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Incentives And Risks From OTC Drug Monograph Revamp

By **Albert Cacozza, Steven Gonzalez and Jenna McCarthy** (May 29, 2020, 6:14 PM EDT)

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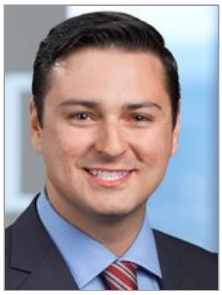

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On March 27, President Donald Trump signed into law the Coronavirus Aid, Relief and Economic Security Act, also known as Phase 3 of the coronavirus stimulus legislation. Title III, Subtitle F of the CARES Act, a provision unrelated to the current coronavirus pandemic, is an overhaul to the over-the-counter drug monograph system in the U.S.

This article analyzes the five key provisions of the OTC monograph reform, with a particular focus on the first four:

- An outline of the status of currently marketed OTC monograph drugs;
- An administrative process by which the U.S. Food and Drug Administration will establish/amend a monograph (as opposed to notice and comment rulemaking), including expedited procedures for imminent public health hazards;
- An 18-month exclusivity period for certain administrative orders;
- The creation of a user fee program; and
- Proposed modifications to the Sunscreen Innovation Act of 2014.

Background

Overview of the Current OTC Monograph System

Prior to the passage of the CARES Act, the FDA regulated OTC drugs using one of two regulatory pathways: the OTC monograph review process and the new drug approval process under Section 505 of the Federal Food, Drug, and Cosmetic Act.

The previous monograph process was established to evaluate the safety and effectiveness of OTC drug products marketed in the U.S. before May 11. For each therapeutic class, an advisory panel[1] reviews active ingredients to determine whether they are generally recognized as safe and effective, or GRASE, reviews claims and recommends appropriate labeling.

The panel's conclusions are published in the Federal Register in the form of an advanced notice of proposed rulemaking and interested parties may respond. The FDA then reviews active ingredients and publishes its conclusions in the Federal Register in the form of a tentative final monograph, or TFM, which is open for public comment. Finally, the FDA publishes a final monograph that establishes the conditions under which certain OTC drugs are GRASE, which allows companies to make and market an OTC product according to those conditions without seeking FDA preapproval.

If a drug meets each of the conditions contained in Title 21 of Code of Federal Regulations 330,[2] each of the conditions contained in any applicable OTC drug monograph, and other applicable regulations, it is considered GRASE, not misbranded, and is not required by the FDA to obtain a new drug application approval under Section 505 of the FDCA.

Conversely, an OTC drug that does not conform to a final monograph cannot be marketed without an NDA. A drug company may petition to change a final monograph to include additional ingredients or to modify the required labeling. In the absence of a final monograph for a particular active ingredient or indication, the FDA has generally

not pursued regulatory action against OTC products if they are marketed in conformance with conditions proposed in a TFM.[3]

Issues with the Current OTC Monograph System

The current OTC monograph system has been criticized for being cumbersome and inefficient.[4] For example, during a 2017 hearing in the House Subcommittee on Health that discussed potential OTC monograph reforms, Rep. Diana DeGette, D-Colo., described problems with the system, including the fact that it does not respond to emerging safety issues and the extremely burdensome process the FDA must use to update and change monographs.[5]

The FDA has acknowledged that the process does not provide the agency with a way to efficiently address safety issues, keep up with new scientific developments and ensure the consistent safety and effectiveness of various formulations.[6] Due to the lengthy and complicated nature of the OTC monograph process, some OTC monographs, such as the oral health care anti-gingivitis/anti-plaque monograph, have never been finalized.[7]

The OTC monograph system also has been criticized for not providing incentives for innovation. Unlike the NDA and Biologics License Application processes, the current OTC monograph system does not grant exclusivity under any circumstances to an OTC drug manufacturer.[8]

The CARES Act overhauls the existing OTC monograph system to address these concerns by, among other things, (1) creating an exclusivity period for certain innovative OTC products; (2) deeming certain TFMs as GRASE; (3) providing the FDA with expedited procedures to address safety issues; (4) replacing notice-and-comment rulemaking with an administrative order process; and (5) establishing user fees to facilitate prompt review and oversight of the OTC drug market.

Substantive Provisions of the OTC Reform

Drugs Subject to Current OTC Monographs

Ingredients included in OTC monographs are classified in three categories:[9] Category 1 — GRASE for the claimed therapeutic indication;[10] Category 2 — not GRASE or unacceptable indications;[11] and Category 3 — insufficient data available to permit final classification.[12]

The CARES Act amends the FDCA to add Sections[13] 505G(a)(1), (3) and (4), which describe the GRASE status and marketing requirements of drugs previously included in a monograph depending on the category for the drug and whether it was subject to a proposed, tentative,[14] or final monograph.[15]

Under the new law, both final monographs and Category 1 drugs subject to a TFM are deemed to be final administrative orders.[16] Category 3 ingredients subject to a TFM remain pending — i.e., are not automatically deemed GRASE, but will not require an NDA or be subject to the prescription requirements of Section 503(b)(1).[17]

Category 1 ingredients that are deemed GRASE in a proposed monograph or ANPRM will also remain pending in the same manner. Category 2 ingredients subject to a TFM or ingredients that are found not GRASE in a proposed rule have six months from the enactment of the CARES Act before they are deemed unapproved new drugs.[18]

Administrative Order Process

Current law requires OTC drug monographs to undergo the time-consuming notice-and-comment rulemaking process. The CARES Act replaces this requirement with a more rapid administrative order process.[19]

Under Section 505G(b), a drug is not a new drug and does not require approval under Section 505 if:

- The Secretary of Health and Human Services determines there are conditions under which the drug[20] is GRASE and is not subject to the prescription requirements in Section 503(b)(1);[21] and

- The drug is marketed in conformity with an administrative order under Section 505G(b), meets the general requirements for nonprescription drugs,[22] and, if applicable, meets the requirements for minor changes in dosage form.[23]

The secretary can issue an administrative order either by his/her own initiative or at the request of any person or group of persons marketing, manufacturing, processing or developing a drug. The administrative order process provides for an abbreviated public comment process, formal dispute resolution, hearings and judicial review of final agency actions.

Administrative Orders Initiated by the Secretary

If the secretary initiates a proposed administrative order, he/she must follow certain sponsor notification and Federal Register publication procedures.[24] The notification and publication procedures are different if the proposed order is a finding that a Section 505G(a)(3) drug — the existing monograph drugs that remain pending — is not GRASE.[25]

If, after public comment, the secretary determines it is appropriate to issue a final administrative order, the order and a detailed statement of reasons will be published in the Federal Register. The final order will not take effect until the time for requesting judicial review has expired.

In certain cases of harm to the public health or to mitigate a risk of serious adverse event, the secretary can issue an interim final administrative order that bypasses the proposed order process and can be effective immediately, rather than after the period for judicial review expires.[26]

Administrative Order Initiated at the Request of a Requester

A requester may initiate an administrative order to determine that a drug, or a change to a condition of use of a drug is GRASE, does not require an approved application under Section 505, and is not subject to the prescription requirements of 503(b)(1).[27] If a request is sufficiently complete, the secretary will file it and initiate the same notice, publication and public comment procedures as administrative orders initiated by the secretary.

A request for a change to a condition of use of a drug is limited to specific situations outlined in Section 505G(b)(5)(B)(i). A GRASE request for an entirely new active ingredient must include certain information to demonstrate prima facie safe nonprescription marketing and use of such drug.[28]

No Administrative Order Needed for Minor Changes in Dosage Form

Sponsors may make minor changes to the dosage form of an OTC drug and market it without an administrative order if the change meets the requirements in Section 505G(c). Among other requirements, the underlying drug must be GRASE and the change must not affect the safety and effectiveness of the drug or materially affect the absorption or other exposure to the active ingredient (compared to a reference product).

Dispute Resolution, Hearings and Judicial Review

Any requester subject to a final administrative order may request formal dispute resolution.[29] Only a person who participated in each stage of formal dispute resolution of a final administrative order with respect to a drug may request a hearing, and only those who are eligible to request a hearing are entitled to judicial review.[30] No decision of the final administrative order, dispute resolution, or hearing may take effect until the period for judicial review has expired (other than for expedited procedures).

Exclusivity

Unlike NDAs and BLAs, the OTC monograph process did not confer exclusivity to OTC drug manufacturers or otherwise provide incentives for innovation.

The CARES Act remedies this by providing an 18-month exclusivity period to requesters of final administrative orders in two scenarios: (1) where a drug contains an active ingredient not previously incorporated in certain specified drugs, or (2) where there is a change in the conditions of use of a drug where the requester conducts, sponsors or has an exclusive right of reference to certain clinical trials or studies that are essential to issuance of the order.[31]

Only one 18-month exclusivity period will be granted under each final order, which will start on the date the requester may lawfully market the drug.

User Fee Program

Prescription drugs have long been subject to a variety of fees for applications, program or facility fees, or for submitting drug master files to provide the FDA with adequate resources to process applications in a timely manner and support its oversight of a product area.[32] The CARES Act establishes a user fee program for OTC monograph drugs, including (1) a facility fee, and (2) an OTC monograph order request fee (for administrative orders requested by requesters).

Owners of facilities that meet the definition of an "OTC monograph drug facility" are required to pay an annual fee and submit certain required information about that facility.[33]

Each requester that submits an OTC monograph order request will be subject to a fee, the amount of which will depend on whether the request is classified as Tier 1 or Tier 2 (Tier 2 is a lower fee).[34] A Tier 1 request is defined as any request not determined to be a Tier 2 request. The act lists a number of Tier 2 requests that generally do not

impact safety or efficacy, and the secretary may, at its discretion, characterize any other request as Tier 2.[35]

A requester will be exempt from the OTC monograph order request fee if the request makes certain changes to the drug facts labeling in a way that would add to or strengthen the safe use of the product.[36]

Treatment of Sunscreen Innovation Act

The CARES Act substantially overhauls the Sunscreen Innovation Act[37] by providing amendments to the GRASE review process in Section 586, while also sunsetting the entire section at the end of fiscal year 2022. The administrative order process established in Section 505G (as outlined above) is intended to take its place, and sponsors currently subject to proposed sunscreen orders may elect to transition review to the new process.[38]

The CARES Act also provides for an 18-month exclusivity period for requesters of a change in a final sunscreen order permitting an active sunscreen ingredient not previously incorporated in a sunscreen marketed under the final monograph for sunscreen products or a final administrative order.

Insights for Industry

Many different stakeholders have emphasized the need to modernize the OTC monograph system, which has remained largely unchanged since 1972. Trade association groups praised the CARES Act for increasing the efficiency of the monograph process, and providing the FDA with resources and tools necessary to protect and promote consumer health.[39] The FDA lauded the OTC drug reform as a landmark step that will have a long-lasting impact and that grants the FDA transformative authority to modernize OTC drug development and review.[40]

The CARES Act could significantly impact both existing products and innovation for new products. Sponsors of OTC drugs that fall under existing monographs need to evaluate whether their products may have different regulatory requirements or may require an administrative order for continued marketing. Sponsors may soon receive notices from the FDA for drug listings for which administrative orders are being sought by other sponsors or for those initiated by the agency.

Entities that market, manufacture, process or develop certain OTC drug products will now be able to request administrative orders instead of participating in notice-and-comment rulemaking, which should expedite the review and approval process. This will be particularly impactful for new active ingredients or certain changes to the conditions of use for drugs, the approval for which could grant the requester 18 months of exclusivity. Some products may bypass the administrative order process entirely if they constitute only a minor change to the dosage form.

While these necessary reforms will provide sponsors and manufacturers with new incentives and tools for streamlined market entry and changes, they may also result in increased FDA scrutiny and enforcement activity. With a less cumbersome process and an infusion of revenue from user fees, the FDA is unlikely to continue its trend of generally lax oversight in the OTC monograph space.[41]

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[1] The Commissioner of Food and Drugs will appoint panels of qualified experts, and may include persons from lists submitted by organizations representing professional, consumer, and industry interests. See 21 C.F.R. 330.10.

[2] Including, for example, registration and listing, labeling, and current Good Manufacturing Practice requirements. 21 C.F.R. 330.1.

[3] See Over-the-Counter Drug Monograph System – Past, Present, and Future; Public Hearing, February 24, 2014, 79 FR 10168, 10169 (https://www.federalregister.gov/d/2014-03884/p-13).

[4] See Testimony before the Committee on Energy and Commerce, Subcommittee on Health, United States House of Representatives, September 13, 2017, https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Testimony-Moore-HE-Hrg-on-Modernizing-FDA%E2%80%99s-Regulation-of-Over-the-Counter-Drugs-09-13-17.pdf.

[5] See Modernizing FDA's Regulation of Over-the-Counter Drugs, September 13, 2017, House of Representatives, Subcommittee on Health, Committee on Energy and Commerce.

[6] Id.

[7] See 21 C.F.R. 356.

[8] See 21 C.F.R. 314.108; section 351(k)(7) of the PHSA; 21 C.F.R. 316.31.

[9] See 21 C.F.R. 330.10.

[10] An example of a category I ingredient is benzoyl peroxide used in topical acne products. See Classification of Benzoyl Peroxide as Safe and Effective and Revision of Labeling to Drug Facts Format; Topical Acne Drug Products for Over-the-Counter Human Use; Final Rule (March 4, 2010), https://www.regulations.gov/document?D=FDA-1981-N-0114-0001.

[11] Category II ingredients are also referred to as "excluded from the monograph." There does not appear to be a comprehensive list of nonmonograph ingredients. One example of a nonmonograph ingredient is colloidal silver for the treatment and/or prevention of disease. Strangely, the Federal Register notice also states that there is an absence of data demonstrating that ingredients present are GRASE, which risks conflating Category II and Category III. See 61 FR 44653, 44654 (August 17, 1999), https://www.govinfo.gov/content/pkg/FR-1999-08-17/pdf/99-21253.pdf.

[12] See 21 C.F.R. 310.545.

[13] Any reference simply to a "section" in this Alert refers to a section of the Federal Food, Drug, and Cosmetic Act.

[14] Any reference to a monograph in the CARES Act refers to the most recently applicable proposal or determination for a drug.

[15] Drugs in section 505G(a)(1)–(2) are deemed to be subject to a final administrative order. See section 505G(b)(8).

[16] Section 505G(b)(8).

[17] See section 505G(a)(3).

[18] See section 505G(a)(4).

[19] See section 505G(p) (stating that the requirements of subsection (b) ["Administrative Orders"] shall apply with respect to orders issued under this section instead of the requirements of 5 U.S.C. §§551–559).

[20] Including a class of drugs or combination of drugs. See section 505G(b)(1)(A).

[21] Drugs that "because of [their] toxicity or other potentiality for harmful effect . . . [are] not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or . . . is limited by an approved application . . . to use under the professional supervision of a practitioner." See section 503(b)(1)(emphasis added).

[22] Including those explicitly preserved in section 505G(k).

[23] See section 505G(c).

[24] See section 505G(b)(2).

[25] See section 505G(b)(2)(B).

[26] See section 505G(b)(4)(A)–(B).

[27] See section 505G(b)(5)(A).

[28] See section 505G(b)(6).

[29] The bill does not specify the granular procedures applicable for this formal dispute resolution, although CDER and CBER currently carry out such dispute resolution in accordance with 21 C.F.R. §§ 10.75, 312.48(c), and 314.103(c). See also FDA, Guidance for Industry—Formal Dispute Resolution: Sponsor Appeals Above the Division Level (Nov. 2017), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-dispute-resolution-sponsor-appeals-above-division-level-guidance-industry-and-review-staff.

[30] Judicial review will follow the procedures described in section 505(h), except that review must be sought in the appropriate district court, rather than the appellate courts.

[31] See section 505G(b)(5)(C).

[32] See Prescription Drug User Fee Amendments, https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments; Generic Drug User Fee Amendments, https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments.

[33] An OTC monograph drug facility is defined as a foreign or domestic establishment that manufactures or processes (or contract manufactures or processes) a finished dosage form of an OTC monograph drug. An establishment counts as a single facility if it is under one management (direct or indirect) and at one geographic location or address. See section 744L(10)(A).

[34] See section 744M(a)(2)(A).

[35] For a full list of Tier 2 requests, see Section 744L(8)–(9).

[36] See section 744M(a)(2)(C)(i)–(iii).

[37] See section 586.

[38] Upon a sponsor's written notification of transition, the proposed sunscreen order will be deemed a request for an administrative order and also deemed accepted for filing.

[39] See CHPA Statement Regarding OTC Measures in COVID-19 Legislation, Consumer Healthcare Products Association, https://www.chpa.org/Monograph_FSA_CARES.aspx.

[40] FDA on Signing of the COVID-19 Emergency Relief Bill, Including Landmark Over-the-Counter Drug Reform and User Fee Legislation, March 30, 2020, https://www.fda.gov/news-events/press-announcements/fda-signing-covid-19-emergency-relief-bill-including-landmark-over-counter-drug-reform-and-user-fee.

[41] See Over-the-Counter Drug Monograph System – Past, Present, and Future; Public Hearing, February 24, 2014, 79 FR 10168, 10169 (https://www.federalregister.gov/d/2014-03884/p-13).
