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US FDA Cracks The Door Open To Resolving Quality Issues After Approval

by Bowman Cox

Draft guidance explains how agency intends to consider therapeutic context in benefit-risk framework to, in rare cases, set aside CMC issues for later resolution under "quality postmarketing agreements."

The US Food and Drug Administration has characterized just how much it is cracking the door open for approval of drugs and biologics prior to resolving concerns about their quality by using what it now calls “quality postmarketing agreements.”

The FDA still will not approve applications when there are still unresolved quality issues “under most circumstances,” the agency says in 9 May *draft guidance*.

However, in what the agency describes as “rare circumstances” when it determines that the product’s benefits outweigh the residual risks, it may allow postapproval quality submittals.

For example, there might be a product quality issue that could not feasibly be resolved prior to approval and yet would pose little risk if handled postapproval, such as a photostability issue that might shade the film-coat color.

Or there may be a product that serves an unmet medical need or is so much better than anything on the market that some residual quality-related risk would be more palatable, the FDA said, adding that “the more significant the residual risk, the greater the benefit would need to be to outweigh that risk.”

The FDA said there also are “rare circumstances” where it would allow QPAs for generic drugs such as when there is a public health emergency or a pervasive drug shortage.

The agency said it would decide case-by-case on QPAs for abbreviated new drug applications based on "the type and extent of information that will be expected postapproval to resolve the issue and potential effect on similarly situated ANDAs."

CMC Commitments By Another Name

The FDA used to call QPAs chemistry, manufacturing and controls postmarketing commitments or CMC postmarketing agreements, the agency explained in a footnote, adding that the International Council on Harmonisation Q12 postapproval changes guideline calls them postapproval CMC commitments.

The new wording helps distinguish the quality-related commitments from those that are related to safety and efficacy: the postmarketing requirements or PMRs for studies and clinical trials required to assess risks of serious adverse drug experiences and other postmarketing commitments related to safety, efficacy, pharmacology or toxicology.

Where Quality Fits In Benefit-Risk Framework

The draft guidance outlines the FDA's approach to informing product quality assessments with the therapeutic context and clinical benefit, referencing a broader benefit-risk framework the agency had outlined in September 2021 draft guidance. (Also see "*Beyond Individual Patients: FDA Emphasizes Public Health Role In Certain Benefit-Risk Decisions*" - Pink Sheet, 30 Sep, 2021.)

The agency drafted that guidance to meet a commitment it made to industry in the Prescription Drug User Fee Act *commitment letter* for fiscal years 2018-2022.

The agency agreed in that letter to further its use of structure benefit-risk assessment, including its incorporation of the "patient's voice" in drug development and decisionmaking.

More Therapeutic Context

Understanding more about the patient population, the disease or condition and any unmet medical need "help 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 care providers."

This in turn could help assessors address quality risks differently depending on the circumstances.

Some quality issues might be less concerning for an antibody-drug conjugate if it sharply reduces side effects compared to existing options for cancer patients.

Other therapeutic factors could make a difference in the quality assessment: whether the product

is for use in healthy or vulnerable populations, whether it's for chronic or acute conditions, whether it's for pediatric or geriatric patients.

Similarly, the potential for imprecise dosing would be a bigger risk for drugs that have narrow therapeutic indexes.

Answering Increasingly Challenging Quality Questions

The draft guidance follows a series of developments that have changed perspectives on drug approval processes and the role of quality assessment.

Accelerated review for breakthrough therapies has put growing pressure in recent years on the CMC development timeline, often putting it on the critical path for approval, and leading industry to pressure the FDA for ways to complete the work postapproval.

The advent of autologous chimeric antigen receptor T-cell therapies in 2017 added to the pressure, given their extraordinary efficacy and new quality challenges.

The further acceleration required for COVID-19 vaccines and therapeutics, the supply surges for generic medicines required to treat hospitalized COVID-19 patients, and the related global supply chain disruptions all added fuel to the challenge of balancing needs for safety, efficacy, quality and availability.

As pressures on CMC review increased, so too have the share of applications derailed by CMC-driven complete response letters.

More Guidance Planned

The FDA has committed to taking more steps on benefit-risk assessment in the *PDUFA letter* for fiscal years 2023-2027.

The agency said it will issue a request for information before July 2023 on methodological issues like submitting and evaluating patient experience data in the context of benefit-risk assessment and follow up with workshops on the issues raised.

The agency will also work on understanding "how patient preference informs meaningful benefit or benefit-risk tradeoffs in therapeutic areas."

The agency plans to publish draft guidance in FY 2026 on supporting regulatory decision making with patient preference information.

The FDA notes as well in that letter that it already has been training reviewers in its centers for drugs and biologics on using the structured benefit-risk framework in the regulatory review of

marketing applications.