U.S. FOOD & DRUG ADMINISTRATION

APR 20 2018

The Honorable Bob Goodlatte
Chairman
Committee on the Judiciary
House of Representatives
Washington, D.C. 20515-6216

Dear Chairman Goodlatte:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the July 27, 2017, hearing before the Subcommittee on Regulatory Reform, Commercial and Antitrust Law, House Committee on the Judiciary, entitled "Antitrust Concerns and the FDA Approval Process." This letter is a response for the record to questions posed by the committee.

If you have further questions, please let us know.

Sincerely,

John Martin
Principal Associate Commissioner
for Legislative Affairs

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We have restated your questions below in bold, followed by our responses.

The Honorable Tom Marino

1. **Under the DESI process, FDA has discretion to remove generics from the marketplace, ease generics off the marketplace, or allow them to remain if it is in the best interest of the patient community. What factors or criteria are used to make these determinations?**

DESI drugs are not the same as "generic drugs" subject to section 505(j) of the FD&C Act and these DESI drugs have not been approved by FDA. FDA assumes that the question's reference to "generics" was intended to mean drug products related to the DESI process, which is explained below.

By way of background and context, the Drug Efficacy Study Implementation (DESI) is the FDA's administrative implementation of the 1962 Kefauver-Harris amendments to the Federal Food, Drug, & Cosmetic (FD&C) Act. The 1962 amendments required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962 through the new drug approval process. FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to initially evaluate the effectiveness of these products. FDA reviewed and re-evaluated the findings of the NAS/NRC panels and published its findings on the effectiveness of these products, sometimes referred to as "DESI drugs," in the Federal Register. The Agency provided a notice of opportunity for hearing (NOOH) for any indication for which a product subject to a DESI proceeding was found to be less than fully effective. Currently, there are very few DESI proceedings for which a final determination regarding effectiveness has not yet been made.

Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Drug products that are IRS to the products listed in a DESI notice are also considered to be subject to the DESI proceeding. As noted above, these IRS drugs are not the same as "generic drugs" subject to section 505(j) of the FD&C Act. In addition, they have not been approved by FDA.

FDA's current policy on drug products subject to an ongoing DESI proceeding, including IRS drug products, is outlined in FDA's Compliance Policy Guide (CPG) (Marketed Unapproved Drugs CPG, at p. 10) published in 2011. Specifically, the CPG in part states that "[i]t is the Agency's longstanding policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding."

Once a DESI proceeding is completed, if the products subject to it are found not effective for a particular indication, FDA generally will evaluate on a case-by-case basis whether the Agency does not intend to object to a period of continued marketing for IRS products. The factors we may consider in such a situation are enumerated in the Marketed Unapproved Drugs CPG (at pp. 6-7), and include the following:

- the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug);
- the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application;
- the burden on affected parties of immediately removing the products from the market;
- the Agency's available enforcement resources; and
- any special circumstances relevant to the particular case under consideration.

For additional information on DESI proceedings and related enforcement aspects, see 21 CFR 310.6 and the Marketed Unapproved Drugs CPG. See *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf.*

2. **What is FDA doing to ensure that there are no drug shortages when, under the DESI process, the agency asks generic manufacturers to leave the marketplace? I am greatly concerned that we will be in a situation where my constituents don't have access to potentially life-saving drugs.**

As discussed in the response to Question 1 and in the Marketed Unapproved Drugs CPG, one factor FDA may consider when deciding whether it does not intend to object to continued marketing for a period of time is "the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug)" (Marketed Unapproved Drugs CPG, p. 6).

FDA's Center for Drug Evaluation and Research's Office of Compliance consults with FDA's Drug Shortages Staff before instituting any regulatory action to remove a drug from the market, to proactively prevent or mitigate any shortage which may occur from its removal. This process is used regardless of the regulatory status of the drug being removed from the market. For more information that describes FDA's efforts to prevent the shortage of potentially life-saving drugs, please visit FDA's Drug Shortages website: *https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm.*

3. **While companies are going through the ANDA approval process, what steps can FDA do to ensure that there is a smooth transition in the marketplace thereby ensuring that patients are not harmed nor lose access to lower cost alternatives? I want to ensure that my constituents maintain access to lower cost alternatives and not held hostage to the pricing decisions of one manufacturer.**

FDA strongly agrees it is important to expand access to affordable medicines. First, FDA's Office of Generic Drugs prioritizes and expedites the review of certain generic drug applications, including potential first generics that can open the market to competition for the first time. FDA recognizes these applications as public health priorities and expedite their review with the goal of

expanding access to affordable medicines. This policy is set forth in the Center for Drug Evaluation and Research's Manual of Policy and Procedures (MAPP) 5240.3, Revision 3, "Prioritization of the Review of Original ANDAs, Amendments and Supplements."[1]

Second, FDA has taken steps to target the specific problem you reference – namely, sole source drug products vulnerable to potential price gouging by unscrupulous bad actors. It recently published an updated list[2] of off-patent, off-exclusivity brand drugs for which FDA has not approved a generic, and encouraged generic companies to submit applications for these drugs. FDA will expedite the review of any such applications. This, too, is described in the MAPP referenced above. By law, FDA generally cannot approve a generic drug until patent and exclusivity protections on the innovator product have been exhausted.

Third, to foster competition broadly, FDA has developed a Drug Competition Action Plan. Under the plan, FDA is implementing new initiatives to streamline the generic drug application review process, enhance the development and review of difficult-to-develop complex generic drug products, and crack down on brand company "gaming" that frustrates and delays the approval and/or marketing of generic drugs that would compete with the branded drug. FDA held a public meeting on July 18, 2017, to solicit stakeholder input on these initiatives. It received feedback from stakeholders in the public docket for these initiatives, which closed November 17, 2017. For your reference, the public docket comments can be accessed at *www.regulations.gov* using docket number FDA-2017-N-3615.

About half of all generic drugs FDA has approved are no longer marketed, marketed intermittently, or were not initially marketed until long after approval. Sometimes this is for valid commercial reasons or because the standard of care has evolved. In other cases, generic drug manufacturers view FDA approval as an option to market, and realize the value of the option by deferring marketing pursuant to patent settlement or like agreements with the brand company. Anticompetitive conduct is within the purview of the Federal Trade Commission (FTC). A senior FTC official was a co-panelist at FDA's recent public meeting, and FDA is exploring opportunities to further collaborate with FTC.

4. **On June 23, 2017, the Subcommittee on the Constitution and Civil Justice held a hearing titled "Examining Ethical Responsibilities Regarding Attorney Advertising." That hearing examined the ethical issues around some attorney advertising about FDA regulated and approved products. Does the FDA have the authority to regulate legal advertising about FDA approved and regulated products including biopharmaceuticals,**

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[1] Center for Drug Evaluation and Research's Manual of Policy and Procedures (MAPP) 5240.3, Revision 3, "Prioritization of the Review of Original ANDAs, Amendments and Supplements". See *http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf.*

[2] FDA's List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic. See *https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM564441.pdf.*

medical devices, and regulated consumer healthcare products is sufficient to ensure patient safety?

The FD&C Act and its implementing regulations provide authority for FDA to regulate advertising for prescription drugs. By way of background, under section 502(n) of the FD&C Act (21 U.S.C. 352(n)) and 21 CFR Part 202, a prescription drug marketed in the United States is misbranded unless advertisements issued by the "manufacturer, packer, or distributor thereof" meet specific requirements, including that they contain accurate information about the drug, addressing both risks and benefits, and that the advertising is truthful, balanced and not misleading. It is a prohibited act under section 301(a) of the FD&C Act (21 USC 331(a)) to introduce (or cause to be introduced) or deliver (or cause to be delivered) into interstate commerce a misbranded drug.

The FD&C Act also gives the Agency authority over the advertising of restricted medical devices (21 U.S.C. 352(q) and (r)). Devices may become restricted by regulation issued under section 520(e) of the FD&C Act (21 U.S.C. 360j(e)), by performance standard issued pursuant to section 514(a)(2)(B)(v) (21 U.S.C. 360d(a)(2)(B)(v)), or by order approving an application for premarket approval (i.e., a PMA) pursuant to section 515(d)(1)(B)(ii) (21 U.S.C. 360e(d)(1)(B)(ii)). Section 502(r) of the FD&C Act requires a "brief statement of intended uses" and relevant risk information in restricted-device advertising issued by the device manufacturer, packer, or distributor. Section 502(q) of the FD&C Act provides that restricted-device advertising that "is false or misleading in any particular" misbrands the device.

The legal advertisements you refer to are disseminated by lawyers seeking clients for their legal services; they are not advertisements for the medical product itself issued by a manufacturer or other party responsible for marketing the drug or restricted device within the scope of section 502 of the FD&C Act.

5. **Some legal advertising about FDA approved and regulated products use the FDA's logo as part of that advertising. Is the use of the FDA's logo sanctioned by the FDA? If not, should Congress prohibit the use of the term "Food and Drug Administration," "FDA," the FDA's insignia or provide the FDA the authority to regulate the use of those or related terms and insignia?**

FDA has not authorized, or sanctioned, the use of the FDA logo in attorney advertising. FDA notes that there are existing legal authorities that may be applicable to use of the FDA logo in attorney advertising, such as the Lanham Act (15 U.S.C. 1125 et seq.), section 5 of the Federal Trade Commission Act (15 U.S.C. 45), and relevant case law, which address the fair use of terms and logos (a/k/a "trade names" and "marks"), the infringement of trade names and marks, and unfair or deceptive acts or practices affecting commerce.

6. **With respect to citizen petitions, several scholars have called for increased transparency to make data on citizen petition filings and dispositions more publicly available. Do you have any concerns about increasing the disclosure of such information?**

All citizen petitions received by FDA are assigned a docket number and made available on *www.regulations.gov*. The website currently has several features that allow the public to identify citizen petitions filed with the Agency, determine the status of citizen petitions, and be notified when a change to the status occurs. The public can identify citizen petitions that have been submitted to FDA by using the advanced search feature available on *www.regulations.gov* (*www.regulations.gov/AdvancedSearch*) by using both the "By Agency" (i.e., FDA) and Document Type (i.e., Citizen Petition) filters. The public can identify the status of citizen petitions by opening the relevant docket folder, which will allow them to see whether comments have been submitted and whether FDA has issued a response (interim or final). Additionally, *www.regulations.gov* includes a feature that allows any individual to receive email updates if there are changes to a citizen petition docket. Any individual who does not have access to the internet can view citizen petition dockets by visiting FDA's Dockets Management Staff at 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FDA believes the availability of citizen petitions through the *www.regulations.gov* website and through FDA's Dockets Management Staff provides an appropriate level of transparency.

The Honorable Darrell E. Issa

1. **The FDA website currently lists forty-two products with FDA authorized risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU). Of those forty-two reference products, how many have been subject to at least one abbreviated new drug application filed or biologics license application? How many of the forty-two reference products have been subject to multiple ANDA filings?**

As of December 15, 2017, there are 43 approved drugs that have risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU), covering a total of 68 new drug applications (NDAs). Of these 68 NDAs, 23 have at least one approved abbreviated new drug application (ANDA). Fifteen of the 68 have multiple pending ANDAs, eight have just one pending ANDA, and 22 have no pending ANDAs. In addition, 10 of these 43 REMS are for products approved under biologic license applications (BLAs) licensed under section 351(a) of the Public Health Service Act (i.e., "stand-alone" BLAs). There are no biological products that have been licensed under section 351(k) as biosimilar to any of the biological products on this list. In addition, FDA is not aware of any company that has publicly announced the submission of a 351(k) BLA for a proposed biosimilar to any biological product on the list.

2. **How many products are in shared systems? How many times has FDA exercised its existing authority to grant a waiver from shared REMS?**

There are seven approved single, shared systems (i.e., REMS shared between NDA and the ANDAs referencing them). Collectively these seven shared REMS cover 130 applications (38 NDAs and 92 ANDAs). To date, FDA has granted three waivers of the single, shared system REMS requirement and permitted ANDA holders to use a separate system for the ETASU. These programs are: the Buprenorphine-containing Transmucosal Products for Opioid Dependence (BTOD) REMS, the Shared System for Alosetron, and Shared System REMS Program for Sodium Oxybate Oral Solution.

3. **How many of those forty-two REMS ETASU reference products are considered by the FDA to be older, off-patent, off-exclusivity drugs without an approved generic or biosimilar? If any REMS ETASU are considered to be older, off-patent, off-exclusivity drugs without an approved generic please name them.**

The only reference product with an ETASU REMS considered by FDA to be an older, off-patent, off-exclusivity drug without an approved generic is Bosentan (NDA 021290). The Agency's defined criteria for an off-patent, off-exclusivity drug can be found at *https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM564441.pdf.*

The Honorable Doug Collins

1. **I would like to hear what the Agency is doing to enforce the [FDA's unapproved drug] policy, [Compliance Policy Guide Sec. 440.100 "Marketed New Drugs Without Approved NDAs and ANDAs" (CPG)], which was published in 2006 and revised in 2011] as well as what action the Agency plans to take to complete removal of phenobarbital products that have come to the market in contravention of FDA policy after September 19, 2011.**

Phenobarbital is an example of a medically necessary drug that has never been approved by FDA. Because patients rely on phenobarbital, it has been a low priority for FDA enforcement action. FDA's position is that the best course of action is to encourage manufacturers to seek FDA approval of their phenobarbital products.

FDA's current policies regarding marketed unapproved drugs are articulated in the Compliance Policy Guide Sec. 440.100 "Marketed New Drugs Without Approved NDAs and ANDAs" (CPG), which was published in 2006 and revised in 2011. Both versions of the CPG made clear that "any product that is being marketed illegally is subject to FDA enforcement action at any time" and encouraged firms to submit applications for their unapproved new drugs.

Despite the publication of the CPG in 2006, new unapproved drugs continued to be added to the market each year. FDA issued an update to the CPG on September 19, 2011, clarifying how the Agency expects to prioritize its compliance actions.

The purpose of the revisions to the CPG was to further discourage manufacturers from introducing new unapproved drugs on the market, not to provide special marketing rights to unapproved drugs already being marketed. Nevertheless, manufacturers of pre-2011 unapproved drugs often advocate for FDA enforcement action against their post-2011 competitors based upon the revisions in the 2011 CPG, while ignoring that all illegally marketed unapproved drugs, whether pre-2011 or post-2011, are subject to FDA enforcement action at any time, as clearly stated in both the 2006 and 2011 versions of the CPG.

There are both pre-2011 and post-2011 unapproved versions of phenobarbital on the market. Before taking action against any unapproved phenobarbital product, FDA would carefully evaluate whether the action might cause a shortage. The initial marketing date of specific unapproved versions of phenobarbital is not necessarily the best public health criterion to use when deciding whether to remove medically necessary unapproved products such as phenobarbital from the market. FDA does not have information supporting a conclusion that the pre-2011 unapproved phenobarbital drug products are any better in terms of safety, efficacy, or quality than the post-2011 unapproved versions. However, FDA will evaluate any information that becomes available about the marketed products and will continue to encourage firms to submit applications for approval.