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MEMORANDUM

Summary of the OTC Monograph Drug Review Reform Provisions in The Coronavirus Aid, Relief, and Economic Security Act (CARES Act) 2020

On March 27, 2020, President Trump signed into law the CARES Act which includes an array of COVID-related provisions. CARES Act, Pub. L. 116-136 (2020). Among these provisions, the over-the-counter (OTC) monograph reform legislation, which has been stalled in Congress for more than two years, finally found its way to becoming law. The OTC monograph reform legislation has been supported by both U.S. Food and Drug Administration (FDA) and regulated industry as a means to modernize the, what some people have identified as archaic and cumbersome, existing OTC monograph system which had become bogged down by the requirements of the rulemaking process, limited resources, and other constraints.

The OTC monograph reform provisions of the CARES Act appear in Subtitle F. Congress did not name the law. Part I provisions address the reform of the review process and are added to the Food, Drug, and Cosmetic Act (FDC Act) in new section 505G. For purposes of our summary, we refer to this Part I as the OTC Monograph Reform, or OMR. Subtitle F Part II covers the new OTC monograph user fee provisions adding sections 744L and 744M to the FDC Act. For purposes of our summary we refer to these provisions as the OTC monograph user fee act (OMUFA). References below are to sections of the FDC Act unless otherwise noted.

The overarching purpose of the OMR is to move the OTC monograph drug review framework from one of notice and comment rulemaking to an administrative order process exempt from certain requirements of the Administrative Procedures Act. In addition, the OMR is designed to provide for innovation such as additional active ingredients, new indications, and new dosage forms. Importantly, it also is intended to give FDA the means to more quickly respond to and address safety concerns.

This memorandum summarizes the main provisions of the new provisions. We are happy to help anyone work through the details.

Part I: OTC DRUG REVIEW: REFORM OF OTC MONOGRAPH DRUG REVIEW

Background

Generally, any "new drug" must undergo FDA review for safety and efficacy to obtain marketing approval before it may be legally marketed. FDC Act § 505(a). However, if the drug is "generally recognized as safe and effective" (GRASE), then it is exempt from regulation as a "new drug" and may be marketed without prior approval. Id. § 201(p)(1). This provision of the statute remains intact.

In 1972, FDA initiated the comprehensive review of safety, effectiveness, and labeling (that is, a review of the GRASE status) of OTC drugs then on the market, known as the OTC Drug Review, or the OTC Review. The process involved three phases of review for each category of OTC products culminating in a determination by FDA, in the form of a federal regulation, that certain active ingredients are GRASE for specific uses, and that drugs meeting those conditions may be marketed without premarket review.

Based on a review of data and other information, ingredients were classified as GRASE and not misbranded (Category I), not GRASE (Category II), or lacking sufficient data on safety or efficacy to permit classification (Category III). Part of this determination included recommendations for dosage instructions, warnings, and claims that could be made in OTC drug labeling. As part of the notice and comment rulemaking, FDA would issue an advanced notice of proposed rulemaking (ANPR), a proposed rule (also referred to as the tentative final monograph or TFM) and, finally, the final rule or final monograph which would be codified in the code of federal regulations, 21 C.F.R. part 330 et seq. While some monographs have been finalized, many have not, leaving drugs covered by those unfinished monographs in the uncertain regulatory status of being marketed under a TFM or ANPR subject to FDA's enforcement discretion for years and, in some cases, decades.

Revised Status of Drugs Currently Covered by the OTC Drug Review Under OMR

- Final monographs: under OMR , final monographs are deemed final administrative orders and drugs marketed in conformity with a final monograph will not be considered a new drug requiring premarket approval.
- Unfinished monographs subject to a TFM or ANPR:
  - Sunscreen Drugs – the OMR includes provisions specifically for sunscreen drugs (discussed further below).
    - A drug that is classified as category I for safety and effectiveness under a TFM (or ANPR) and conforms with the requirements of that TFM or

ANPR (i.e., meets the ingredient, labeling, and other conditions of the TFM or in the preamble of the ANPR) will not be considered a new drug requiring premarket approval; it will be treated as if the ANPR or TFM had been finalized.

- A drug that is classified as category III for safety or effectiveness under a TFM and conforms with the proposed requirements of that TFM for category I ingredients also will not be considered a new drug requiring premarket approval; it will be treated as if the TFM had been finalized, unless and until FDA issues a final administrative order determining that it is not GRASE.
- A drug that is classified as category II for safety or effectiveness under a TFM or ANPR, or category III under an ANPR is deemed a new drug requiring premarket approval. Note that a category II classification because of safety or efficacy will cause the drug to be a new drug regardless of the classification for the other requirement. Thus, a drug that was classified as category I for effectiveness but category II for safety in the TFM will be considered a new drug, unless FDA takes action to allow its continued marketing. This does not mean that a Category II drug currently on the market must be immediately removed. However, FDA could prohibit future shipments of the drug unless the Agency grants an extension, or the drug is upgraded to GRASE or gains new drug approval.

- The OMR also recognizes drugs in dosage forms existing for "a material time and a material extent" at the time of enactment as not being considered new drugs. In effect, this provision does away with the difficult-to-implement concept that to be covered by a monograph, a drug had to be in a dosage form in which the particular drug was marketed before 1972 – a provision that was proving to be less relevant as time went on, as well as difficult to enforce.

New Administrative Orders

The new framework includes an administrative order process that replaces notice-and-comment rulemaking. Orders may be issued on FDA's initiative or upon a party's request. FDA may issue an ordinary order or an expedited order.

Proposed Ordinary Orders Issued on FDA's Initiative

Orders initiated by FDA under the ordinary procedure will entail public notice, opportunity for comment, a dispute resolution procedure, an opportunity for an administrative hearing, and an opportunity for judicial review. Before FDA issues a proposed administrative order, it must "make reasonable efforts, not later than 2 business

days before issuance," to notify sponsors who have a drug listing in effect for drugs that will be affected by the order. The proposed order must be published on FDA's website along with the reasons for it (essentially the information that has previously been included in the Federal Register preamble for a proposed rule). FDA must publish a notice of availability of the proposed order in the Federal Register. If after the notice and comment period, FDA issues a final order, it will not take effect until after the time for requesting judicial review has expired. (See *Appeals and Hearings* below.)

Imminent Hazard Orders and Safety Labeling Changes

One of the issues the OMR was designed to resolve was FDA's inability to address safety issues in a timely fashion. To that end, it includes a specific expedited procedure for administrative orders initiated by FDA. It distinguishes two types of safety issues: those that pose an "imminent hazard to the public health" and those that require certain safety labeling changes.

Imminent hazard to public health: If the Secretary of Health and Human Services (this authority may not be delegated) determines that a drug, or class or combination of drugs poses an imminent hazard to the public health, the Secretary may issue an interim final administrative order with a detailed statement of reasons for the order. As with the ordinary procedure, the Secretary must make reasonable efforts to provide notice no less than 48 hours before issuing the interim final order to those who have a listed affected drug. FDA must publish a notice about the availability of the interim final order in the Federal Register and provide for a 45-day public comment period.

Labeling safety: In the case of safety labeling changes, FDA may issue an interim final order to require a change in the labeling in a drug, or class or combination of drugs reasonably expected to mitigate a "significant or unreasonable risk of a serious adverse event associated with the drug." FDC Act § 505G(b). This type of expedited order may require new warnings and other information required for safe use of the drug. The same notice and comment period requirements as for an imminent hazard order apply.

FDA is authorized to issue an interim final order before providing an opportunity for comment, a hearing or judicial review.

Orders Initiated on Request

Any party may submit a request to FDA for an administrative order that a drug is GRASE or that a change to a condition of use of a drug is GRASE. The request must be sufficiently complete and properly formatted. The requestor may withdraw a request and if the request is withdrawn, FDA may cease its review. Procedures for dispute resolution and an administrative hearing and judicial review are provided.

The OMR defines two tiers of OTC monograph requests. A "Tier 2 OTC monograph order request" is defined as including a request for reordering existing information in the Drug Facts for an OTC monograph drug; addition of information to the "other information" section of the Drug Facts; modification to the "Directions section" of the Drug Facts label consistent with otherwise approved changes; standardization of a concentration or dose; nomenclature change; or addition of an interchangeable term and any order request which FDA determines to be Tier 2. A Tier 1 request is anything that is not Tier 2.

Exclusivity

A new concept for OTC monograph drugs is the opportunity to obtain exclusivity. An 18-month period of exclusivity is available for requestors if an order is issued for a new active ingredient or a change in an existing monograph for which new human data studies essential to issuance of the order were conducted or sponsored by the requestor (or for which requestor has an exclusive right of reference).

For purposes of exclusivity, "new human data studies" means clinical trials of safety or effectiveness including actual use studies, pharmacokinetic studies, and bioavailability studies. "Non-human data" means data from tests other than with human subjects that provide information concerning safety or effectiveness that have not been relied on and do not duplicate a study that was relied on to support a proposed or final determination that a drug is GRASE or for approval of a new drug application (NDA) or abbreviated NDA.

The period of exclusivity begins on the date the requestor may lawfully market the drug pursuant to the order. The OMR does not provide a specific remedy for violation of the exclusivity or require specific action on the part of FDA to police the marketplace for violators.

Appeals and Hearings Related to Final Orders

The OMR also adds an appeal process similar to what is already available to NDA sponsors. Sponsors [text of the statute uses "requestors," but this appears to be a technical error] of drugs that will be subject to the order will have the opportunity for formal dispute resolution up to the level of the Director of the Center of Drug Evaluation and Research (CDER). The initial request for formal dispute resolution must be made within 45 calendar days after issuance of the final administrative order and for subsequent levels of appeal, within 30 calendar days of the prior decision.

If there is still a dispute after the appeals process has been exhausted, any party that participated in each stage of the formal dispute resolution may request a hearing concerning the final administrative order. Such a request must be submitted within 30 days after receipt of the final decision of the formal dispute resolution process.

FDA may deny the request for a hearing if it concerns a final order related to a drug that was in category III and for which no "human or non-human data studies" relevant to the safety or efficacy of the drug have been submitted to FDA since the issuance of the most recent TFM. "Human data studies" in this context are clinical trials including actual use studies, pharmacokinetic studies, and bioavailability studies. "Non-human data" are data from testing other than with human subjects which provide information concerning safety or effectiveness.

The request for a hearing will be denied if FDA determines that the request does not identify the existence of a "genuine and substantial question of material fact" after considering only information and data that are based on relevant and reliable scientific principles and methodologies. If more than one party requests a hearing for the same administrative order, a single hearing may be conducted in which all who requested a hearing may participate. The presiding officer of the hearing will be designated by the Secretary (whom we can expect will delegate to the FDA Commissioner) and must not be an employee of CDER or have been involved in the development of the relevant order or in proceedings related to the order.

A request for judicial review of the final decision must be filed within 60 days of issuance of a final order, a denial of a hearing, the date of final decision regarding a hearing, or if no hearing has been requested, the date on which the time for requesting a hearing expires. The request must be filed with an appropriate U.S. District Court of the United States.

Minor Changes in Dosage Form

Under the original OTC monograph system, FDA had taken the position that only those dosage forms available at the time the monograph was established were eligible for marketing under a monograph. This impediment to innovation was seen as a major shortcoming of the system and has been addressed, in part, by a new provision allowing for minor changes in dosage form without issuance of an order provided the information necessary to demonstrate that the change will not affect the safety or effectiveness of the drug or materially affect the extent of absorption or other exposure to the active ingredient compared to a "suitable reference product." Records relating to the change must be provided within 15 days of a request from FDA. If the sponsor fails to provide the requested records or FDA determines the information does not support the change, the drug as modified (i.e., in the different dosage form) will be deemed a misbranded new drug. The OMR directs FDA to issue an order and guidance on how to determine whether a change will qualify as minor.

Packaging

FDA orders may include requirements for the packaging of a drug to encourage use of the drug in accordance with labeling. With some limitations, packaging requirements may include unit dose packaging, requirements for products intended for use by pediatric populations, requirements to reduce the risk of harm from unsupervised ingestion, and other appropriate conditions.

Special Provisions Concerning Sunscreens and the Sunscreen Innovation Act

As mentioned earlier, the OMR includes provisions for current OTC sunscreen monograph drugs separate and apart from those for non-sunscreen OTC monograph drugs. Specifically, the OMR provides that a sunscreen monograph drug will be considered GRASE if it conforms with the 1999 final monograph, and the testing and labeling requirements in 21 C.F.R. § 201.327. The 1999 final monograph has never been effective because it was stayed for almost 20 years until Feb. 26, 2019. At that time, FDA issued a proposal to amend and finalize the sunscreen monograph. Sunscreen Drug Products for Over-the-Counter Human Use, 84 Fed. Reg. 6,204 (Feb. 26, 2019). As explained in the proposal, FDA had concluded that changes in conditions in the nearly 20 years since the publication of the 1999 rule meant that additional safety data were needed to establish that certain of the active ingredients included in the 1999 monograph are GRASE for use in sunscreen products. The 2019 proposed rule (the TFM) was comprehensive in that it addressed the standards for safety, dosage forms, testing, and labeling of sunscreen drug product. However, the OMR does not reference the 2019 TFM and instead refers to the 1999 final monograph. Likely this is the result of the

legislation languishing in Congress for several years even after the House and Senate were in accord on almost all its provisions.

Although the OMR states that the 1999 sunscreen monograph drug products will be considered GRASE, it also mandates that FDA amend and revise the 1999 sunscreen monograph. Specifically, no later than 18 months after enactment of the OMR , FDA must issue a revised order with an effective date of at least one year after the publication of the revised order. The OMR does not specify the contents of the amendments. However, if the revised order does not include provisions related to sun protection factors (SPFs) and all known dosage forms, FDA must submit a report to the authorizing committees with a rationale and plans to address those provisions. Since provisions regarding SPFs and dosage forms were addressed in the 2019 TFM, that TFM seems an excellent starting point for the mandated revised order.

The OMR also includes provisions regarding orders pending under the 2014 Sunscreen Innovation Act (SIA), which provided a process for the review of safety and effectiveness of OTC sunscreen active ingredients for which Time and Extent Application (TEA) had been pending for more than a decade. However, since FDA never proposed any orders under the SIA and, under the OMR, the SIA will sunset at the end of fiscal year 2022, the provisions addressing the SIA are unlikely to be relevant for anyone.

Pediatric Indications for Cold and Cough Products

For quite some time, FDA has been in the process of revisiting the pediatric doses of cold and cough products because of concerns about safety. Although the OMR does not set a deadline or specify a timeline for FDA, it does require that FDA annually submit a letter describing its progress in the evaluation of cough/cold monograph drugs marketed under the final monograph for children under age six. Once FDA has finalized its evaluation and issued a final order addressing cold and cough products for this category of children, the obligation to submit annual letters ends.

Guidances

The OMR requires that FDA issue several guidances, including guidance on:

- the procedures and principles for formal meetings between FDA and sponsors or requestors;
- the format and content of data submissions;
- the format of electronic submissions;
- consolidated proceedings for appeal and related procedures; and,
- recommendations on the information required to support a minor change in dosage form.

Miscellaneous

A GRASE determination will constitute a finding that the drug is safe and effective and may be relied upon for purposes of an application under section 505(b)(2). All submissions must be electronic. Provisions are included to allow for certain information submitted by industry to not be made public. FDA is directed to establish procedures for allowing industry to meet with FDA to obtain advice on studies and submissions, and to facilitate efficient participation by multiple sponsors or requestors in various proceedings.

Timing/FDA Goals Letter

Other than for certain actions, such as those related to the sunscreen monograph, the OMR does not specify the timing of actions by FDA. Those are described in FDA's goals letter incorporated by reference into the law.

On June 7, 2017, FDA submitted to Congress a user fee goals document describing its planned activities if Congress were to enact a monograph reform bill and authorize FDA to charge user fees. FDA, Over-the-Counter Monograph User Fee Program Performance Goals and Procedures - Fiscal Years 2018-2022 (Goals Letter), https://www.fda.gov/media/106407/download. FDA prepared this goals letter in cooperation and based on discussions with stakeholders, and on the then proposed OTC monograph review bill.

The Goals Letter details how FDA plans to implement the various provisions of the OMR. Broadly speaking, the goals for the first five years are:

- Building basic infrastructure to meet the goals of monograph reform (hiring and training new personnel and development of information technology)
- Enabling industry-initiated innovation
- Enabling streamlining of industry and FDA safety efforts
- Enabling efficient completion of Category III final GRASE (determinations requested by industry or initiated by FDA (or mandated by Congress))
- Development of measures to track success and agency accountability

As mentioned above, FDA must develop several guidances laying out procedures applicable for the revised OTC drug review process. As explained in the Goals Letter, FDA expects that its activities in the first three years will focus on building infrastructure and developing guidance and procedures to implement the provisions under the OMR, specifically the procedures concerning industry requests for orders. FDA set timelines

and performance goals for industry requests for orders submitted in year 4 and 5. Requests submitted before year 4 will be reviewed as time permits, in order of receipt.

As noted in the Goals Letter, FDA's activities will not be limited to the activities included in summary table, Table II.J.3. The monograph review staff will also be involved in many "baseline" activities, which at that time included finalizing the rulemaking for antiseptics as well as activities under the SIA. As detailed in the Goals Letter, FDA committed to publish, by October 1 of each year, a nonbinding listing of monograph issues FDA intends to address in the next three years.

Part II: USER FEES; THE OTC MONOGRAPH USER FEE ACT

A core component of OTC monograph reform is the introduction of a user fee program, the OTC Monograph User Fee Act (OMUFA).

As noted previously, the process of completing and updating monographs had moved at a glacial pace in large part due to FDA's lack of resources. Because OTC monograph drugs are not required to obtain an NDA or abbreviated NDA, the resources provided by other user fee programs (PDUFA and GDUFA) have not been allocated for use in developing monographs. In 2016, FDA initiated meetings and discussions with stakeholders about the potential of a user fee program for OTC monograph drugs. See Over-the-Counter Monograph User Fees: Public Meeting; Request for Comments, 81 Fed. Reg. 29,275 (May 11, 2016). FDA indicated that the creation of a user fee program could result in a "stable and predictable source of adequate funding" that would allow FDA to more quickly complete OTC drug reviews. Id. at 29, 277. FDA, industry, and other stakeholders agreed that a user fee program was needed to support the modernization of OTC monograph activities. The resources generated by a user fee program would be used to support improving the timeliness of review activities, facilitating innovation on behalf of consumers, and enabling the agency to better respond to urgent safety issues.

Fees authorized by OMUFA will be dedicated to OTC monograph drug activities, as set forth in the goals letter.

Facility Fees

Under new section 744M, each person that owns a monograph drug facility on December 31 or at any time in the preceding year shall be assessed a facility fee unless the facility has ceased all activities related to monograph drugs by December 30 of the year immediately preceding the applicable fiscal year. For example, for the user fees to be assessed for FY2021 (the first year for which the fees will be assessed), the relevant

date to determine if a facility is subject to a fee will be whether the facility was registered on December 30, 2019.

The Act provides that FDA must set the facility fee for FY2021 no later than the second Monday in May 2020 (i.e., May 11, 2020). In subsequent years, FDA must set the fee no later than the second Monday in March. However, the date is not relevant in light of the provision that FDA may only collect and obligate user fees in the amount provided in advance in an appropriations act. As of August 2020, legislation providing appropriation for the user fees has not been enacted. Thus, when fees will be due remains uncertain.

Facility fees will be due 45 days after FDA publishes the notice setting forth the fee amount. For subsequent years, the facility fees will be due the later of the first business day in June or the first business day after enactment of the appropriations authority. Failure to pay the facility fee within 20 days after the due date causes all the drugs manufactured by the facility to be misbranded. Moreover, the "delinquent" facility will be placed on a public arrears list. Fees not received by FDA after a grace period will be treated as a U.S. government claim.

OMUFA defines two types of facilities subject to fees, OTC monograph drug facilities and contract manufacturing organizations. Contract manufacturing organizations are subject to 2/3 of the fee for an OTC monograph drug facility.

New FDC Act § 744L defines an "OTC monograph drug facility" as a foreign or domestic entity at "one geographic location or address engaged in [the] manufacturing or processing the finished dosage form of an OTC monograph drug." Separate buildings in one geographic location under the supervision of the same local management are treated as a single facility. The term monograph drug facility does not include research suppliers, testing facilities, and entities that are solely engaged in placing outer packaging on packages containing multiple products when the products included are already in final packaged form. The term "Contract manufacturing organization" is defined as a monograph drug facility where neither the owner nor any affiliate sells the OTC monograph drug produced at the facility directly to wholesalers, retailers, or consumers in the United States.

The target fee collections from facility fees are set for FY2021 through FY2025. As with other user fee programs, the OMUFA is subject to reauthorization which will set target fee collections for subsequent years.

Order Fees

Industry-initiated OTC monograph order requests discussed above are subject to "order fees." For FY2021, fees are set at $500,000 for Tier 1 requests and $100,000 for Tier 2 requests. Note, however, that industry order requests for safety-related label changes (as explained earlier, such requests would be tier 2) are exempt from the fee. Fees will be due on the date of submission of the request. For subsequent years, the fees will be adjusted for inflation.

If a Tier 1 request is reclassified by FDA as a tier 2 request, FDA will refund the difference between the Tier 1 and Tier 2 fee. If the sponsor withdraws the order request before it has been accepted or refused for filing, or if FDA refuses filing, 75% of the order fee will be refunded. FDA has discretion to refund part of the fee if the order request is withdrawn after filing. FDA's decision regarding a refund is not reviewable.

Reports

FDA must prepare two reports under OMUFA, a performance report and a fiscal report. Both reports must be prepared annually within 120 days of the end of the fiscal year.

The performance report must describe FDA's progress and future plans for meeting the performance goals which FDA previously has identified in the Goals Letter. The fiscal report must address FDA's implementation of its fee authority, fee uses, and collections.

As mentioned previously, the user fees have been authorized for FY2021 through FY2025. FDA must work with various stakeholders in preparing recommendations for reauthorization of the program beyond FY2025. FDA must prepare and post (for comments), a recommendations report and submit final recommendations (a new Goals Letter) by January 15, 2025.