FDA Regulatory and Compliance Monthly Recap

MARCH 2019

KEY FINDINGS

NCI Director Ned Sharpless to serve as acting FDA commissioner as Gottlieb steps down

Scott Gottlieb is stepping down after two years serving as the head of the Food and Drug Administration (FDA), to be replaced on an interim basis by Norman "Ned" Sharpless. At this point, it's not clear whether Sharpless will assume the position on a permanent basis.

FDA Commissioner Scott Gottlieb says he is stepping down after two years in the position, despite initial expectations that he would stay with the agency. His resignation letter to Department of Health & Human Services Secretary Alex Azar provided no indications as to the reasons for his departure. In his stead, Ned Sharpless, director of the National Cancer Institute (NCI), will assume the role of acting commissioner. Sharpless assumed the role of NCI director in 2017 and prior to that served as director of the University of North Carolina Lineberger Comprehensive Cancer Center. He has also cofounded two biotech companies, G1 Therapeutics and HealthSpan Diagnostics. Serving as acting commissioner, Sharpless will be responsible for the ongoing search for a permanent commissioner and the subsequent nomination proceedings, which can be a drawn-out process.

Under Gottlieb's tenure, the FDA heightened its focus on drug competition and supported the Federal Trade Commission's (FTC) effort to address anti-competitive practices—a focus an FTC spokesperson says will continue. Gottlieb was also focused on innovation in drug development, modernizing the regulatory framework and addressing drug pricing. Sharpless has worked with the agency in the past as part of strategic partnerships between the NCI and FDA on issues such as tissue sample mislabeling and as part of the Interagency Oncology Task Force fellowship program. In his recent work as NCI director, Sharpless has focused on extending the eligibility criteria for institute-sponsored clinical studies to facilitate patient recruitment and accelerate R&D. He has also

focused on developing a scientific workforce at the NCI and using big data to better inform research.

It's unclear at this stage whether Sharpless will stay on as permanent commissioner, though Gottlieb has reportedly recommended that Sharpless be officially named to the position.

OPDP issues untitled letter to Phoenix Molecular Imaging Center over director's blog on investigational diagnostic agent

The untitled letter takes issue with a blog suggesting in a promotional context that an unapproved investigational drug is safe and effective for the intended use for which it's being tested. Although the blog states that the drug is available under an expanded access program, it doesn't describe its status as an investigational drug.

In its first enforcement action of 2019, the Office of Prescription Drug Promotion (OPDP) sent an untitled letter to Phoenix Molecular Imaging Center over a blog post written by Medical Director Dr. Fabio Almeida that, in a promotional manner, makes conclusory representations about the safety and efficacy of the investigational new drug Sodium Acetate C-11 (11C-Acetate), which has not been approved by the Food and Drug Administration.

The OPDP determined that 11C-Acetate is misbranded, as it's described as a useful PET scan agent for diagnosing recurrent prostate cancer, a use for which adequate directions for lay use cannot be written because it requires the oversight of a physician. In order to qualify for an exemption from the adequate directions for use requirements, a sponsor or investigator cannot make claims of efficacy or safety in a promotional context. The OPDP found, however, that the blog contains such claims, including claims comparing the investigational drug with approved products for PET imaging.

Specifically, the letter takes issue with claims suggesting both 11C-Choline and 11C-Acetate are "useful for detecting recurrent disease" and suggesting there are "no clear clinical differences" between the agents. It also takes issue with claims citing data to "explain the apparent lower performance of [Axumin (fluciclovine F 18)] compared to 11C-Acetate and Choline," and indicating that "Axumin … does not appear to perform nearly as well as Acetate or Choline." The letter also raises concerns about the blog making efficacy claims that have not been established, including a claim that the investigational drug is "a valuable and accurate tool" that provides "a better understanding of the location and extent of local recurrences and distant disease." These claims suggest not only that the unapproved investigational agent is safe and effective, but also that it is superior to approved therapies, creating a misleading impression of its usefulness and regulatory status.

The letter points out that while the blog includes a statement indicating that 11C-Acetate "is available under expanded access clinical trials at multiple institutions," it fails to describe the investigational nature of the product, doesn't disclose its status as an unapproved treatment, and doesn't dispel the impression that it's safe and effective. The OPDP calls on Phoenix Molecular Imaging Center to provide a list of promotional materials for the investigational drug that contain similar statements and to outline a plan for suspending the use of such violative material.

FDA issues draft guidance on risk-based monitoring, finalizes guidance on enrichment strategies amid efforts to modernize clinical trials

The guidance documents describe enrichment strategies industry can adopt in clinical trials to demonstrate the effectiveness of drugs and biologics and outline risk-based monitoring practices that can be used in place of traditional on-site monitoring. They reflect the Food and Drug Administration's (FDA) ongoing efforts to modernize clinical trials to support novel opportunities for precision medicine.

The FDA published two guidance documents amid its ongoing efforts to modernize clinical trials and establish a regulatory framework for precision medicine. FDA Commissioner Scott Gottlieb says the guidances are part of the agency's efforts to ease some of the cost and resource barriers of the traditional clinical research enterprise to speed up product development. He says the FDA has worked with stakeholders such as the Clinical Trial Transformation Initiative to explore innovative trial designs and the role of decentralized trials and mobile technologies, but continues to see reluctance from industry to adopt such approaches. Amid such hesitance from industry, Gottlieb says, "New research paradigms are needed to break down barriers between real-world data and clinical research, so that evidence can be shared rapidly to improve both domains across a learning health care system."

The final guidance discusses the use of enrichment strategies, which involve using a patient characteristic to select a study population in clinical studies designed to demonstrate the effectiveness of a drug or biologic. While the guidance is specific to trials testing efficacy, particularly randomized controlled trials, it notes that similar strategies can be leveraged in safety assessments and other designs, such as single-arm trials. The guidance outlines design options for enrichment strategies and discusses how to interpret the results of studies using such strategies. It deals with three categories of enrichment strategies:

1. Strategies to reduce variability—choosing patients with baseline measurements of a disease or biomarker characterizing the disease in a limited range and leaving out patients whose disease or symptoms improve spontaneously or whose measurements are highly variable.

2. Prognostic enrichment strategies—selecting patients with a higher chance of having a disease-related endpoint event or substantial worsening in condition. Such strategies may include event-based studies.

3. Predictive enrichment strategies—choosing patients who are more likely than others to respond to the drug treatment.

Per the guidance, enrichment designs should be clearly described in the protocol and final report, with full details on the enrichment tactics used and their effects on the interpretation of results. Since interpreting studies using enrichment designs can be complex, the guidance recommends sponsors discuss their plans with the FDA early in the development process. In deciding whether to use an enrichment design, the FDA recommends sponsors consider whether patients with an increased likelihood of response can be defined prior to treatment using a straightforward method, whether the drug may be useful in a broader study population and the extent of data that should be available in a nonenriched subgroup. The guidance indicates that labeling for drugs approved based on an enriched trial needs to accurately describe the enrichment strategies used, including any limitations or concerns such strategies raise for clinical use of the treatment. The FDA will seek to ensure labeling is truthful and doesn't overstate the likelihood or magnitude of response, or the predictiveness of the enrichment factor.

The draft guidance describes risk-based approaches to monitoring investigational studies of drugs and biological products, medical devices, and combinations. The draft Q&A guidance is designed to help sponsors plan and conduct risk-based approaches to monitoring. It recommends that sponsors conduct a risk assessment to identify the nature, sources, likelihood of detection and potential causes of risks that could impact the collection of data or hinder processes, which should form the basis of a monitoring plan. A risk-based approach to monitoring should direct oversight activities toward preventing or mitigating likely risks, as well as those risks less likely to occur but which may have a significant impact on the study quality. Monitoring plans should include a synopsis of the study and should identify critical data and processes; trial-specific risks; monitoring methods and rationale;

criteria for determining the timing, type and extent of monitoring activities; and specific activities for each monitoring method used. It should also identify protocol deviations and failures that would impact study integrity should they occur and describe processes for reporting significant monitoring issues.

FDA issues draft guidance on quality considerations for drugmakers implementing continuous manufacturing

The guidance provides recommendations to help manufacturers implement continuous manufacturing (CM) for brand and generic drugs. It reflects the Food and Drug Administration's (FDA) efforts to support the use of modern manufacturing processes and coincides with similar efforts by other regulatory bodies across the globe. Officials say CM is easier to control than traditional manufacturing and helps ensure more consistently made products while facilitating scaling to meet demand.

The FDA issued draft guidance discussing quality considerations for implementing CM to produce small-molecule, solid oral dose products overseen by the Center for Drug Evaluation and Research. The guidance defines CM as "a process in which the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system." It provides recommendations on how to address CM quality considerations in drug applications, including new drug applications (NDAs), supplements and abbreviated NDAs, but does not provide specific recommendations for the use of CM biological products submitted under a biologics license application. The guidance reflects the FDA's efforts to support pharmaceutical innovation and modernization, with the goal of reducing drug shortages, as well as its efforts to implement a risk-based approach to pharmaceutical quality assessment.

Per the guidance, the FDA has the same expectations for a science- and risk-based approach to the control of processes and product quality for CM as it does for traditional manufacturing. Since CM processes are dynamic and process parameters and quality attributes are kept within a target range rather than a steady-state condition, understanding process dynamics is critical to identifying and mitigating risks to product quality. As such, the guidance notes that risk assessments should consider process understanding of the integrated system, in addition to each unit operation. It further notes that developing a robust pharmaceutical quality system for a CM process requires developing an effective control strategy that pays close attention to mitigating the risk of potential disturbances to product quality. The FDA recommends that manufacturers strengthen their use of in-process control strategy elements to ensure the process remains in a state of control and to detect temporary process disturbances and segregate nonconforming materials from the system.

While the ICH Q8, Q9 and Q10 guidance on process validation is applicable to CM processes, the guidance notes that manufacturers may find some process validation stages are more concurrent and interrelated with CM processes compared with batch manufacturing processes because the development of a CM process generally uses commercial-scale equipment. This may minimize scaling issues often experienced with batch manufacturing; subsequently, certain process qualification and verification activities may be better performed during the process design stage. For instance, it may be more appropriate to complete equipment qualification before completing validation studies, as those studies may provide data to meet some of the expectations for process performance qualification.

The draft guidance notes submissions to the FDA should describe enhanced process development approaches and include information unique to CM. The guidance provides a list of data requirements for CM applications, including a description of the method or approach used to characterize process dynamics and science- and risk-based assessment of the factors that may impact those process dynamics, a material traceability strategy,

justification of the finished product sampling strategies, a rationale for advanced process control approaches, a process flow diagram outlining the continuous flow of operations, and a summary of the overall control strategy, among other information.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use accepted an FDA proposal to develop guidance on CM, with the goal of finalizing the guidance by 2021. The harmonized guidance will help brand and generic drugmakers obtain approvals for products made using CM processes in multiple regions. The FDA also requested funding in the 2019 budget to advance the development and implementation of CM.

CDRH implements least-burdensome flag program for 510(k) submissions following pilot

The program will explore a new approach to resolving issues in 510(k) submissions, as part of the Food and Drug Administration's (FDA) mandate to implement the least-burdensome provisions. Though the FDA was quiet about the pilot, the director of the Center for Devices and Radiological Health (CDRH) says it provides "opportunity for sponsor to 'throw the flag' during review," similar to an NFL coach throwing a flag to question a call by a referee.

During a webinar held by the CDRH, Joshua Silverstein, regulatory advisor at the Office of Device Evaluation, said the FDA is implementing the least-burdensome flag program for 510(k) submissions to serve as a performance metric for the implementation of least-burdensome requirements.

According to the webinar, the CDRH conducted a pilot on the flag program from February to September 2018 across seven review branches. The program allows 510(k) submitters to request an informal review by upper management if they believe a request from the agency isn't the least burdensome or if they believe they are being held to an inappropriate review standard. During the pilot, requests for additional information for a 510(k) application that didn't raise not substantially equivalent (NSE) issues included an attachment offering sponsors the option of using the flag. The pilot limited flags to deficiencies related to biocompatibility and sterility. Least-burdensome flags expired 60 days after the request for additional information was sent. Under the program, sponsors using the flag were sent feedback within 21 days.

During the pilot, the FDA issued 132 letters requesting additional information and two submitters (1.5 percent) opted to use the flag. The received feedback came from one-third of submitters who didn't use the flag as well as the two submitters who did. The feedback indicates that most respondents understood the flag and its process and appreciated the opportunity to seek feedback but decided not to use it, either because the deficiencies were reasonable or because the issues were resolved in another manner, generally through phone calls or the branch chief. Though a few commenters suggested the pilot was too limited or had concerns about using official meetings, all respondents indicated that they would use the flag if they didn't agree with the FDA's request for information. Respondents also indicated that they'd be more likely to use the flag than an appeal. Of the two flags used, the FDA was able to resolve the issues in "a straightforward manner" within the 21-day time frame.

The FDA determined that the feedback and results of the pilot support the program, as it provides an easier process than an appeal, and industry members believe it provides a meaningful opportunity to raise concerns about a submission. The program was officially implemented on March 4 and will be available for all 510(k) requests for additional information that aren't potential NSE decisions. Submitters should email the lead reviewer, their manager and 510(k) staff a summary of the deficiencies being flagged, a reason why the request isn't least burdensome or reflects an unsuitable review standard, and a summary of relevant communications and a proposed path forward. The FDA will then hold an internal meeting and, if it is unable to resolve the issue itself, will schedule a teleconference with the submitter.