FDA Regulatory and Compliance Monthly Recap

DECEMBER 2019

KEY FINDINGS

OPDP issues enforcement letters to Rockwell Medical, Alkermes for misleading advertisements

The office sent an untitled letter to Rockwell over a webpage making misleading claims about the benefits of an iron replacement therapy and issued a warning letter to Alkermes over promotional print material for an opioid dependence treatment that left out serious risks associated with the drug. The letters continue an upward trend in OPDP enforcement, bringing the total enforcement actions to 10—up from seven in 2018.

The FDA's Office of Prescription Drug Promotion (OPDP) issued an untitled letter to Rockwell Medical after determining that its webpage for iron replacement therapy Triferic made false or misleading information about the benefits of the product and failed to disclose risk information and omitted material facts about its approved indication. The letter, which is the seventh untitled letter issued by the OPDP in 2019, takes issue with the webpage making claims about the benefits of the drug without disclosing material information about adverse events, which creates a misleading impression about its safety. It also raises concerns about claims misleadingly suggesting Triferic is safer and more effective than other IV iron replacement products, which has not been demonstrated and is not supported by cited references. In addition, the OPDP cites a failure to provide material information about the full FDA-approved indication for Triferic, including its limitations of use. The letter directs Rockwell to cease violating the Federal Food, Drug, and Cosmetic Act and provide a list of violative materials and a plan for discontinuing their use.

Separately, the OPDP issued a warning letter to Alkermes after determining that a print advertisement for Vivitrol misbranded the opioid dependence treatment by omitting warnings about serious risks associated with the drug. The warning letter, which is the office's third of 2019, cites a failure to "adequately present important risk information in a truthful and non-misleading manner." Per the letter, the print ad contains claims and representations about the benefits of the treatment, which is used as part of a medication-assisted treatment for opioid use disorder, but fails to disclose information from the warnings and precautions section of prescribing information about vulnerability to opioid overdose. As such, the ad creates a misleading impression about Vivitrol's safety. The letter notes that a statement in small print at the bottom of the ad directing users to "adjacent pages" for additional prescribing information does not mitigate the misleading omission of material information in the main body of the ad. The letter directs Alkermes to immediately cease advertising practices that misbrand the drug and to provide a plan to disseminate truthful, non-misleading and complete corrective messages to address the cited issues.

CBER issues untitled letter to Chara Biologics for promoting stem cell product as treatment for autism, other conditions

The letter reprimands Chara for using patient stories to promote an unapproved stem cell product as a treatment for children with autism or people who suffer from conditions such as traumatic brain injury, dementia and autoimmune disorders. The FDA says Chara's product doesn't qualify for statutory exceptions for human cells, tissues, and cellular and tissue-based products and requires a valid BLA.

The Center for Biologics Evaluation and Research (CBER) sent an untitled letter to Chara Biologics after a review by the Office of Compliance and Biologics Quality found the company was promoting an "umbilical cord-derived cellular product" known as CharaCore as a treatment for serious or life-threatening diseases or conditions, including autism.

According to the letter, which is the CBER's third enforcement action of 2019, Chara markets the product as "suitable for all forms of injections, to assist the body's ability to repair and regenerate." It also uses case studies to promote the product as a treatment for autism and traumatic brain injury, while making claims that it is "the most comprehensive and potent stem cell product on the U.S. market." The letter also cites claims that the product can be "safely dosed at regular intervals" as a "remarkable anti-aging therapy" and can be provided to patients with "various chronic conditions."

The CBER states that CharaCore appears to be a human cell, tissue, or cellular or tissue-based product (HCT/P) that does not qualify for a statutory exception under 21 CFR 1271.15. As such, the product is subject to regulation as a drug under the Federal Food, Drug, and Cosmetic Act and a biological under the Public Health Service Act and requires a valid biologics license application (BLA). While in the development stage, such products can be distributed for clinical use in humans only if a sponsor has a valid investigational new drug application approved by the FDA.

The untitled letter raises particular safety concerns about the product given its higher-risk routes of administration, including IV, which can cause a range of adverse events if contaminated. The letter directs Chara to consult the FDA's regenerative medicine policy framework for HCT/Ps.

FDA publishes draft guidance outlining process for requesting Certificates of Confidentiality for research participants

The draft guidance outlines the process for sponsors to request Certificates of Confidentiality as a means of preventing researchers from being compelled to disclose identifiable, sensitive information about research participants. The guidance follows the implementation of a policy at the National Institutes of Health to ensure NIH-funded investigators don't have to apply for a CoC, which will be issued automatically to NIH-funded research that collects or uses identifiable, sensitive information.

The FDA published draft guidance to implement revised provisions for issuing a Certificate of Confidentiality (CoC) under the Cures Act. A CoC is meant to help protect the privacy of human research participants by protecting researchers from being compelled to disclose identifiable and sensitive information during research. The Cures Act extended protections for researchers by barring CoC holders from disclosing such information unless a specific exception applies.

The Cures Act made it mandatory that CoCs be issued for federally funded research involving human subjects that collects or uses identifiable, sensitive information. The guidance describes the process for requesting a CoC for non-federally funded research, referred to as a discretionary CoC. While the process for issuing a CoC differs for discretionary and mandatory CoCs, the guidance notes that the protections afforded and the statutory responsibilities are the same. The FDA has been issuing discretionary CoCs on a case-by-case basis since the implementation of the Cures Act. The draft guidance outlines a revised process for discretionary CoCs to minimize burdens on researchers and accelerate the process by reducing the information needed in a request.

The FDA recommends that only sponsors or sponsor-investigators submit requests for discretionary CoCs to reduce duplicative requests for the same research and ensure CoCs are issued to those who can comply with the requirements of the statutory provisions. The guidance also recommends that those requesting a discretionary CoC assess the research to determine whether it involves the collection of identifiable, sensitive information. The guidance defines identifiable, sensitive information as information "(A) through which an individual is identified; or (B) for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual."

Per the guidance, requestors should consider four questions before submitting a request to the FDA for a discretionary CoC:

(1) Is the requestor involved in research involving human participants in which identifiable, sensitive information is collected?

(2) Is the requestor a sponsor, sponsor-investigator or authorized representation (i.e., the person with responsibility for or who initiates the clinical investigation)?

(3) Does the research involve the use or study of a product subject to the FDA's jurisdiction and regulatory authority?

(4) Are the requestor's research measures adequate to protect the confidentiality of the identifiable, sensitive information?

If the answer is yes to all four questions, the FDA recommends a request for a discretionary CoC be made. Requests should include descriptive information, such as the FDA application number and ClinicalTrials.gov identifier and assurances to show the requestor understands the obligations to comply with the statutory provisions. Once the FDA completes the request review, it will send an electronic response letter to the requestor indicating whether or not the CoC has been granted. If granted, that response letter will serve as the CoC.

FDA finalizes guidance on adaptive trial designs for drugs, biologics

The finalized guidance discusses the appropriate use of adaptive trial designs in support of a demonstration of effectiveness and safety for a drug or biologic. It outlines what information sponsors need to submit to facilitate FDA review of trials with adaptive designs in support of INDs, NDAs, BLAs or supplemental applications.

The FDA published final guidance on the appropriate use of adaptive designs for clinical drugs used to support the effectiveness or safety of products submitted under investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs) or supplemental applications. It outlines principles for designing, conducting and reporting the results from adaptive trials and discusses what types of information sponsors should submit to allow the FDA to assess such trials. The guidance defines adaptive design as "a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial."

The guidance delineates four key principles for the design, conduct and analysis of adaptive clinical trials being used to demonstrate the effectiveness of a product:

(1) The change of erroneous conclusions should be adequately controlled – Given their role in premarket decision-making, clinical trials need to be assessed for their probability of inaccurate conclusions of safety or effectiveness or misleading estimates that contribute to the assessment of the benefit-risk profile.

(2) Estimation of treatment effects should be sufficiently reliable – Clinical trials need to yield sufficiently reliable treatment effect estimates in order to support an assessment of the benefit-risk profile and properly label new drugs. For trial designs for which methods are not available to adjust estimates to reduce or remove bias, the extent of bias in estimates should be evaluated and treatment effect estimates and associated confidence intervals should be presented with appropriate cautions about their interpretation.

(3) Details about the design should be completely prespecified – The details of the adaptive design should be completely specified and documented accordingly before starting the trial, including prespecification of the expected number and timing of interim analyses, the type of adaptation and statistical inferential methods to be used, and the algorithm governing adaptation decisions.

(4) Trial integrity should be appropriately maintained – Access to comparative interim results should be limited to people with pertinent expertise who are independent of those involved in conducting or managing the trial. Planning for an adaptive trial should include a consideration of possible sources and consequences of trial conduct issues, along with plans to mitigate such issues.

Per the guidance, the increased complexity of some adaptive trial designs and uncertainties about their operating characteristics may warrant earlier and more extensive interactions with the FDA than is customary. The guidance recommends that sponsors who have questions regarding adaptive design elements in early-phase exploratory trials seek FDA feedback. At later phases of development, the agency will have a more extensive role in assessing the design and analysis plan to ensure trials will provide sufficiently reliable results to inform regulatory decision-making. The guidance notes that earlier interaction can facilitate more iterative discussions without slowing product development.

In order for the FDA to review a marketing application based on adaptive trials, the guidance notes that applications should include all prospective plans and supporting documentation, information related to compliance with the planned adaptation rule and data access procedures to maintain trial integrity, records of deliberations and participants for any interim discussions by committees involved in the adaptive process, results of interim analyses used for adaption decisions, and appropriate reporting of the adaptive design and results.

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