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The Over-the-Counter Monograph Safety, Innovation, and Reform Act Is Enacted: Top Five Takeaways for Manufacturers of OTC Drug Products

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INTRODUCTION

On March 27, 2020, President Trump signed into law the Over-the-Counter Monograph Safety, Innovation, and Reform Act (OTC Monograph Reform Act), as part of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act).[1] This ends a multiyear legislative effort to reform the monograph system for over-the-counter (OTC) drugs and to introduce new mechanisms for OTC product changes and innovation.

From 2015 to 2017, the US Food and Drug Administration (FDA) held a series of meetings with industry representatives to discuss how to reform the OTC monograph process. These meetings culminated in the drafting of the Proposed OTC Monograph User Fee Program Performance Goals and Procedures (FY 2018-2022) (Performance Goals), which were transmitted to Congress on June 7, 2017.[2] On September 13, 2017, Center for Drug Evaluation and Research (CDER) Director Janet Woodcock testified before the US House of Representatives Energy & Commerce Subcommittee on Health on the Performance Goals, explaining that the current monograph process has "not kept up" and emphasizing the need for monograph reform to streamline processes and provide user fees to address resource challenges.[3]

During the 115th and 116th Congresses, legislation reflecting the Performance Goals was introduced in both chambers. Although the OTC Monograph Reform Act had wide bipartisan and bicameral support, it stalled amid disagreements

[1] For more information on the CARES Act, please reference our Advisory and webinar on the broader legislation.
[2] Over-the-Counter Monograph User Fee Program Performance Goals and Procedures—Fiscal Years 2018-2022, FDA.
[3] Testimony of Janet Woodcock before the Energy & Commerce Subcommittee on Health (Sep. 13, 2017).

regarding various aspects of the bill, including whether (and how long) to provide market exclusivity and the structure of the user fee program.

Now that the OTC Monograph Reform Act has been enacted, here are the top five takeaways that should be on the radar of OTC drug manufacturers:

Authorizes Agency Action By Administrative Order

The OTC Monograph Reform Act makes significant changes to the cumbersome and time intensive notice-and-comment rulemaking process that has governed the development of OTC drug monographs by introducing administrative orders as a replacement to rulemaking for the development of such monographs.[4]

Under the OTC Monograph Reform Act, the HHS Secretary has the authority—either at his/her own initiative or at the request of a requestor (e.g., a drug manufacturer)—to issue administrative orders to propose, finalize, or change OTC drug monographs.[5] A requestor can seek an administrative order determining whether (1) a drug or (2) a change to a condition of use of a drug is: generally recognized as safe and effective ("GRASE") under Federal Food, Drug, and Cosmetic Act (FDCA) Section 201(p)(1); exempt from FDCA Section 503(b)(1); and not required to be the subject of an approved application under FDCA Section 505.[6] Furthermore, the legislation deems existing final monographs and tentative final monographs to be final administrative orders that can be amended, revoked, or otherwise modified in accordance with the new procedures established by the legislation.[7]

In order for a drug to be deemed GRASE, it has to satisfy three criteria: (1) the drug is subject to adequate and well-controlled clinical investigations that establish the product as safe and effective; (2) such investigations are published in the scientific literature available to qualified experts; and (3) experts generally agree, based on such published studies, that the product is safe and effective for its intended uses. At a minimum, the general acceptance of a drug as GRASE must be supported by the same quality and quantity of scientific and/or clinical data necessary to support the approval of a new drug application. A drug product determined to be GRASE must be marketed consistent with the conditions set forth under a final monograph and all other applicable OTC requirements. Additional new requirements imposed by the OTC Monograph Reform Act for requests that new active drug ingredients be recognized as GRASE are discussed below.

The OTC Monograph Reform Act provides for two types of administrative orders: (1) general administrative orders and (2) expedited administrative orders. The Secretary can issue an expedited administrative order if it is determined either that: (1) a drug poses an imminent hazard to the public health; or (2) that a change in the labeling of a drug is reasonably expected to mitigate a significant or unreasonable risk of a serious adverse event associated with use of the drug. Expedited administrative orders allow for an interim final order to go into effect on a date specified by the Secretary (i.e., in advance of certain opportunities for comment and dispute resolution).

Administrative orders can be issued by the Secretary or at the request of a requestor, such as a drug manufacturer. Although the same general process is followed regardless of whether the administrative order is initiated by the Secretary or requested by a requestor, there are certain threshold steps that must be taken for administrative orders requested by a requestor.

[4] OTC Monograph Reform Act § 505G(b).
[5] *Id.*
[6] *Id.* § 505G(b)(5)(B).
[7] *Id.* § 505G(b)(8).

	General Administrative Order	Expedited Administrative Order
Initiated by Requestor[8]	Steps to be taken by requestor: • Submit a request to initiate proceedings for an administrative order in the form and manner specified by the Secretary. Steps to be taken by Secretary: • Determine whether the request is sufficiently complete and formatted to permit a substantive review. • If the request is determined to be sufficiently complete and formatted to permit a substantive review, then the Secretary will: o File the request; and o Initiate general proceedings to issue the administrative order (using the processes and timelines described immediately below for administrative orders initiated by the Secretary). • If the Secretary determines that a request does not meet the requirements for filing or is not sufficiently complete and formatted to permit a substantive review, then requestor may demand that the request be filed over protest, and the Secretary is required to initiate proceedings to review the request.	
Initiated by Secretary[9]	Steps to be taken by Secretary: • At least two business days before issuing the proposed order, informally notify the sponsors of drugs who have a listing in effect under FDCA Section 510(j) for the drugs that will be subject to the administrative order. • Publish the proposed order on the FDA website. • Publish a notice of availability in the *Federal Register*. • Provide for a public comment period of no less than 45 calendar days. • Issue the final administrative order, together with a detailed statement of reasons (but the administrative order cannot take effect until the time for requesting judicial review has expired).	Steps to be taken by Secretary: • Determine that either: (1) a drug poses an imminent hazard to the public health; or (2) that a change in the labeling of a drug is reasonably expected to mitigate a significant or unreasonable risk of a serious adverse event associated with use of the drug. • At least 48 hours before issuing the proposed order, make reasonable efforts to informally notify the sponsors of drugs who have a listing in effect under FDCA Section 510(j) for the drugs that will be subject to the administrative order. • Issue an interim final administrative order, together with a detailed statement of the reasons for the order. The order will go into effect on the date specified by the Secretary. • Publish a notice of availability in the *Federal Register*.

[8] *Id.* § 505G(b)(5).
[9] *Id.* § 505G(b)(2), (4).

	• Publish a notice of the final administrative order in the *Federal Register*. • Allow requestors of drugs that will be subject to the order the opportunity for formal dispute resolution. If the administrative order seeks to determine that a drug is *not* GRASE, then the Secretary must also include in the proposed order: (1) the general categories of data the Secretary has determined necessary to establish that the drug is GRASE; and (2) the format for submissions by interested persons. The Secretary must also generally provide for a public comment period of 180 calendar days. Any person that submits data in the comment period must include a certification that they have submitted all evidence created, obtained, or received by that person that is both within the categories of data identified in the proposed order and relevant to a determination as to whether the drug is GRASE.	• Provide for a public comment period of at least 45 calendar days. • Issue a final order within six months of the close of the comment period. • Publish a notice of availability in the *Federal Register*. • Allow sponsors of impacted drugs the opportunity for formal dispute resolution.

Drugs with New Active Ingredients

The OTC Monograph Reform Act includes specific requirements for requests that new active drug ingredients be recognized as GRASE. Requests that nonprescription drugs which contain new active ingredients (i.e., ingredients not previously incorporated in a monograph drug) be recognized as GRASE will be denied by the Secretary and subject to NDA requirements unless such requests include information sufficient for a *prima facie* demonstration that the drug has a verifiable history of being marketed and safely used as an OTC drug by consumers in the US under comparable conditions of use. However, if the drug has not been previously marketed in the US as a nonprescription drug, then the GRASE request must include information sufficient for a *prima facie* demonstration that the drug was marketed and safely used under comparable conditions of marketing and use in a country listed in FDCA Section 802(b)(1)(A) or designated by the Secretary (e.g., Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and many EU countries). With certain exceptions, if the Secretary refuses to file a GRASE request for such drugs, the requestor may not file such request over protest.[10]

[10] *Id.* § 505G(b)(6).

Packaging Requirements

An administrative order may include requirements for the packaging of a drug. Such requirements may include unit dose packaging, requirements for products intended for use by pediatric populations, requirements to reduce risk of harm from unsupervised ingestion, and other appropriate requirements.[11]

Hearings & Judicial Review

With limited exceptions, the OTC Monograph Reform Act provides for hearings concerning any final administrative orders issued by the Secretary, whether initiated by the Secretary or a requestor.[12] Judicial review is available for administrative orders according to the procedures described in FDCA Section 505(h). Such requests for judicial review must be filed in an appropriate federal district court (rather than in a federal appellate court). A request for judicial review must be filed no later than 60 calendar days after the latest of:

1. The date the administrative order is published;
2. The date a hearing on the administrative order is denied;
3. The date a final decision is made following a hearing; or
4. If no hearing is requested, the date by which a hearing must be requested.13

Establishes a Process for Minor Changes in Dosage Forms

The OTC Monograph Reform Act provides for minor changes to be made in the dosage form of a monograph drug without the issuance of an administrative order. The legislation also requires the Secretary to issue administrative orders and guidance documents specifying the requirements for determining whether a change is to be considered "minor."

To make such minor changes, a requestor must demonstrate that the change will not affect the safety or effectiveness of the drug and will not materially affect the absorption or other exposure to the active ingredient in comparison to a suitable reference product. Furthermore, the requestor must demonstrate that the change is in conformity with all requirements established by the Secretary. The sponsor of a drug must submit records requested by the Secretary relating to a minor change request within 15 business days of receiving the request. If the Secretary determines that the information contained in such records is insufficient, then the Secretary has the option to inform the sponsor of the insufficiency and provide them with a reasonable opportunity to submit additional information. However, if the sponsor fails to provide additional information, or if the Secretary determines that the additional information remains insufficient, then the drug as modified is considered a new drug and will be deemed misbranded.[14]

Defines Requirements for Treatment of OTC Drugs as GRASE or New Drugs

The OTC Monograph Reform Act provides for the treatment of certain categories of existing drugs as GRASE if specific requirements are met:

[11] *Id.* § 505G(b)(7).
[12] *Id.* § 505G(b)(3).
[13] *Id.*
[14] *Id.* § 505G(c).

Category	Requirements for Treatment as GRASE
Drugs Subject to a Final Monograph[15]	1. In conformity with: a. Requirements for nonprescription use of a final monograph; b. General requirements for nonprescription drugs; *and* c. Requirements under the OTC Monograph Reform Act relating to administrative orders, procedures for minor changes, and existing regulations governing nonprescription drugs as affected by the OTC Monograph Reform Act; *and* 2. In a dosage form that has been used "to a material extent" and "for a material time" except as permitted by an administrative order or an order issued in accordance with the procedures for minor changes.
Category I Drugs Subject to a Tentative Final Monograph[16]	1. Classified as Category I for safety and effectiveness under a tentative final monograph (TFM) that is the most recently applicable proposal; *and* 2. In conformity with: a. Proposed requirements for nonprescription use of the TFM; b. General requirements for prescription drugs; *and* c. Requirements under the OTC Monograph Reform Act relating to administrative orders, procedures for minor changes, and existing regulations governing nonprescription drugs as shaped by the OTC Monograph Reform Act; *and* 3. In a dosage form that has been used "to a material extent" and "for a material time" except as permitted by an administrative order or an order issued in accordance with the procedures for minor changes.
Category III Drugs Subject to a Tentative Final Monograph[17]	1. Classified as Category III for safety and effectiveness under a tentative final monograph that is the most recently applicable proposal; *and* 2. In conformity with: a. Conditions of use (including indication and dosage strength) described in the TFM; b. Proposed requirements for drugs classified in the TFM as Class I; *and* c. General requirements for nonprescription drugs and requirements under the OTC Monograph Reform Act relating to administrative orders and existing regulations governing nonprescription drugs as shaped by the OTC Monograph Reform Act; *and* 3. In a dosage form that has been used "to a material extent" and "for a material time."

[15] *Id.* § 505G(a)(1).
[16] *Id.*
[17] *Id.* § 505G(a)(3).

Category	Requirements for Treatment as GRASE
Category I Drugs Subjected to a Proposed Monograph or ANPRM[18]	1. Classified in Category I for safety and effectiveness under a proposed monograph or advance notice of proposed rulemaking (ANPRM) that is the most recently applicable proposal; *and* 2. In conformity with: a. Requirements for nonprescription use of the proposal or ANPRM; *and* b. Any applicable subsequent determination by the Secretary of Health and Human Services; *and* c. General requirements for nonprescription drugs and requirements under the OTC Monograph Reform Act relating to administrative orders and existing regulations governing nonprescription drugs as shaped by the OTC Monograph Reform Act; *and* 3. In a dosage form that has been used "to a material extent" and "for a material time."

The OTC Monograph Reform Act also provides that certain categories of drugs will be deemed "new drugs" that cannot legally be marketed without an approved new drug application. First, under the legislation, drugs classified in Category II for safety and effectiveness under a TFM or subject to a determination in the most recent proposed rule that the drug is not GRASE, will be deemed new drugs beginning 180 days following the enactment of the Act.[19] However, the legislation empowers the Secretary of Health and Human Services to extend the period during which drugs in this category can be marketed without a new drug application if it is "in the interest of public health."[20] Additionally, if a final determination has been made that a drug is not GRASE, it will be deemed a new drug.[21] Finally, the legislation designates as new drugs all other OTC drugs that are not subject to FDCA Section 503(b)(1) and do not fall into one of the categories of OTC drugs described above as eligible for GRASE determinations.[22]

Exclusivity Period for Certain Newly-Approved OTC Drugs

As an incentive, the OTC Monograph Reform Act provides for an exclusivity period for certain OTC drugs approved for marketing pursuant to the administrative order process established under the Act.[23]

Requestors of OTC drug monographs will be entitled to 18 months of market exclusivity for (1) drugs containing an active ingredient not previously addressed in an OTC monograph; or (2) a change in the conditions of use of a drug for which new human data studies were required and were conducted or sponsored by the requestor of the OTC drug monograph.[24]

[18] *Id.*
[19] *Id.* § 505G(a)(4).
[20] *Id.*
[21] *Id.* § 505G(a)(5).
[22] *Id.* § 505G(a)(6).
[23] *Id.*§ 505G(b)(5)(C).
[24] *Id.* § 505G(b)(5)(C)(ii).

Exclusivity will not be available for changes relating to Tier 2 OTC Monograph Order Requests,[25] safety-related changes, or changes related to methods of testing safety or efficacy.[26]

Establishes an OTC User Fee Program

The OTC Monograph Reform Act gives FDA authority to collect fees from manufacturers of OTC drugs to fund the review of OTC monograph requests, similar to the user fee programs for prescription drugs and other FDA-regulated products.[27]

Under the legislation, FDA is required to collect fees from owners of OTC monograph drug facilities and contract manufacturing organization facilities, as well as submitters of OTC monograph order requests beginning with fiscal year 2021.[28] For OTC monograph orders, the legislation establishes fees of $100,000 (Tier 2 OTC monograph) or $500,000 (Tier 1 OTC monograph).[29] Facility fees will be determined annually to meet a "total facility fee revenue amount" for the preceding year.[30]

The legislation also modifies FDCA Section 502 to include in the definition of "misbranded" drugs those drugs manufactured at a facility not current in its payments under the OTC drug fee program.[31]

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The OTC Monograph Reform Act will create important new opportunities for developers and manufacturers of OTC drugs, and it will be important for companies to closely monitor implementation of the law by the FDA. Our team will continue to monitor these developments, and we stand ready to advise you on compliance with the new law, as well as forthcoming regulatory guidance and regulations. Please feel free to contact us with any questions about the topics addressed in this Advisory.

[25] Tier 2 OTC Monograph Order Requests are defined in the legislation as requests relating to, among others, the reordering of existing information on the label of an OTC monograph drug, a change to ingredient nomenclature to align with the nomenclature of a standards-setting organizations, or minor changes made in accordance with procedures established by the OTC Monograph Reform Act. *Id.* § 744L(9)(A).
[26] *Id.* § 505G(b)(5)(C)(iv).
[27] *Id.* § 744M.
[28] *Id.* § 744M(a).
[29] *Id.* § 744M(a)(2).
[30] *Id.* § 744M(b).
[31] *Id.* § 744M(e)(1)(A)(ii).

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