Benefit-Risk Considerations for Product Quality Assessments

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Natalia Comella at 301-796-6226.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2022
Pharmaceutical Quality/CMC

Benefit-Risk Considerations for Product Quality Assessments

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2022
Pharmaceutical Quality/CMC

TABLE OF CONTENTS

Benefit-Risk Considerations for Product Quality Assessments Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the benefit-risk principles applied by FDA when conducting product quality-related assessments of chemistry, manufacturing, and controls (CMC)[2] information submitted for FDA assessment as part of original new drug applications (NDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), original biologics license applications (BLAs) under section 351 of the Public Health Service Act (PHS Act), or supplements to such applications, in addition to other information (e.g., inspectional findings) available to FDA during its assessment.

This guidance discusses how FDA assesses risks, sources of uncertainty, and possible mitigation strategies for a product quality-related issue and how those considerations inform FDA's understanding of the potential effect on a product.[3] The product quality assessment determines whether an applicant's product development studies, manufacturing process, and control strategy will consistently result in a finished product of acceptable quality when manufactured at the facilities named in the application. When a regulatory decision regarding the approval of an NDA or BLA is made, FDA considers the overall benefit(s) and risk(s) identified for the product, including any residual risk related to unresolved product quality issues. This guidance also discusses how unresolved product quality issues may be addressed in the context of regulatory decision-making.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] FDA regulations refer to chemistry, manufacturing, and controls. The term *product quality* is used in this guidance to encompass chemistry, manufacturing, and controls as used in FDA implementing regulations. As used in this guidance, product quality applies to both drug substances and drug products.

[3] For the purposes of this guidance, all references to *drug*, *drug product*, and *product* refer to both human drugs and biological products unless otherwise specified.

This guidance is not intended to address the review by other disciplines or sections of a marketing application (e.g., clinical, nonclinical, biostatistics, pharmacology).

Sections II and III of this guidance focus on product quality assessment in the context of FDA's review of an NDA or BLA. Although not specifically addressed in sections II and III, product quality assessments are also done for abbreviated new drug applications (ANDAs).[4] However, the product quality assessment of an ANDA can be different to the extent that the ANDA relies on FDA's finding that the reference listed drug (RLD)[5] identified is safe and effective. As with NDAs and BLAs, an ANDA will not be approved if the applicant's product development studies, manufacturing process, and control strategy will not consistently result in a finished product of acceptable quality when manufactured at the facilities named in the application.[6] Section IV of this guidance, which discusses how unresolved product quality issues may be handled in the context of regulatory decision-making, specifically addresses how FDA may handle such issues as part of its review of an ANDA.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Product Quality-Related Statutory and Regulatory Requirements

Before approving an application, FDA must determine whether the drug product is both safe and effective for use under the conditions prescribed, according to the product labeling and the instructions it contains.[7] Section 505(b) and (d) of the FD&C Act identify the key components required for approval of a new drug under an NDA. Among them are product quality-related requirements to demonstrate the applicant has developed a drug product and drug substance, manufacturing process, and control strategy that will consistently result in a drug product of

[4] An ANDA is an application submitted and approved under section 505(j) of the FD&C Act for a drug product that is a duplicate of a previously approved drug product. An ANDA may not be submitted if clinical investigations are necessary to establish the safety or effectiveness of the proposed drug product. See the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] The RLD "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 341.3(b)).

[6] See 21 U.S.C. 355(b)(1)(B)-(F), (j)(2)(A)(vi).

[7] See section 505(b)(1) and (d) of the FD&C Act (21 U.S.C. 355(b)(1) and (d)).

acceptable quality to ensure it is both safe and effective for use.[8] Specifically, section 505(b)(1)(C) and (D) of the FD&C Act requires a new drug applicant to submit a full statement of the composition of such drug as well as a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of such drug; this information informs the Agency's assessment of whether the applicant can ensure the identity, strength, quality, and purity of the drug substance and drug product. Regulations further describe these requirements.[9]

Likewise, BLAs have similar considerations with respect to product quality-related requirements. Under section 351(a)(2)(C) of the PHS Act,[10] FDA will approve a BLA based on a demonstration that the biological product is safe, pure, and potent and that the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to ensure the biological product continues to be safe, pure, and potent.

B. Evidence Supporting Product Quality-Related Requirements

Applicants must submit data and supporting information to demonstrate that they can ensure and preserve a drug product's identity, strength, quality, and purity for NDAs[11] or a biological product's safety, purity, and potency for BLAs.[12] The information available to FDA at the time of the assessment, namely the relevant sections of the marketing application and other information (e.g., an inspection report) about the facilities named in the application, are assessed during the product quality assessment of the application.

FDA will approve an NDA, BLA, or supplement to an NDA or BLA after it determines that the product meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling.[13] Although the statutory standards apply to all drugs, the diversity of drugs and the wide range of processes used to manufacture those drugs demand flexibility in applying the standards. Thus, FDA exercises its scientific judgment to determine the type and quantity of

[8] See section 505(d) of the FD&C Act (21 U.S.C. 355(d)); 21 CFR 314.50(d)(1).

[9] For example, 21 CFR parts 210 and 211, 21 CFR 314.50(d)(1).

[10] See 42 U.S.C. 262(a)(2)(C); see also 21 CFR 601.2.

[11] Section 505(b)(1)(D) of the FD&C Act (21 U.S.C. 355(b)(1)(D)) requires an applicant to submit a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug. See also 21 CFR 314.50(d)(1). FDA must refuse to approve an NDA if "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity" (section 505(d)(3) of the FD&C Act (21 U.S.C. 355(d)(3))). See also 21 CFR 314.125(b)(1).

[12] Section 351(a)(2)(C) of the PHS Act (42 U.S.C. 262(a)(2)(C)) states that FDA will approve a BLA based on a demonstration that the biological product is safe, pure, and potent and that the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe, pure, and potent.

[13] See 21 CFR 314.105(c) and 21 CFR 601.20.

data and information an applicant is required to provide to enable FDA to make a determination whether a product meets the statutory standards for approval.[14]

Product quality assessments consider every aspect of a drug's components and formulation, manufacturing, and control strategy to determine the drug's overall quality. For example, the assessment for a small molecule drug product examines the method of synthesis and isolation of the drug substance to ensure purity and control over levels of any impurities and degradation products including mutagenic impurities; the stringency of validation and suitability of the analytical procedures; and the processing and related process controls to ensure that they are designed and controlled to ensure consistent product quality, including, when appropriate, ensuring product sterility. For biological products, a product quality assessment may examine the expression system used, the quality of the production cell banks, the manufacturing process, control of any microbial contaminants, and potential process-related impurities as well as product-related variants. The appropriateness of end product or release testing is evaluated; microbial control (for drug substance) and, as applicable, sterility assurance (for a drug product) are also assessed.

C. The Product Quality Assessment and How It Contributes to FDA's Overall Premarketing Benefit-Risk Assessment

Using the information available to the Agency, a product quality assessment identifies any product quality issues and evaluates the risk of harm posed by the issues, along with the uncertainties associated with those issues and risks. Typical sources of product quality-related uncertainty may include, but are not limited to, gaps in current knowledge, such as projecting performance at the end of shelf life based on extrapolation given the limited stability data provided for small molecule drug products. Other illustrative examples for potential sources of uncertainty for small molecule drug products include new technologies or dosage forms, potential frequency of an observed issue, and limited commercial manufacturing experience when the manufacturing process might behave differently on scale up. Additionally, uncertainty could come from gaps in process understanding, sources of variability, and the probability of detection of problems.[15] Many of the principles and concepts noted in the International Council for Harmonisation (ICH) guidance for industry *Q9 Quality Risk Management* (June 2006) are generally applicable during FDA's product quality assessment and may help determine whether the product meets the requirements for the identity, strength, quality, and purity for a drug, or safety, purity, and potency for a biological product.

When conducting a product quality assessment, the Agency identifies potential risks to product quality associated with the formulation, manufacturing process, and packaging components. The Agency analyzes the potential effect of the risk on safety and/or effectiveness and assesses the proposed control strategy for mitigating those risks. The regulations allow for the assessment to be iterative, with the Agency engaging applicants to better understand the issues or areas of uncertainty, while at the same time, exploring possible options to mitigate the issue or

[14] See 21 CFR 314.105(c).

[15] See the International Council for Harmonisation (ICH) guidance for industry *Q9 Quality Risk Management* (June 2006).

uncertainty.[16] How FDA views the identified product quality issues depends on whether the control strategy can adequately address the risk. When there remains an unresolved product quality issue, the Agency will factor into its decision-making process any residual risk posed by the product quality issue. How FDA addresses the outstanding issue(s) is informed by relevant published guidance documents but may also depend on certain application-specific parameters (see section IV., Product Quality Assessment Conclusions and Handling of Unresolved Quality Issues).

Product quality assessors may also use the interdisciplinary team's understanding of the therapeutic context and the assessment of benefit during the product quality assessment. A greater understanding of the patient population and disease or condition helps to frame the importance of a product within the overall therapeutic armamentarium that is available to patients and health care providers and may facilitate an evaluation of the potential significance of risks identified during the assessment to inform FDA's recommendation regarding the risk mitigation or reduction.

When determining whether a drug or biological product meets the standard for approval, FDA conducts an overall benefit-risk assessment that "takes into account the extensive evidence of safety and effectiveness submitted by a sponsor . . . as well as many other factors affecting the benefit-risk assessment."[17] Benefit-risk assessments are the foundation for FDA's regulatory evaluation of human drugs and biological products. Benefit-risk assessment in the FDA regulatory context involves making a judgment regarding whether the benefits (with their uncertainties) of the product outweigh the potential risks (with their uncertainties and approaches to managing risks) under the conditions of use defined in labeling.

[16] The regulations under 21 CFR 314.102 describe communications between FDA and applicants. The regulation states, "FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process" (21 CFR 314.102(a)). FDA's regulation at 21 CFR 314.102(b) further states:

> FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application or abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or abbreviated application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed.

[17] See "Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA V Implementation Plan - February 2013, Fiscal Years 2013-2017," p. 1 and pp. 5–7, available at https://www.fda.gov/media/84831/download. See also "Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA VI Implementation Plan (FY 2018-2022)," pp. 3–4, available at https://www.fda.gov/media/112570/download.

FDA's vehicle for conducting these assessments is the Benefit-Risk Framework.[18] To inform the process, FDA conducts an interdisciplinary assessment in which each included discipline (such as clinical, product quality, nonclinical, pharmacology, biostatistics) assesses the relevant sections of the marketing application and provides key inputs into the overall Benefit-Risk Framework for Human Drug Review; the conclusions of the product quality assessment are considered in the Benefit-Risk Framework if there are product quality issues that pose risks. When a regulatory decision regarding approval or licensure is made, FDA considers the overall risks, including those related to unresolved product quality issues, in the context of the overall benefits to determine whether the statutory requirements have been met.

III. APPLIED PRINCIPLES FOR PRODUCT QUALITY ASSESSMENTS

FDA considers the following guiding principles during product quality assessments of marketing applications.

A. The Interrelationship Among Therapeutic Context, Potential Benefits, and Product Quality-Related Risk Considerations

The determination of a drug's overall clinical benefit(s) is outside the scope of the product quality assessment and is not addressed in this guidance.[19] However, as previously mentioned, an understanding of the therapeutic context and the clinical benefit may inform the product quality assessment and its conclusions.

During the product quality assessment, assessors may use the interdisciplinary team's understanding of the therapeutic context and the assessment of benefit to:

- Gain a greater understanding of the patient population and disease for which the product will be used
- Identify whether the drug addresses an unmet medical need
- Identify potential sources of product quality risk that, if unmitigated, could result in a risk to the patient

A greater understanding of the patient population, disease or condition, and whether there is unmet medical need helps to frame for the product quality assessor and team the importance of the product within the overall therapeutic armamentarium that is available to patients and health

[18] For more information regarding the Benefit-Risk Framework, see the draft guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (September 2021) (when final, this guidance will represent the FDA's current thinking on this topic). This draft guidance was developed in accordance with the PDUFA VI commitment goals letter titled "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022," section I.J.2., available at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-fiscal-years-2018-2022.

[19] See the draft guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products*.

care providers and may provide context used to evaluate the potential significance of risks identified during the assessment to inform FDA's recommendation regarding the risk mitigation or reduction. Some sources of product quality risk will be independent of the therapeutic context (e.g., sterility failure). However, there are instances where the sources of product quality risk relate directly to the therapeutic context (e.g., Size 00 capsules used for a therapy intended to treat young pediatric patients). Assessment teams use the therapeutic context to identify additional potential sources of product quality risk that arise from who would use the product or how it is intended to be used.

Although adverse events typically result from the pharmacological activity of a product, failure of a product to perform as intended due to product quality defects may also pose a risk to patients. One example of a risk caused by potential product quality defects is failure of the drug's release mechanism (e.g., dose dumping from modified-release products). Another example is a solid oral dosage form that is too large in size for the intended use population, resulting in a choking hazard. As the efficacy and safety profile becomes better understood by FDA, identified benefits (i.e., new drug without a known side effect or a new drug for a medical condition without any treatment options) may inform how a product quality issue is evaluated and addressed during the product quality assessment.

Section IV.A., Quality Determination, discusses how the benefits provided by the product and information relating to currently available treatment options could inform the product quality assessment.

B. Assessment of Risks Posed by a Product Quality Issue or Set of Issues

Although each application will contain unique information on CMC strategies, FDA routinely applies the following principles when evaluating quality issues during its assessment.[20]

- **Risk-based considerations related to therapeutic context.** As noted in section III.A., The Interrelationship Among Therapeutic Context, Potential Benefits, and Product Quality-Related Risk Considerations, understanding the therapeutic context and benefit can inform how an identified issue is evaluated and addressed during the product quality assessment. The assessment considers relevant characteristics of the target population and whether certain product quality attributes are intended to address specific unmet needs such as alternative dosage forms and/or delivery systems that may ease administration of the drug, provide a targeted drug delivery (e.g., a drug product with antibody drug conjugates technology relative to a drug without it), or provide continuous delivery over the course of treatment. Other clinical issues, such as use in healthy individuals (e.g., birth control), the duration of use, and use in vulnerable populations (e.g., pediatric population and geriatric patients), are considered as well.

  The evaluation of risk is informed by the combination of these considerations. For example, if the same impurity is found in multiple drugs at similar levels, but the therapeutic context differs for each application (e.g., chronic use for pediatric population

[20] The list of principles is not intended to be exhaustive given the diverse and unique product quality attributes associated with each drug or biological product.

versus acute use in adults), the Agency may come to different conclusions with respect to whether the application should be approved, depending on the vulnerability of the patient population, condition treated, and dosing regimen (e.g., length and frequency of exposure). To give another example, the risk associated with imprecise dosing can depend on whether the drug has a narrow therapeutic index, which would mean potential over or under dosing a patient, or if the dose of the drug is saturating its intended target, which would mean that a certain level of variation could occur without affecting the drug's safety or effectiveness. The level of risk associated with the product quality issue is directly linked to the potential effect on the target patient population.

- **Extent of impact on safety and/or effectiveness.** In all cases, drug products should be designed to meet the needs of the intended patient population and to deliver consistently the intended product performance.[21] The quality target product profile forms the basis of design for the development of the product. It is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. Although all product quality issues are evaluated for their potential likelihood of harm, not all product quality issues pose the same level of risk to the intended product performance and patient safety. Being unable to ensure a drug product's intended product performance would raise concerns about the safety and/or effectiveness of a drug product for the patient population. For example, a manufacturing process and/or container closure system that cannot ensure the sterility of a parenteral product will raise a concern about the safety of the drug product. In other instances, an identified issue, such as inconsistent dosing of the product, may raise concerns relating to the effectiveness or safety, or both, of the product.

- **Totality of product quality information.** When evaluating product quality, the Agency considers the totality of information available and relevant to the product during the assessment. Most of the information is provided in an applicant's marketing application. However, the Agency may examine other sources of information associated with the drug development program, such as information from the product's investigational new drug application that is not contained in the marketing application or any relevant communications with the sponsor before submission of the marketing application. Other relevant information includes, but is not limited to, the effectiveness of the pharmaceutical quality system to ensure consistent product quality through robust monitoring and control systems,[22] clinical experience during pivotal trials, scientific literature, and/or the Agency's knowledge of a given issue or class of drugs.

- **Inspectional findings.** FDA uses a risk-based approach to determine whether a preapproval or prelicensure inspection is needed using information provided in the application and information FDA may have regarding the facilities named in the

[21] See the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (2009). Pharmaceutical development should include and define the quality target product profile as it relates to quality, safety, and efficacy, considering, for example, the route of administration, dosage form, bioavailability, strength, and stability.

[22] See the ICH guidance for industry *Q10 Pharmaceutical Quality System* (2009).

application. The Agency may also use information from a previous surveillance inspection to inform a decision on the need for a preapproval or a prelicensure inspection or in lieu of such an inspection. A credible surveillance inspection may have been performed by FDA or by a national regulatory authority found capable under section 809 of the FD&C Act (21 U.S.C. 384e).

Preapproval inspections for NDAs verify readiness for commercial manufacturing, conformance to the application, and data and information provided in the application. Prelicensure inspections for BLAs are intended to verify that: (1) the facilities continue to comply with the standards set and described in the BLA for the product and process; (2) the facility adheres to current good manufacturing practice requirements; and (3) the information and data regarding the product and the manufacturing process support what is described in the application. The inspectional findings will determine if the proposed manufacturing facilities listed in the application meet those criteria or if there are outstanding manufacturing risks needing to be addressed to support approval.

When manufacturing or quality issues requiring adjustments to the control strategy are identified during an inspection, the nature and magnitude of the observed issues, and the mitigation strategies available to address those issues, inform the level of risk posed by the drug.

- **Other considerations that could affect the product quality assessment.** Each marketing application undergoes the same type of assessment during the decision-making process regardless of the product, using the principles noted above. There may be additional considerations regarding unique aspects of a drug's development or advancements in pharmaceutical science. FDA may need additional or new information (such as additional testing for nitrosamine contaminants in drugs[23] found at risk for their presence) to better understand potential risks previously not known or considered. These considerations may raise additional or new product quality issues and concerns. For example, a novel combination of a drug or biological product with another medical product, such as a medical device, or the introduction of a novel technology in the manufacturing process or analytical testing methodology could introduce additional complexity to the decision-making process by adding new risks and uncertainties relating to product quality. Other circumstances, such as development of or revisions to applicable compendial standards, also could affect the product quality assessment.

- **Possible mitigation strategies.** A key consideration in assessing any observed or potential risks associated with product quality issues identified is an applicant's ability to mitigate or reduce the risk associated with an identified product quality issue. Some product quality issues may be easier to address (e.g., confirmation of water vapor transmission rate for a new blister lidding material or whether a tablet can be split easily and consistently as directed in labeling). Identification of a possible mitigation strategy(ies) and the applicant's ability to implement that strategy(ies) to address the product quality issue are evaluated during the assessment for acceptability. Any

[23] See the guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (February 2021).

mitigation strategy that introduces a new product quality issue or exacerbates other already identified product quality issues may further confound the benefit-risk profile and/or result in an unsatisfactory resolution of the issue.

As noted earlier, this list is not a comprehensive list of considerations given the ever-evolving advancement of pharmaceutical science and unique considerations that arise during a particular product quality assessment. These considerations, when viewed together, inform the product quality assessment as to whether the applicant's development program has adequately addressed the elements supporting the intended product performance.[24] These considerations set up a framework by which FDA considers product quality issues in light of the benefit(s) and therapeutic context, thereby informing FDA's assessment of the overall quality of the drug and the robustness of an applicant's product quality system to produce the product with the intended product performance.

IV. PRODUCT QUALITY ASSESSMENT CONCLUSIONS AND HANDLING OF UNRESOLVED QUALITY ISSUES

A. Quality Determination

A product quality assessment ultimately results in a determination about the quality of the drug and whether the proposed drug meets the regulatory requirements for identity, strength, quality, and purity for NDAs or safety, purity, and potency for BLAs. This determination reflects FDA's assessment of whether an applicant has developed a product, manufacturing process, and control strategy that will consistently result in the quality attributes appropriate to meet the intended product performance throughout the shelf-life of the product. At the end of the assessment, the product quality assessment team provides its recommendation to approve or not approve a marketing application from the product quality perspective.

B. Unresolved Quality Issues

Under most circumstances, when unresolved quality issues remain, the Agency will not approve the application. However, in rare circumstances, an application may meet the standard for approval despite the presence of certain unresolved quality issues (as determined by the Agency). In such a case, the residual risk posed by the unresolved quality issue may be outweighed by the benefits of the product and of having the product on the market more quickly. In situations like this, the Agency may allow certain information to be submitted postapproval. These circumstances include:

- When the Agency determines it is not feasible for the product quality issue to be resolved before approval AND it can be addressed postapproval without an unacceptable level of risk. One example could entail providing postapproval confirmatory photostability data to address a change in film-coat composition that affects shading of film-coat color.

[24] See ICH Q8(R2).

- When the residual risk, in the context of the overall benefit of the drug product, is found to be acceptable to allow certain confirmatory information to be provided in an agreed-upon postapproval time frame. This could be the case when there is an unmet medical need, such as a serious disease or condition for which there is no available therapy. An unmet medical need may also exist where there are available therapeutic options but an additional clinically important benefit (such as superiority over current treatment options or comparable efficacy with a more favorable safety profile) has been observed. In these instances, the overall benefits observed (with the associated uncertainties) would need to outweigh the overall risks, including the residual risk, and this would be considered on a case-by-case basis; the more significant the residual risk the greater the benefit would need to be to outweigh that risk.

In such cases, FDA may use a quality postmarketing agreement (QPA) for a product quality issue.[25,26] A QPA is not a substitute for an applicant satisfying statutory and regulatory requirements for approval or licensure and should not be part of an applicant's planned development program. A QPA is an agreement, between FDA and the applicant, specifying the supporting data or information to be provided within a certain time frame postapproval. In such cases, the Agency will determine whether a QPA is appropriate as it concludes the product quality assessment. The data or information should be submitted postapproval within an agreed-upon, defined time period. The applicant should submit this data or information in the agreed-upon reporting mechanism and provide a status update in an annual report until the agreement has been fulfilled.[27]

C. ANDAs

A drug product approved in an ANDA relies on FDA's finding that the RLD identified in the ANDA is safe and effective, and therefore, relies on FDA's determination that the RLD provides benefits that outweigh its known and potential risks. This reliance is premised on the generic drug product having the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD, as well as

[25] Historically, QPAs have been referred to as CMC postmarketing commitments or CMC postmarketing agreements; the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) refers to them as postapproval CMC commitments. When this *Benefit-Risk Considerations for Product Quality Assessments* guidance is finalized and implemented, FDA will refer to CMC postmarketing commitments as QPAs. These QPAs differ from postmarketing requirements (PMRs) imposed under section 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)(3)), which are required studies and clinical trials that relate to risks of serious adverse drug experiences. They also differ from postmarketing commitments relating to clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that are subject to the statutory reporting requirement of section 506B of the FD&C Act (21 U.S.C. 356b); 21 CFR 314.81(b)(2)(vii). CMC postmarketing commitments are subject to a separate reporting requirement (21 CFR 314.81(b)(2)(viii)).

[26] In rare instances, FDA may require a PMR that relates to a product quality issue if the issue poses a risk of a serious adverse drug experience. See sections 505(o)(2)(C) and (3) and 505-1(b) of the FD&C Act.

[27] The regulations under 21 CFR 314.81(b)(2)(viii) require submission in an annual report of the status of any postmarketing study not included under 21 CFR 314.81(b)(2)(vii) that is being performed by or on behalf of an applicant. This includes any CMC studies that the applicant has entered into an agreement with FDA to conduct as well as all product stability studies.

demonstrating that the generic drug product is bioequivalent to the RLD.[28] FDA will not approve an ANDA if there is insufficient evidence of the foregoing or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to ensure and preserve the drug's identity, strength, quality, and purity.[29] Drug products that are approved in ANDAs are generally considered by FDA to be therapeutically equivalent to their RLD.[30] Products classified as therapeutically equivalent can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.

Given the Agency's knowledge and experience with the RLD at the time an ANDA is received, many of the considerations discussed in this guidance for new drug and biological product assessments generally are not applicable to the assessment of a generic drug product, including the use of QPAs. However, in rare circumstances, FDA may determine that a QPA may be appropriate in the context of a generic drug that will address an urgent clinical need (e.g., a public health emergency or pervasive drug shortage). The decision that a QPA would be appropriate for a particular ANDA would likely consider the type and extent of information that will be expected postapproval to resolve the issue and potential effect on similarly situated ANDAs. A QPA does not relieve a generic drug applicant from satisfying all the statutory and regulatory requirements for approval of an ANDA, does not correct a deficient ANDA, and should not be part of the applicant's planned development program.

[28] See sections 505(j)(2)(A), 505(j)(2)(A)(iv), 505(j)(4), and 505(j)(4)(F) of the FD&C Act and 21 CFR 314.94, 21 CFR 314.127, and 21 CFR 320.21(b).

[29] See section 505(d)(3) of the FD&C Act and 21 CFR 314.127(a)(1).

[30] Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. See 21 CFR 314.3; see also FDA's Approved Drug Products with Therapeutic Equivalents (the Orange Book), preface to the 41st edition, at page vii.