components with the same net charge. The limit of minimum purity was set at 85.0%. At the time of commercialization, the ion-exchange column was discontinued by the vendor, and replaced by the drug manufacturer with a new monolithic ion-exchange column. As a result of this technological advancement, a component of the main peak resolved into two peaks, one of which is a separate small peak accounting for a reduction in relative purity of approximately 5%. In such a situation, adopting old limits for the new method would be inappropriate, and a statistical approach used to create limits for the old method may not be applicable in establishing limits for the new method. The peak resolved by the new method was fully characterized as an isoform containing oxidized methionine in the Fc portion of the antibody, with no effect on potency. In addition, it was demonstrated that the level of oxidation in most recent lots ranged from 4% to 5%. In such a case, the manufacturer should request a revision of the specifications for the main peak without an additional specification for oxidized methionine in the Fc portion. An alternative approach would be to sum up two peaks that were not resolved in the original method.

Chromatographic profiles for biopharmaceutical products present a special challenge. Even at the early stages of development, analytical methods are capable of resolving different isoforms. Understanding their structure–function relationships, however, may require several more years. Therefore, at early stages of development, this limited understanding of isoforms and post-translational modifications may lead scientists to establish specifications exclusively with respect to product purity. In such cases, the levels of product-related forms can be inferred from the relative area of the main peak. The fact that specifications are not designed around product impurities should not prevent the manufacturer from tracking individual peaks (likely containing multiple molecular entities) in another system different from

specifications. These data can be part of the characterization data collected during the course of development. The data could be very useful at later stages of development.

Precision and Significant Figures

The precision of analytical methods is linked to data reporting, whereas specifications limits are linked to method precision.[6–9] Therefore, it is very important to use consistent practices regarding the number of significant figures or decimal places reported by analytical methods that is consistent with the number of significant figures or decimal places in the specification limits (acceptance criteria).

The reporting interval (number of decimal places) should be derived from the standard uncertainty, which can be expressed in the form of standard deviation or coefficient of variation (relative std. dev). Published approaches should be evaluated.[7,9] The most commonly adopted is the recommendation from the American Society for Testing and Materials (ASTM), which proposes that the results of analytical measurements should be rounded to a decimal place corresponding to not less than 1/20 of the determined standard deviation.

In the biological and biotechnology industries, precision of methods frequently is assessed during qualification and confirmed during method validation.[5,10–11] Therefore, appropriate precision studies should be performed before specifications are established.

SUMMARY

The purpose of this paper, which has been developed by the Biologics and Biotechnology Working group on specifications of the Pharmaceutical Research and Manufacturers of America (PhRMA), is to provide guidance on a lifecycle approach to setting global specifications for biological and biotechnology-derived products. This Part 1 includes sections 1 to 3 of the paper, covering terminology, the stages of the lifecycle of a product, and components of a biological and biotechnology product specification. Parts 2 and 3 of this article will be published in the next two issues of *BioPharm International.* Those parts will include section 4, covering current issues related to the development of specifications; and section 5, which suggests an approach for developing and maintaining a total quality system.

Izydor Apostol, PhD, is scientific director, analytical and formulation sciences, at Amgen Inc., Thousand Oaks, CA; **Timothy Schofield** is senior director, nonclinical statistics, at Merck Research Laboratories, Merck & Co., West Point, PA, and the corresponding author, timothy_schofield@merck.com 215.652.6801; **Gerhard Koeller, PhD,** is vice president, quality and compliance biopharmaceuticals, at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; **Susan Powers, PhD,** is biotech quality technology leader, Wyeth Pharmaceuticals, Collegeville, PA; **Mary Stawicki** is associate director, regulatory affairs biopharm CMC, at GlaxoSmithKline, Collegeville, PA, and **Richard A. Wolfe, PhD,** is director and team leader, biopharma operations, at Pfizer Global Manufacturing, Chesterfield, MO.

REFERENCES

1. International Conference on Harmonization. Q6b, Specifications: Test procedures and acceptance criteria for biotechnological/biological products. Geneva, Switzerland; 1999.

2. Swarbrick J, Boylan JC. Encyclopedia of pharmaceutical technology. New York: NetLibrary, Inc.; 2001.

3. Koren E, Zuckerman LA, Mire-Sluis AR. Immune response to therapeutic proteins in human—clinical significance, assessment and prediction. Curr Pharm Biotechnol. 2002;3:349–360.

4. Graves DJ, Martin BL, Wang JH. Co- and post-translational modification of proteins. Chemical principles and biological effects New York: Oxford University Press; 1994.

5. Apostol I, Kelner D. Managing the analytical lifecycle for biotechnology products: A journey from method development to validation. BioProcess Int. 2008; in press.

6. Horwitz W, Albert R. A heuristic derivation of the Horwitz curve. Anal Chem. 1997;69: 789–790.

7. ASTM. Standard Practice for using significant digits in test data to determine conformance with specifications. In ASTM Designation: E 29–04 ed. 2005; p 1–5.

8. Holme DM, Peck H. Analytical Biochemistry. 3rd ed. Upper Saddle River, New Jersey: Prentice-Hall, Inc.; 1998, p 9–19.

9. Agut C, Segalini A, Bauer M, Boccardi G. Relationship between HPLC precision and number of significant figures when reporting impurities and when setting specifications, J Pharm Biomed Anal. 2006;41:442–448.

10. International Conference on Harmonization. Q2R1, Validation of analytical procedures. Geneva, Switzerland; 2005, p 1–13.

11. Ritter NM, Advant SJ, Hennessey J, Simmerman H, McEntire J, Mire-Sluis A, Joneckis C. What Is test method qualification? Proceedings of the WCBP CMC strategy forum, 24 July 2003. BioProcess Int. 2004;2,32–46.

Related Content:
Regulatory/GMP Compliance | Quality/GMPs | Quality Control/Quality Assurance | BioPharm International-06-01-2008

UK Approves Treatment for Sleep Onset Insomnia in Children and Adolescents

FDA User Fees Reauthorized

FDA Grants Fast Track Designation to Cue Biopharma

UK Approves Treatment for Sleep Onset Insomnia in Children and Adolescents

October 6, 2022
BioPharm International Editors

The UK's MHRA has approved Colonis' melatonin oral solution for sleep onset insomnia in children and adolescents with ADHD.

Colonis, a subsidiary company of the Clinigen Group, announced on Oct. 4, 2022 that the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) has approved its melatonin 1mg/mL oral solution for sleep onset insomnia in children and adolescents aged 6–17 years with attention-deficit hyperactivity disorder (ADHD).

According to a company press release, melatonin has the potential to decrease sleep latency and increase sleep efficiency in children with ADHD and chronic sleep onset insomnia. Children with ADHD are statistically more likely to have sleep onset insomnia than non-ADHD children. The prevalence of sleep onset insomnia in children with ADHD ranges from 25–50% and can affect their mood, attention, behavior, and school performance.

"We welcome the MHRA's approval for a condition that negatively affects the quality of life for children and adolescents diagnosed with ADHD and increases the burden for support networks," said Henno Welgemoed, director of medical affairs at Colonis, in the release. "This approval provides a valuable treatment option for children and adolescents suffering with ADHD and sleep onset insomnia, adding further breadth to Colonis' growing pediatric portfolio while supporting Clinigen Group's mission to deliver the right medicine to the right patient at the right time."

Source: Clinigen

Related Content:
Industry News | Regulatory Authority Actions | Quality/GMPs

FDA Grants Fast Track Designation to Cue Biopharma

Biologic Standards in the Pharmacopoeias: An Update

Advances in Real-Time Supply Chain Operation Technology Can Address Drug Product Security Challenges

FDA User Fees Reauthorized

October 5, 2022
Jill Wechsler

FDA keeps its user fees but fails to gain important reforms.

As expected, Congress reauthorized four key user fee programs last week, as part of a must-pass measure to fund the federal government for another two months. The Continuing Resolution (CR) signed on Sept. 30, 2022 averted a federal government shutdown by extending the Oct. 1, deadline for approving a federal spending plan for fiscal year 2023 to Dec. 16, 2022—after the mid-term elections in hopes that this will enable the legislators to reach a viable budget compromise.

The CR reauthorizes fees for drugs (Prescription Drug User Fee Amendments [PDUFA]), generic drugs (Generic Drug User Fee Amendments [GDUFA]), biosimilars (Biosimilar User Fee Amendments [BsUFA]), and medical devices (Medical Device User Fee Amendments [MDUFA]) for the next five years, 2023–2028. In confirming FDA's authority to collect fees from manufacturers, the

agency avoids having to notify thousands of fee-supported staffers of looming layoffs. That prospect already had eroded agency morale and undermined efforts to recruit and hire needed staffers, as FDA struggled for months to maintain and expand its professional workforce during the added hardships imposed by the pandemic and in a very competitive labor market.

Medical product user fees generate some $2 billion in agency revenues, approximately 40% of FDA's non-tobacco budget. While Congressional leaders on both sides of the aisle support this program to bolster key agency operations and innovations, the broader political debate over escalating government spending generated concerns about new fee-supported initiatives that extend the agency's authority.

Even so, FDA officials, manufacturers, and research advocates gave a loud sigh of relief following the Congressional action. Commissioner Robert Califf praised the user fee reauthorization measure, while thanking agency staffers for their diligence in engaging in this "prolonged, demanding and, at times, frustrating process." He noted that the bill avoids "a devastating impact" on FDA's ability to carry out its "independent and transparent review of medical products."

New initiatives

Califf added that FDA is committed to working with Congress to enact additional policy changes to benefit public health, but for now, is moving fast to implement multiple new fee-supported policies and programs. Similarly, Patrizia Cavazzoni, director of the Center for Drug Evaluation and Research (CDER), praised the new fee programs for supporting CDER's commitment to monitoring the safety of marketed products, protecting patients in clinical trials, and facilitating review of treatments for life-threatening diseases.

In an effort to make up for lost time in meeting tight deadlines for implementing new PDUFA-backed initiatives, FDA quickly posted a new webpage outlining criteria for manufacturers to participate in the new Split Real Time Application Review (STAR) program to accelerate patient access to critical therapies. The pilot aims to shorten the review time for efficacy supplements to approved drugs and biologics through earlier review of certain submissions before clinical study reports are final. FDA also provided information on a new Rare Disease Endpoint Advancement (RDEA) pilot to develop novel efficacy endpoints for critical treatments. Still to come are multiple new policies described in the PDUFA VII commitment letter.

Enhancements in GDUFA III aim to reduce the number of assessment cycles for generics, support the development and approval of complex generics, and help manufacturers resolve quality issues more quickly. First off the line are new draft guidance documents on assigning review goal dates based on a manufacturing facility's readiness for inspection and on early assessment of APIs to speed application review. There's new guidance on expediting development of "competitive" generic therapies and on policies for reviewing complex generic products. More information on GDUFA III is available at FDA.gov.

And for biosimilars, BsUFA III priorities involve expediting the review of certain supplements and launching a new regulatory science program to advance biosimilars and interchangeable products, already posted in a new FDA webpage outlining new pilots to improve the efficiency of biosimilar development and for interchangeable products. Further program revisions are listed out in the BsUFA commitment letter.

Moving forward

The “skinny” user fee reauthorization dropped multiple high-profile proposals for revising how FDA regulates *in vitro* diagnostics, dietary supplements, and cosmetics, as well as the agency’s accelerated drug approval program and the regulation of artificial intelligence medical devices. Advocates for developing critical new antibiotics back the PASTEUR Act to establish a new funding mechanism to support the development and proper utilization of drugs to fight resistant diseases. There is bi-partisan support for this “subscription” model for new cures, but its estimated cost of $11 billion over 10 years makes it a hard sell.

In past user fee reauthorization campaigns, a deadline to prevent fee expiration encouraged legislators to slip numerous pet proposals into this must-pass legislation. All parties recognized that this year would be much trickier, with a sharply divided Congress heading into mid-term elections and unwilling to agree on much in the policy arena. The short-term budget agreement avoids a government shutdown and funding crisis at FDA, but it dims prospects for enacting controversial or complex new measures.

About the author

Jill Wechsler is Washington editor for *BioPharm International*.

Related Content:
Industry News | Quality/GMPs | Regulatory Authority Actions | Regulatory Filings and Submissions

Biologic Standards in the Pharmacopoeias: An Update

Advances in Real-Time Supply Chain Operation Technology Can Address Drug Product Security Challenges

Advancing Global Collaboration for Drug Testing, Regulation, and Manufacturing

FDA Grants Fast Track Designation to Cue Biopharma

October 4, 2022

BioPharm International Editors

FDA has granted Fast Track designation for CUE-101, a treatment of recurrent/metastatic head and neck squamous cell carcinoma.

Cue Biopharma, a clinical-stage biopharmaceutical company focused on injectable biologics designed to selectively target tumor-specific T cells directly within a patient’s body, announced on Oct. 4, 2022 that FDA has granted Fast Track designation to CUE-101 for the treatment of patients with human papilloma virus (HPV16+) recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) as a monotherapy and in combination with KEYTRUDA (pembrolizumab).

Fast Track is a process designed to facilitate the development and expedite the review of drug candidates to treat serious conditions and fulfill an unmet medical need. Therapeutic candidates with Fast

Track designation may be eligible for accelerated approval and priority review if supported by clinical data.

CUE-101 is currently being evaluated in a Phase Ib trial as a monotherapy for the treatment of second line and beyond patients with HPV16+ R/M HNSCC and as a first-line treatment in a Phase I dose escalation and expansion trial in combination with pembrolizumab for the same patient population.

“We are very pleased to have received Fast Track designation from the FDA for CUE-101. This designation not only underscores the large unmet need for patients with R/M head and neck cancer who currently rely on available non-targeted therapies, but also highlights the potential of CUE-101 to provide a significant clinical benefit,” said Matteo Levisetti, senior vice-president, clinical development of Cue Biopharma, in a company press release. “To date in its Phase Ib clinical trials, CUE-101 has demonstrated a favorable tolerability profile and single-agent anti-tumor activity in monotherapy as well as encouraging anti-tumor clinical activity in combination with pembrolizumab, supporting the potential to improve overall survival for these patients. We look forward to providing periodic updates and remain committed to advancing the development of CUE-101 to provide patients with a potentially more effective and better tolerated treatment option. We anticipate initiating a registrational trial for CUE-101 monotherapy by mid-2023.”

Source: Cue Biopharma

Related Content:
Biopharma News | Industry News | Regulatory Authority Actions | Quality/GMPs

Advances in Real-Time Supply Chain Operation Technology Can Address Drug Product Security Challenges

Advancing Global Collaboration for Drug Testing, Regulation, and Manufacturing

Industry’s Best Secret