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Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

Coming Soon: FDA Over-The-Counter Drug Approval Overhaul

By **Rebecca Dandeker, Ann Begley, Kathleen Sanzo and Suzanne Bassett**
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Rebecca Dandeker


Ann Begley


Kathleen Sanzo


Suzanne Bassett

A new pathway for over-the-counter products could be on the horizon, as both houses of Congress have proposed bills to revise the U.S. Food and Drug Administration's procedures to allow OTC medications to be marketed, and to permit the FDA to collect user fees, potentially expediting a newly created OTC drug review process. The FDA is preparing for an eventual passage of the law, and so should OTC drug manufacturers and private label distributors.

The U.S. House of Representatives voted on July 17, 2018, to pass a bill to reform the OTC monograph process, entitled the Over-the-Counter Monograph Safety, Innovation and Reform Act of 2018.[1] The Senate companion bill cleared the Health, Education, Labor, and Pensions Committee on April 24, 2018, and is pending a floor vote.[2]

The bills would add new sections to the Food, Drug, and Cosmetic Act to remove the current notice-and-comment rulemaking procedures governing the market introduction of OTC drugs, and instead institute a different, possibly more efficient, administrative order process. Some political analysts predict that the bills could become law in the near future.

Background

The FDA regulates most OTC drugs under the OTC monograph process, although manufacturers have the option to file a new drug application, or NDA, for novel OTC products. The OTC monograph process was created by the FDA in 1972 to review the safety and efficacy of active ingredients contained in thousands of medicines marketed without a prescription.

Rather than having each product approved by the agency, the monographs established conditions under which active ingredients, combinations of active ingredients, indications, dosage forms and labeled directions are considered "generally recognized as safe and effective," or GRASE, for use.

There are three categories under the OTC monograph process. Category I comprises ingredients that are GRASE and can be marketed without FDA review. Category II includes ingredients that are not considered GRASE and cannot be lawfully marketed,

except through the FDA's NDA approval process. Category III covers ingredients for which the FDA requires more data to determine GRASE status.

Over the 40-plus-year rulemaking process, FDA enforcement discretion has allowed almost all proposed Category I and Category III ingredients to continue to be marketed in the absence of a safety concern. Under the existing system, once the FDA issues a final monograph with the final Category I ingredients identified, all Category III ingredients must be removed from the market. Today, this process remains incomplete, with several significant monographs still pending as "tentative" final monographs or TFMs (e.g., sunscreen, antimicrobials, external analgesics).

The current monograph process has been criticized as being slow and a barrier to the introduction of new OTC ingredients to the U.S. market. The proposed bills attempt to modernize the process, by allowing the FDA to make OTC product decisions through an administrative order process that replaces the existing notice-and-comment rulemaking procedures.

The House and Senate bills provide a process for public comments, mandate alternative dispute resolution concerning ingredient decisions and allow manufacturers to request GRASE determination of new ingredients or new conditions for use through administrative orders — all of which will occur in a much shorter timeframe than the current process. The bills also authorize the FDA to move quickly to categorize products as not GRASE if no data is submitted.

Further, the legislation establishes a user fee program to pay for the FDA's review, based on new ingredient/uses and annual facility registrations. The fees currently proposed for order requests are either $100,000 or $500,000, depending on the complexity of review, and annual facility fees are to be established yearly by the FDA to meet statutory fee revenue requirements.

The bills will incorporate the existing final monographs and TFMs by reference in the statute, and automatically classify any Category I ingredient in a final monograph or TFM as GRASE. The bills will continue to allow Category III ingredients presently subject to a TFM, and Category I ingredients subject to an advanced notice of proposed rulemaking, or ANPRM, to be marketed without an approved new drug application, unless otherwise directed by an administrative order.

Notably, except in the case of a "minor change" or as permitted under an order, these ingredients can be marketed only in a dosage form that has been used to a material extent and for a material time immediately prior to enactment of the proposed bill. However, a "minor change" to a dosage form is allowable where it does not change the safety, effectiveness or absorption of, or exposure to, the ingredient.

Such a minor change would be allowed without the need to update or amend the order, and the bills direct the FDA to issue necessary administrative orders and guidance to clarify for industry when a "minor change" meets these conditions. Furthermore, the bills adopt a "safety in labeling" clause that allows the FDA to quickly make changes to any final order if new evidence becomes available to suggest a particular drug or class of drugs poses an unreasonable risk of an adverse event and requires a label or other change.

The most significant substantive change to the regulatory framework is that both bills allow the FDA to grant market exclusivity for either an active ingredient not previously included in a monograph or order, or a new condition for use, so long as new human studies were conducted that were essential to the issuance of a final administrative order. The bill provides no direction on how the FDA will assess

whether the ingredients or conditions for use are the same as those previously marketed. Moreover, the House and Senate bills diverge on the effective dates and lengths of exclusivity to be granted, which is the only major difference between the two bills.

The House bill would allow an 18-month market exclusivity period, while the Senate bill extends the exclusivity to 24 months. The Senate bill also starts the clock on exclusivity when the FDA grants a sponsor's request through an administrative order, while the House delays the effective date of the exclusivity period until a sponsor submits an updated drug listing after the issuance of the final order. This latter approach may be closer to the company's actual market launch date.

Key Highlights and Takeaways

The Senate and House versions of the bill are largely similar, with the exception of the exclusivity provisions. Therefore, manufacturers can reasonably rely on the major provisions of the bill, such as the administrative procedures, application of user fees and adoption of monographs by reference, to remain the same or similar if the bill is passed into law.

Because the regulatory process will be streamlined and the FDA will presumably have more resources and staff through the addition of user fees, manufacturers can expect a faster review time for FDA decisions on new active ingredients or dosage forms. However, the OTC review time will not be as swift as the NDA review time of 10–12 months.

As indicated in the FDA's 2018–2022 OTC Monograph Goals Letter,[3] the proposed review timeframes are 17.5 months after receipt of an OTC monograph order request for Tier 1 innovations that do not have numerous or substantive public comments, and 23.5 months for Tier 2 requests that garner substantive comments. However, as with NDA reviews, these are "expected" average times, and likely will be extended due to submissions deemed by the FDA to be deficient.

Manufacturers can start preparing for the proposed new review system by organizing their current OTC product portfolio according to the ingredients' current monograph classification. Manufacturers should be cognizant of their Category III active ingredients subject to a TFM, Category I ingredients subject to an ANPRM and Category II drugs. These ingredients are at risk for more immediate FDA action that could quickly impact their regulatory and marketing status.

Manufacturers interested in changing a condition for use or an ingredient in a monograph will have the ability to do so by making a request to the FDA through an OTC monograph order request, or OMOR. Minor changes to dosage forms that do not impact safety, effectiveness, absorption or exposure to the active ingredient would not require a new order, but must meet conditions set forth in relevant FDA administrative orders and guidance.

The future OMOR exclusivity period (either 18 months or two years) will apply to OTC monograph products with new active ingredients, combinations of new ingredients or new conditions for use for which clinical studies were essential to the issuance of the order. It is not clear how different an ingredient or condition for use must be in order to obtain exclusivity. Furthermore, the exclusivity will only block the sale of OTC products that seek to enter the market during the exclusivity period with the new active ingredient(s) or new condition for use.

Finally, the legislation is silent, and the FDA has not commented, on how the public will be notified of exclusivity periods, or on whether some type of certifications of status will be required in the OMORs.

Rebecca L. Dandeker, Ann M. Begley and Kathleen M. Sanzo are partners and Suzanne Bassett is an associate at Morgan Lewis & Bockius LLP.

[1] Over-the-Counter Monograph Safety, Innovation and Reform Act, HR 5333, 115 Cong. (2018).

[2] Over-the-Counter Drug Safety, Innovation, and Reform Act, S 2315, 115 Cong. (2018).

[3] Food & Drug Admin., Over-the-Counter Monograph User Free Program Performance Procedures — Fiscal Years 2018-2022.