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FDA issues draft guidance on promotional labeling for reference and biosimilar products as it outlines plan to collaborate with FTC on false promotion

The draft guidance indicates that representations creating the impression that there are clinically meaningful differences between a reference product and biosimilar are likely to be false or misleading. The draft follows criticisms from various industry groups and biopharmas regarding the way information has been presented about biosimilars and their reference products. It comes as both the FDA and FTC look to crack down on anticompetitive practices in the biological products markets.

The FDA issued draft guidance describing how companies can promote reference or biosimilar products in truthful and non-misleading ways and issued a joint statement signaling its intent to collaborate with the FTC to improve the marketplace for biological products, including the adoption of biosimilars and interchangeable products. According to the joint statement, the FDA and FTC will use their respective authorities to address the false or misleading promotion of biosimilars, including misleading statements comparing reference products and biosimilars that may be hindering their uptake in the U.S. by creating misperceptions about their safety or effectiveness. The move is part of the FDA's Biosimilars Action Plan, which delineates four key strategies to accelerate biosimilar competition, including supporting market competition and providing recommendations on promotional materials.

As with other prescription drug promotional labeling and advertising, the guidance notes that determination as to whether biosimilar and reference product advertising is truthful and non-misleading is based on factors such as how the information is presented and the type and quality of data used to support the presentation, as well as contextual and disclosure considerations. The draft guidance recommends that the FDA-approved labeling for a biosimilar product include pertinent data and information from the reference product's

FDA-approved labeling, including the clinical data that supported approval. Typically, a biosimilar product's FDA-approved labeling should include data from the "Clinical Studies" section of the reference product's labeling for the conditions for use for which the biosimilar is licensed. While the FDA has recommended that FDA-approved labeling for a biosimilar generally not include data from trials conducted to support demonstration of biosimilarity, the guidance notes that companies have expressed an interest in communicating such information to health care providers. As such, the guidance recommends that companies apply the principles outlined in the FDA's Q&A guidance on medical product communications consistent with FDA-required labeling, which outlines the agency's views on communicating information not contained in—but consistent with—labeling.

The draft guidance explains that while each promotional presentation involves a fact-specific determination, representations or suggestions that create an impression that there are clinically meaningful differences between a reference and biosimilar are likely to be false or misleading. Such representations include presentations suggesting a reference is safer or more effective than a biosimilar, or vice versa. The guidance also cautions that representations or suggestions that a biosimilar is not highly similar to a reference are likely to be false or misleading, noting that the FDA's licensure of a biosimilar means the FDA has determined the product is highly similar to the reference. The guidance recommends that sponsors carefully assess presentations comparing a reference and biosimilar in order to avoid such misrepresentations. It further cautions that individual statements of accurate information about a reference product or biosimilar may contribute to a misleading presentation when provided in a comparative context. For instance, presentations in promotional materials for a reference comparing the number of indications for which the reference is licensed to that of the biosimilar may create the net impression that the biosimilar is less safe or effective because it is licensed in fewer indications.

The FDA notes that companies can voluntarily seek FDA feedback on promotional materials for reference and biosimilar products prior to disseminating them. The guidance notes that firms are subject to postmarketing reporting requirements for submitting promotional materials to the FDA through Form FDA 2253s and should ensure the promotional materials adhere to FDCA requirements.

FDA publishes draft guidance on biosimilars licensed for fewer than all conditions of use licensed by reference

The guidance addresses instances in which a biosimilar sponsor may choose not to seek licensure in all of the reference product's licensed conditions and provides recommendations for sponsors seeking to submit a supplement to a licensed 351(k) BLA in order to add a condition of use that has previously been licensed for the reference product to the labeling of a licensed biosimilar.

The FDA published draft guidance for sponsors seeking licensure under section 351(k) of the Public Health Service Act for a proposed biosimilar or proposed interchangeable biosimilar for fewer than all of the reference product's licensed conditions of use. Although the FDA recommends that a sponsor seek licensure for a proposed interchangeable product for all of the reference product's licensed conditions, when possible, the draft acknowledges that there are instances in which a sponsor may choose not to do so, including when the reference product is protected by orphan drug exclusivity and when a licensed condition of use of the reference product is protected by a patent. The guidance notes that the FDA doesn't expect an applicant to submit a justification for not seeking licensure for all of the reference product's licensed conditions of use.

Per the guidance, a holder of a 351(k) biologics license application (BLA) may submit a supplement to seek licensure for an additional condition of use that has been previously licensed for a reference product and for which it did not originally seek licensure. The supplement must contain all the data and information required to support licensure in the proposed condition of use, which may include reference to data and information previously

submitted with the BLA with appropriate scientific justification. The guidance notes that under Biosimilar User Fee Amendment (BsUFA) II, the FDA committed to reviewing and acting on original 351(k) BLA supplements with clinical data within 10 months of receipt. When able, however, the FDA plans to review a supplement to a licensed 351(k) BLA within six months, irrespective of whether the product was initially licensed for fewer than all of the reference product's licensed conditions of use or whether the reference product is licensed for a new condition of use after licensure of the biosimilar. While the six-month timeline exceeds BsUFA II goals, the FDA notes that it believes the time frame will generally be appropriate for a supplement so long as it doesn't raise novel review issues.

The guidance directs applicants to develop draft labeling for the proposed biosimilar that includes information from the reference product labeling that is pertinent to the proposed conditions for use of the biosimilar, with proper adjustments. When developing the draft labeling, applicants should "carefully scrutinize" the labeling to ensure pertinent information is included. The FDA will review the labeling to ascertain whether it complies with applicable labeling requirements, including requirements that labeling summarize the essential scientific information required for safe and effective use. In submitting the labeling, an applicant seeking licensure in fewer than the reference product's licensed conditions of use may submit information to inform the agency's review of the draft labeling, such as a justification for why it believes the labeling meets requirements for approval, in light of the conditions for which the applicant is seeking licensure.

FTC files complaint against companies making unsubstantiated health claims, using deceptive testimonials to market products

The complaint seeks to prohibit ZyCal Bioceuticals and EMR from deceptively marketing pills as proven to alleviate joint pain by growing new bone and cartilage. While EMR settled the complaint, the FTC is moving forward with litigation against ZyCal Bioceuticals.

The FTC filed a complaint in the U.S. District Court for the District of Massachusetts seeking permanent injunctive relief against ZyCal Bioceuticals and Excellent Marketing Results (EMR) and claiming violations of the FTC Act. The complaint alleges unfair or deceptive acts or practices, including through the misrepresentation or deceptive omission of material facts and false advertising. The FTC contends that consumers have suffered substantial injury as a result of the violations, and that ZyCal and EMR have been unjustly enriched as a result of their unlawful acts. In addition to injunctive relief, the complaint seeks rescission or reformation of contracts, restitution, the refund of monies paid and the disgorgement of ill-gotten monies.

According to the complaint, EMR and its president marketed StimTein through infomercials and internet sources as a clinically proven treatment for pain associated with debilitating joint ailments such as arthritis. The active ingredient in the product, Cyplexinol, is manufactured and supplied by ZyCal. The FTC alleges that ZyCal recruited EMR as a trade customer and encouraged the company to market Cyplexinol under the finished product StimTein using product information, clinical studies and other promotional materials about the alleged health benefits that it provided. The complaint cites claims prominently displayed in StimTein advertising such as "stimulates cells to grow bone tissue." The complaint also cites testimonials in which former EMR employees provided supposed consumer endorsements without disclosing their connections to the company. The FTC contends that EMR made false or unsubstantiated efficacy claims, false establishment claims and deceptive endorsement claims, and engaged in a deceptive failure to disclose material connections.

The complaint further alleges that ZyCal marketed the Cyplexinol ingredient or oral products containing Cyplexinol to other trade customers, offering them product information and promotional materials with bone and joint claims "substantially similar" to those provided to EMR. The company also advertised and marketed its own line of Cyplexinol products under the brand name Ostinol directly to consumers and

health professionals such as chiropractors, making claims that the products are clinically proven to grow bone and cartilage and substantially reduce joint pain. The FTC alleges, however, that ZyCal and EMR have no competent and reliable scientific evidence that any Cyplexinol product provides the purported health benefits. The complaint alleges that ZyCal provided the means and instrumentalities of deception to EMR and made false or unsubstantiated efficacy claims, false establishment claims and deceptive endorsement claims.

EMR agreed to settle the complaint. Under a proposed court order, EMR and its president are prohibited from making health-related product claims unless they are supported by competent and reliable scientific evidence. The order also forbids them from misrepresenting the results of any scientific study and from deceptively representing that a product endorser's views are representative of the views of an impartial user. Per the proposed order, EMR and its president will need to disclose any material relationships between themselves and product endorsers. The order imposes a $3.6 million judgment. The judgment will be partially suspended upon payment of $145,000, which may be used to provide refunds to consumers.

ZyCal has not settled the claims, and the FTC said it is progressing with litigation against the company and its president.

FDA rolls out gene therapy framework with six final guidances, one draft guidance

The FDA finalized six guidance documents on the development and assessment of gene therapies and published a draft guidance on interpreting the sameness of gene therapies under the orphan drug regulations. The agency said the guidance documents reflect its effort to support innovators and advance gene therapy product development.

As it prepares for an expected surge in new gene therapies, the FDA published six final guidances on the development and assessment of the treatments, along with a draft guidance on interpreting the sameness of the treatments under the orphan drug regulations. With more than 900 investigational new drug (IND) applications ongoing for gene and cell therapy studies, the FDA anticipates it will review and approve between 10 and 20 of the therapies annually by 2025. FDA Commissioner Stephen Hahn says the agency understands that the framework it establishes will "set the stage for continued advancement" of gene therapies. The guidance documents are meant to help establish a "modern structure for the development and manufacture of gene therapies." The FDA stresses that gene therapy developers should leverage expedited programs for products for unmet medical needs, such as breakthrough therapy designation, regenerative medicine advanced therapy designation, fast-track designation, priority review and accelerated approval.

Since it may need to accept some degree of uncertainty about the duration of the response of gene therapies at the time of marketing authorization, the FDA notes that post-market follow-up will be critical in advancing the field of gene therapy. As such, one of the finalized guidance documents addresses the long-term follow-up (LTFU) of gene therapy products. The guidance outlines the product characteristics, patient-related factors, and preclinical and clinical data that should be considered when ascertaining the need for LTFU observations for a gene therapy product. Since the number of subjects receiving gene therapies is often limited during clinical investigations and LTFU observations are often needed after licensure, the FDA recommends that sponsors submit a pharmacovigilance plan when submitting a biologics license application, which may include planned LTFU.

A second final guidance document addresses chemistry, manufacturing and control (CMC) information for gene therapy INDs. The guidance describes how sponsors should provide adequate CMC information to ensure the safety, identity, quality, purity and strength of gene therapy products and combination products that contain a human gene therapy. The guidance cautions that the FDA may place an IND application on clinical hold if it does not contain sufficient CMC information to assess the risks to subjects in the proposed trials. The guidance notes that CMC information submitted in an IND application should describe a sponsor's

commitment to conduct manufacturing and testing of the investigational product. If manufacturing changes are needed as product development progresses, sponsors should submit a supplement to the initial information submitted for the CMC processes.

The draft guidance outlines how the FDA will determine whether orphan exclusivity will be awarded if two gene therapy products are intended for the same use or indication. The guidance notes that if a sponsor requests orphan drug designation for a drug that is the same drug as a drug already approved for the same indication or use, it must provide a "plausible hypothesis that its drug is clinically superior to the previously approved drug." While the orphan drug regulations define "same drug" for large-molecule drugs as one that "contains the same principal molecular structural features" and "is intended for the same use or indication as a previously approved drug," the regulations don't specify how the definition applies specifically to gene therapies. As such, the draft outlines how the FDA interprets the regulatory "sameness" criteria for gene therapies. The FDA explains that the determination of sameness will consider the principal molecular structural features of the gene therapy products. Additional finalized guidance documents provide recommendations for specific development areas, including rare diseases, hemophilia, retinal disorders and retroviral vector-based therapies.

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