



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JAN 08 2015

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the April 7, 2014, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Improving Predictability and Transparency in DEA and FDA Regulation." This letter is a response for the record to questions posed by certain Members of the Committee, which we received on April 24, 2014.

If you have further questions, please let us know.

Sincerely,

Thomas A. Kraus
Associate Commissioner
for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Michael C. Burgess

1. Following up from what was asked during the hearing, I would ask that you provide this Committee with the status of FDA's guidance on biosimilars naming.

a. When will this guidance become final?

FDA is currently considering the appropriate naming convention for biosimilar and interchangeable products. As part of this endeavor, we are carefully reviewing the comments on naming, submitted by stakeholders to FDA's biosimilar draft guidances and public hearing dockets, or that otherwise have been submitted to the Agency. We will take into consideration the comments submitted to FDA as we move forward in developing future policies regarding biosimilar and interchangeable products, including those on naming.

As we are currently considering the appropriate naming convention for products licensed under the Biologics Price Competition and Innovation Act (BPCIA), we cannot comment further at this time. If a draft guidance was issued on this topic, the Agency would adhere to FDA's good guidance practices, which include providing the opportunity for stakeholders to comment before draft guidance is finalized.

b. Has anyone in the administration outside of FDA provided the agency with substantive suggestions or recommendations with respect to this guidance? If so, please provide the name of the person or persons who provided those suggestions or recommendations, the substance of those suggestions or recommendations, and any action FDA took in response to those suggestions or recommendations.

If and when FDA issues a draft guidance on biosimilar naming, it would follow the normal course of review, in accordance with good guidance practices.

2. Does FDA intend to finalize draft guidance that sets an abuse deterrent formulation standard for innovator products? Will you require all new opioids to meet that standard before making final decisions on the approval of affected generic products? Will you make sure the generic versions of abuse-deterrent drug products show they perform as well on all relevant measures as innovator products?

FDA has been working internally on the scientific and regulatory issues surrounding development and evaluation of abuse-deterrent generics. On September 30 and October 1, 2013, FDA attended a meeting about the draft guidance for industry: "Abuse Deterrent Opioids – Evaluation and Labeling." The discussion was part of the Abuse Deterrent Formulation Science meeting organized by the Cross-Company Abuse Liability Consortium and facilitated with the aid of the College on Problems of Drug Dependence to provide an open forum to foster discussion about the draft guidance.

The draft guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated by the Agency, and what type of labeling claims may be approved based on the results of those studies. FDA is reviewing the comments submitted to the draft guidance and plans to issue a final guidance after review is complete.

In addition, FDA held a public meeting on October 30-31, 2014, to discuss the development, assessment and regulation of abuse-deterrent formulations of opioid medications.¹

FDA has not issued guidance on the development and testing of generic versions of drugs with abuse-deterrent properties. However, FDA is actively working on the scientific and regulatory issues surrounding the development and evaluation of abuse-deterrent generics, and we may address this topic in future guidance documents as appropriate.

3. On June 20, 2013, FDA published Draft Guidance on Cyclosporine. This draft guidance contained specific guidance on the design of bioequivalent studies to support abbreviated new drug applications. FDA asked that public comments be submitted by August 19, 2013. When does FDA anticipate providing feedback to stakeholders who commented on this draft guidance and/or when does FDA anticipate issuing final guidance?

As described below, FDA is in the process of reviewing comments on the draft guidance for industry, containing bioequivalence (BE) recommendations for cyclosporine ophthalmic emulsion, to determine whether the Agency needs to revise, finalize, or withdraw the draft guidance. Although that process is not complete, FDA addressed many of the issues raised in the comments in its November 20, 2014, response to a related Citizen Petition.²

Under FDA's good guidance practice regulation process (20 CFR 10.115), the intent of a draft guidance is to describe FDA's thinking and scientific recommendations on a particular policy area and to solicit input from the public on those recommendations. A guidance document, once finalized, represents FDA's current thinking on the topic. Typically, FDA announces the availability of a draft guidance in the *Federal Register* (FR) and opens a public docket to collect comments from the public. The draft guidance also states that it "contains nonbinding recommendations." FDA uses this transparent process to communicate with the public, so that all interested parties can participate in the process by submitting comments. FDA carefully considers all comments received as part of the guidance finalization process. Once finalized, guidance documents do not legally bind the public or FDA (21 CFR 10.115(d)). An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

This is the public process FDA is currently using to propose BE recommendations for numerous drug products, including cyclosporine ophthalmic emulsion. The process is explained in a guidance for industry, "Bioequivalence Recommendations for Specific Products" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072872.htm>), issued on June 11, 2010. This guidance explains that product-specific BE

¹ 79 FR 56810, September 23, 2014, <http://www.gpo.gov/fdsys/pkg/FR-2014-09-23/pdf/2014-22514.pdf>

² <http://www.regulations.gov/#!docketDetail;D=FDA-2014-P-0304>

recommendations would be made available on FDA's website as a way to develop and disseminate product-specific BE recommendations and to provide an opportunity for the public to comment on them. As part of that process, draft recommendations for different products are posted periodically on FDA's website and announced in the FR. With each FR announcement, the public is encouraged to submit comments within 60 days. FDA considers all comments received and either publishes revised draft recommendations for further comment, finalizes the recommendations, or withdraws the draft recommendations.

On June 20, 2013, FDA published an FR notice announcing the availability of draft guidance for industry containing BE recommendations for cyclosporine ophthalmic emulsion (<http://www.regulations.gov/#!documentDetail;D=FDA-2007-D-0369-0229>). People wishing to submit comments were instructed to submit them under docket number FDA-2007-D-0369, either online at www.regulations.gov or by mail. The comments that were submitted can be found at the above-mentioned website and will be taken into careful consideration as FDA reviews the available science to determine whether to revise, finalize, or withdraw the draft guidance.

On February 28, 2014, Allergan, Inc., submitted a Citizen Petition requesting that, among other actions, FDA refuse to accept or approve any ANDA that references RESTASIS (cyclosporine ophthalmic emulsion) if the ANDA does not include data from one or more appropriately designed comparative clinical trials to demonstrate bioequivalence (Docket No. FDA-2014-P-0304). Many of the issues raised in the petition were issues that had been raised in stakeholders' comments on the draft guidance on cyclosporine ophthalmic emulsion. FDA addressed those issues in its November 20, 2014, response to Allergan's petition (copy enclosed). That response reflects the Agency's careful consideration of the information that stakeholders provided in their comments on the draft guidance.

4. In FDA's more recent response to the House Energy and Commerce Committee, FDA specifically states that the agency will not be allowing compounding of medications for administration in a doctor's office or other office-use setting. It's my understanding that in a bipartisan and bicameral fashion, when the Drug Quality and Security Act (DQSA) passed, many statements were submitted for the record by Senators and Representatives expressing that it was Congress' intent when passing this legislation to allow the issue of office-use to continue to be overseen by the States. In those statements, Congress made clear that while reinstating 503A, Congress did not intend to grant FDA authority over office-use compounding. Since FDA's most recent communications to the House indicate that FDA believes it has authority over office use compounding and thus discretion to prohibit office use compounding, I would like to know how the agency arrived at that conclusion despite the fact that Congress has taken every measure necessary to clearly inform FDA that congressional intent is otherwise. Where does FDA feel it is given authority over office-use and why does FDA feel it is not required to follow clear congressional intent?

We believe you are referencing FDA's response for the record to the House Committee on Energy and Commerce, Subcommittee on Health, hearing entitled "Examining Drug

Compounding,” delivered to the Committee March, 7, 2014. A copy of FDA’s response is attached.

In its response to Congresswoman Blackburn’s Question 3 regarding “traditional compounding taking place in an office setting,” FDA specifically said the following:

Since the hearing, the President signed the DQSA. Under the DQSA, hospitals and health care professionals can purchase compounded drugs without a prescription from a compounder that is registered as an outsourcing facility, under section 503B. Section 503A requires, among other things, that, to qualify for the exemptions under section 503A there be a prescription for an identified individual patient. The Agency intends to exercise its authority, as appropriate to protect the public health, against compounded drugs that do not qualify for the exemptions in section 503A or section 503B, and drugs that are adulterated or misbranded or otherwise violate Federal laws.

As noted, section 503A requires that to qualify for the exemptions under section 503A, there must be a prescription for an identified individual patient. FDA stands by the statements in its previous response.

5. In FDA's most recent Warning Letters, FDA has taken the position that pharmacies inspected over a year ago can be held to manufacturers under the recently passed legislation. FDA has sent these Warning Letters to pharmacies located within the 9th Circuit which originally struck down 503A in its courts. It seems pretty clear that in order to hold these pharmacies to these standards, FDA would have to be retroactively applying the law. Therefore, how is FDA holding these pharmacies to a standard of law found within legislation that had not passed when the pharmacy was inspected? In other words, where does FDA feel it is given authority to retroactively apply a law?

FDA did not retroactively apply the law. Before enactment of the Drug Quality and Safety Act (DQSA), there were conflicting judicial decisions regarding the applicability of section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 353a], which exempts compounded drugs from several key statutory requirements, if certain conditions are met. During this time, the Agency’s Compliance Policy Guide 460.200 on Pharmacy Compounding (CPG) (2002) was in effect and applicable in the 9th Circuit. The CPG set forth a non-exhaustive list of factors that FDA considered in determining whether to initiate an enforcement action with respect to the compounding of human drugs. Receipt of valid prescriptions for individually identified patients was relevant for both the CPG and section 503A (see 21 U.S.C. § 353a(a) (providing certain statutory exemptions if, among other things, “the drug product is compounded for an identified individual patient based on the . . . receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient . . .”) and CPG at 2: “FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.”). Although this CPG has been withdrawn in light of new legislation, in its Warning

Letters, FDA applied the law and compliance policy in effect at the time it conducted the inspection and, in appropriate cases, noted that a firm was not entitled to the statutory exemptions described in section 503A of the FD&C Act and did not qualify for the Agency's exercise of enforcement discretion set forth in the CPG at the time of our inspection.

In addition, the Warning Letters informed the recipients of the law that is now in effect going forward as a result of the passage of the Compounding Quality Act (CQA):

Since FDA inspected your facility, Congress enacted and the President signed into law the Compounding Quality Act (CQA), which amended FDCA section 503A by eliminating the advertising restrictions that had been the basis for conflicting judicial decisions. The CQA otherwise left section 503A intact, and so clarified that the remainder of section 503A, including the requirement of valid prescriptions for individually identified patients, is applicable in every federal judicial circuit. Accordingly, the drugs you compound without valid prescriptions for individually identified patients are not entitled to the exemptions in section 503A. [footnotes omitted]³

As noted, Congress did not change the part of the law that speaks to the need for a prescription. The Agency intends to continue to exercise its authority, as appropriate, to protect the public health.

6. The Biologics Price Competition and Innovation Act (BPCIA) established a pathway for the approval of generic biologics or biosimilars. What significant actions has FDA taken to implement BPCIA? Have any biosimilar applications been filed with the FDA to date?

FDA continues to develop rigorous scientific standards to ensure that all biosimilar and interchangeable products licensed under the pathway established by the BPCIA will be safe and effective. To date, FDA has held two public hearings and issued six draft guidances related to implementation of the BPCIA. As directed by the BPCIA, FDA successfully developed recommendations for Congress for a user fee program for biosimilar biological products in consultation with companies that intend to make biosimilar products, patient and consumer advocates, health care professionals, and other public stakeholders. The enactment of the Biosimilar User Fee Act of 2012 on July 9, 2012, as part of the FDASIA, authorizes user fees to support the review of marketing applications for biosimilar biological products.

The November 2010 public hearing provided a forum for interested stakeholders to provide input regarding the Agency's implementation of the BPCIA. FDA considered the presentations and public comments submitted to the docket in developing three draft guidances issued in February 2012.⁴ FDA held a second public hearing in May 2012 to receive input on these draft guidances

³ <http://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm396239.htm>

⁴ "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>; "Quality Considerations in Demonstrating Biosimilarity to a Reference Product," <http://www.fda.gov/downloads/drugs/guidancecomplianceinformation/Guidances/UCM291134.pdf>; "Q & A regarding Implementation of the BPCI Act of 2009," <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>

and in obtaining public input regarding the Agency's priorities for development of future policies regarding biosimilars. FDA issued a fourth draft guidance in March 2013,⁵ a fifth draft guidance in May 2014,⁶ and a sixth guidance in August 2014.⁷ FDA will take into consideration all comments received as we move forward in finalizing these draft guidance documents and developing future policies regarding biosimilar products and interchangeable products.

FDA listed a number of draft guidances related to biosimilars that are under development on CDER's Guidance Agenda for 2014.⁸ The public will be provided with an opportunity to comment on these new draft guidances, when they are published.

In addition, in September 2014, FDA published its first-ever "Purple Book." The "Purple Book" lists biological products, including any biosimilar and interchangeable biological products licensed by FDA under the Public Health Service Act (PHS Act). The Purple Book will also enable a user to see whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product). Biosimilar and interchangeable biological products licensed under section 351(k) of the PHS Act will be listed under the reference product to which biosimilarity or interchangeability was demonstrated. Separate lists for those biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) will be updated periodically (see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>)

FDA continues to actively engage with sponsors regarding biosimilar development. This includes holding development-phase meetings and providing written advice for ongoing development programs. FDA continues to meet with sponsors interested in developing biosimilar products. As of November 30, 2014, 51 programs were in the Biosimilar Product Development (BPD) Program involving the development of biosimilar products to 14 different reference products.

FDA has not approved any biosimilar products to date. FDA is prohibited from publicly disclosing the existence of a biological product file before a biologics license application has been approved, unless the existence of the file has been previously publicly disclosed or acknowledged. FDA is aware that an applicant has publicly disclosed that FDA filed its application for a proposed biosimilar to Neupogen (filgrastim), another applicant has publicly disclosed that FDA filed its application for a proposed biosimilar to Remicade (infliximab), and a third applicant publicly disclosed that FDA filed its application for a proposed biosimilar to Neulasta (pegfilgrastim).

⁵ "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants" <http://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/ucm311811.htm>.

⁶ "Clinical Pharmacology data to support a demonstration of Biosimilarity to a Reference Product," <http://www.fda.gov/Drugs/guidanceComplianceRegulatoryInformation/Guidances/ucm290967>

⁷ Published August 2014, "Guidance for Industry: Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (Draft Guidance)" <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>

⁸ <http://www.fda.gov/downloads/drugs/guidancecomplianceRegulatoryinformation/guidances/ucm314767.pdf>

The Honorable John D. Dingell

1. How many sunscreen ingredient applications are currently pending at the FDA and how much time has passed since they were submitted?

FDA has publicly announced that eight new sunscreen ingredients have satisfied the Time and Extent Application (TEA) eligibility requirements and are being considered for OTC monograph status, and has requested and received submissions of safety and efficacy data for each of these eight ingredients.

FDA received submissions for these eight ingredients between 2002 and 2009.

2. Why has the FDA not been able to take action on these applications? What is the reason behind the holdup?

FDA has been actively examining the important scientific questions for the sunscreen ingredients currently proposed in TEAs, and significant efforts have resulted in FDA recently sending six letters to sponsors providing feedback on safety and efficacy data submitted in support of TEA ingredients. These letters are publicly available in the docket, in accordance with the TEA regulation. The letters that have been issued for the TEA ingredients amiloxate, diethylhexyl butamido triazone, octyl triazone, drometrizole trisiloxane, bisoctrizole, and bemotrizinol describe FDA's review of the scientific record for these sunscreen active ingredients (consisting of material submitted by the TEA sponsors and others, and information identified by FDA from the medical literature), and provide initial determinations that the record is insufficient to establish that any of these ingredients are generally recognized as safe and effective (GRASE) for over-the-counter (OTC) sunscreen use. As described in these letters, given the expansion of sunscreen use and scientific advances since the OTC sunscreen evaluation began, our safety evaluation of these ingredients must consider, not only short-term concerns (such as skin sensitivity) but also long-term concerns (such as the results of systemic exposure), about which little scientific data has been provided.

While evaluating the safety and effectiveness of potential new sunscreen active ingredients has been an important task for FDA, it is not the only major effort regarding sunscreens that FDA has undertaken in the last several years. In 2011, we took several regulatory actions on a number of important sunscreen issues. First, we finalized rules that updated the efficacy testing requirements and related labeling, which applies to sunscreens currently available in the United States.⁹ This final rule prescribes new, improved labeling, including updated Drug Facts

⁹ The new requirements, and several proposed changes to regulations, are discussed in four regulatory documents that include a final rule, proposed rule, an ANPR, and draft guidance for industry. Links to each of these documents are included below:

- Final Rule, Labeling and Effectiveness Testing, <http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14766.pdf>
- Proposed Rule, Revised Effectiveness Determination, <http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14769.pdf>
- ANPR, Dosage Forms for Sunscreens, <http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14767.pdf>
- Draft guidance for industry, Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM259001.pdf>

labeling. The final rule also establishes two effectiveness tests, one that must be done to support the sun protection factor (SPF) of the product, and another if a product claims to be broad spectrum (protecting against both UVA and UVB radiation).

We issued a proposed rule proposing a maximum labeled SPF value of “50+” for all monograph sunscreen products. We also issued an advance notice of proposed rulemaking (ANPR) to seek additional information on the safety and effectiveness of sunscreens formulated as sprays and to address additional questions related to other specific dosage forms of sunscreens. Subsequent rulemaking activity is needed for each of these topics, and FDA has dedicated resources to ensure diligent follow-up.

3. When will there be action on these applications?

FDA’s efforts on the remaining two TEA sunscreen ingredients are actively continuing, and we expect to issue a proposed sunscreen order for each in accordance with the Sunscreen Innovation Act, P.L. 113-195, signed by the President on November 26, 2014. In addition, FDA held a public meeting on September 4-5, 2014, to discuss the information provided in the TEA letters and to provide an opportunity to further clarify FDA’s thinking about the data required to support a GRASE determination for sunscreens.