
Reviewing the Rising Price of EpiPens

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Introduction

Good morning Chairman Chaffetz, Ranking Member Cummings, and members of the Committee. I am Dr. Douglas Throckmorton, Deputy Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to appear today to discuss FDA's role in ensuring the safety, efficacy, and availability of pharmaceutical products, such as epinephrine auto-injectors and generic drugs.

Although FDA does not have a regulatory role in the pricing of drug products, we do play a critical role in ensuring patients have access to beneficial medicines. We also recognize that when more than one version of a drug, especially a generic version, is approved, it can improve marketplace competition and help to provide additional options for consumers. With this role in mind, and as I discuss more fully below, FDA is working hard to support the timely, scientific, and efficient development of new epinephrine auto-injector products.

Overview of the Epinephrine Auto-Injector Market

Epinephrine auto-injectors are a critically important, and potentially life-saving, product for patients who suffer from a severe allergic reaction called anaphylaxis. The most widely used and recognizable product is Mylan's EpiPen. When a patient requires the medication, seconds count, and the epinephrine auto-injector must work every single time. To ensure this, it is critical that both the drug, and the device that delivers the drug, perform as designed.

As a father, I am personally aware of these issues, as my son carries an epinephrine auto-injector for his allergies.

FDA has approved four epinephrine auto-injector products to treat anaphylaxis; two of which are currently on the market. While there are currently no FDA-approved generic epinephrine auto-injectors, we stand ready to quickly review additional applications that come to us from both generic and innovator drug companies. Mylan's EpiPen is the market leader for epinephrine auto-injectors in the United States, and Mylan has recently publicly announced they also will

offer an authorized generic version¹ to be available in the near future. Another firm, Amedra, holds an approval for Adrenaclick, which is also an epinephrine auto-injector. Currently, while the Adrenaclick brand name product is not being marketed, Amedra is marketing its own authorized generic version of the drug. Amedra also previously marketed Twinject under a different approval from FDA, but this product is currently discontinued. Finally, FDA also approved Auvi-Q as an epinephrine auto-injector, although this product was voluntarily recalled from the market in 2015 by Sanofi. We note that Auvi-Q was recently purchased by Kaleo, though this product has not yet returned to the market. In support of increasing the number of safe and effective epinephrine auto-injector products on the market, FDA is working with both Amedra and Kaleo to facilitate the availability of their products.

FDA Efforts In Support Of Epinephrine Auto-Injector Review and Development

In addition to the work that FDA does with individual companies to support their development of specific products, FDA also works to create a publicly-available roadmap describing what companies need to do to bring various types of medical products to market. EpiPen and other epinephrine auto-injector products are considered combination products; that is, these products consist of a drug component and a device component. Because the drug has the primary role in treating the patient, CDER has the lead in regulating these products, with technical input on the device aspects provided by colleagues at the Center for Devices and Radiological Health (CDRH).

FDA understands that development of combination products can be more challenging than for typical drug products, so we have taken a number of steps to help guide industry through the

1. An 'authorized generic' is made under the brand name's existing new drug application using the formulation, process, and manufacturing facilities approved for use by the brand name manufacturer. The labeling is changed to remove the brand name or other trade dress. An authorized generic is not synonymous with an FDA-approved generic, the latter of which requires a separate application and approval from that of the brand name product.

process. First, FDA is continuing to develop, publish, and update guidance documents, which are a kind of roadmap for industry sponsors, explaining FDA's recommendations for the kind of information that should be included in a marketing application.

For example, in February 2016, FDA issued a draft Guidance on *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*,² which describes the different kinds of human factors studies that may be appropriate for certain combination products, including drugs and biologics delivered by auto-injectors. Human factors studies are conducted to better understand how healthcare providers or patients interact with a product's technology and to understand how the user interface affects the quality, experience, and outcomes of that interaction. These kinds of studies, while not recommended for every product, can be important to FDA's evaluation of the device component of a drug-device combination product by helping to determine whether these complex devices can be used by patients. In addition, in June 2013, the Agency finalized a Guidance that provides technical information to industry about designing and testing auto-injectors.³

Guidance documents can provide vital information to drug and device developers for a class of products. FDA recognizes that for more complex products such as epinephrine auto-injectors that contain a drug and a device component, in addition to guidance, one-on-one advice may be needed for sponsors seeking to develop complex products so FDA can address technical and regulatory questions about the pathway to market. Such meetings occur now for both new drugs and generic drugs under development. In addition, FDA regularly responds to specific product-development questions from industry in writing to help companies develop generic drug applications through the process known as Controlled Correspondence. We hope to expand our ability to engage with generic product sponsors through a reauthorization of the Generic Drug

2. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

3. <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>

User Fee Amendments (GDUFA II), where complex product meetings have been described as a key provision of the proposed program.

Further, FDA prioritizes the resources we make available to focus on areas of high public health needs. For example, FDA's Office of Generic Drugs (OGD) has a prioritization and expedited review policy for certain generic drug applications. The policy is set forth in a publicly available document called a Manual of Policy and Procedures (MAPP), which can be found on the FDA website. Pursuant to OGD's prioritization policy, Abbreviated New Drug Applications (ANDAs) for drugs that have "first filer" status or that otherwise are eligible to be the first generic approved are prioritized and given expedited review.

Each of these, and other efforts of FDA, help clarify our expectations and prioritizations concerning specific products so industry can develop and obtain approval of generic versions of branded drugs more quickly.

While FDA is working to lay out a roadmap to support efficient development of complex products like drugs delivered using an auto-injector, consistent with FDA standards, we cannot and will not allow a substandard product, in this or any product area, to come onto the market. For these epinephrine auto-injector products, a patient suffering a life-or-death allergic reaction must be able to pick up and effectively use that device without a moment's hesitation.

The remainder of my statement provides additional information about two factors that influence the development of drug products, including epinephrine auto-injectors, as well as a brief discussion of the limited FDA role in the intellectual property issues that can influence drug development.

Abbreviated Pathways to Approval

There are two abbreviated approval pathways established by the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act allowing for the approval of drug products. The first is the approval of ANDAs, and drug products approved under this pathway are commonly

referred to as generics. Unlike an innovator drug application, a generic drug application does not need to independently establish the safety or effectiveness of the drug. Instead, the generic drug has to show that it is the same as an innovator product in several fundamental ways, such as in active ingredient, dosage form, route of administration, strength, and labeling (except for certain permissible differences in labeling); that the generic drug is absorbed and available at the site where it will act in the body at the same rate and to the same extent as the innovator drug (which is known as bioequivalence); and that it meets the same high standards for drug quality and manufacturing as an innovator product. If the ANDA meets these requirements, the generic applicant can rely on FDA's previous finding of safety and effectiveness of the branded drug product, and need not conduct its own clinical investigations to establish safety or effectiveness.

FDA approval of an ANDA indicates that FDA considers the generic product to be therapeutically equivalent to the branded drug product. This means that the Agency has concluded, among other things, that the generic and branded products can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the innovator product when administered under the conditions specified in the labeling. Therapeutic equivalence ratings are published by FDA in what is commonly known as the "Orange Book." Although FDA does not itself determine when a pharmacy would substitute a generic product in filling a prescription, state pharmacy laws and other regulations that determine substitutability often refer to these "Orange Book" ratings.

The Hatch-Waxman Amendments also established a second abbreviated pathway for drug applications. This pathway, commonly referred to as the "(b)(2) pathway," can be thought of as a hybrid between the pathway for an entirely innovative product and the ANDA pathway for a generic drug. In contrast to an ANDA, a (b)(2) application is submitted in a new drug application and can be submitted for a proposed drug product that differs in certain ways from the previously approved branded drug product, differences that are generally outside those permitted for an ANDA product. For example, the drug product can share common attributes like active ingredient and dosage form with an innovator product, but be approved for a new use. This allows for a shorter approval pathway where applicants also have the flexibility to propose drug products that differ from the branded product in ways generally not permitted in the case of

an ANDA. Unlike generic drugs, products approved under the (b)(2) pathway on approval are not presumed to be therapeutically equivalent to the branded product and, if a (b)(2) applicant seeks a determination of therapeutic equivalence, it must demonstrate this separately.

Drug products for which the sponsor has submitted all of the needed safety and effectiveness information, as well as those approved under the (b)(2) pathway, are approved as New Drug Applications (NDAs). None of the currently approved epinephrine auto-injector products have been approved as generic drugs under the ANDA pathway. We also note that none of the currently approved epinephrine auto-injectors have been rated as therapeutically equivalent to EpiPen. Nonetheless, while generic drug products approved under ANDAs may have a greater impact on competition in the marketplace than competing products approved under NDAs, similar products approved under NDAs can also increase competition in the marketplace.

FDA's Role in the Intellectual Property Landscape

Although FDA can and does encourage generic drug development, and has and continues to streamline and improve its review and approval of generic drug applications, the decisions of whether to seek approval for a proposed generic drug and whether to market an approved generic drug are controlled by the generic drug industry. Further, the extent to which the approval or marketing of generic drugs is delayed because of intellectual property rights or marketing exclusivities is largely controlled by branded-drug manufacturers and others that hold those rights.

With respect to patents, FDA has only a “ministerial” role. First, sponsors of innovator products must submit information regarding certain patents related to their products to FDA. FDA lists these patents, such as those for Mylan's EpiPen, in the “Orange Book.” In any application that seeks to rely on a previously approved NDA, which includes (b)(2) applications and generic drug applications, the applicant must describe whether it intends to challenge those listed patents in court.

As drug applicants often publicly acknowledge, they routinely take the intellectual property rights of previously approved drug products into account when making determinations regarding the design and development of their proposed drug products. While our approval standards are the same whether or not an applicant designs its proposed product around a competitor's intellectual property rights, the proposed products that FDA receives for review and consideration for approval are no doubt impacted by patent considerations.

Conclusion

Thank you for your interest in the important topic of the safety, efficacy, and availability of epinephrine auto-injectors. FDA takes our public health mission seriously and, as discussed above, is working hard to fulfill our role as it relates to this issue. In addition to working to assure the safety and efficacy of life-saving products like epinephrine auto-injectors, it is critical that they be made to high quality standards to ensure they will work as needed. As a part of our mission, FDA also has an important role to play in advancing public health by helping to speed innovations that make medicines more effective, safer and more affordable. For complex medical products such as epinephrine auto-injectors, this means providing a roadmap to developers seeking to market new products and working with them wherever possible in support of new product development. As a part of this work, FDA understands the importance of generic products in the U.S. marketplace. We hope that our efforts, coupled with the work of other groups that also have roles to play, will continue to ensure medications are readily available to patients. I am happy to answer any questions.

Douglas Throckmorton, M.D., Deputy Center Director for Regulatory Programs

As Deputy Director for Regulatory Programs, Dr. Throckmorton shares the responsibility for overseeing the regulation of research, development, manufacture and marketing of prescription, over-the-counter, and generic drugs in the United States. He is committed to ensuring that the benefits of approved drugs outweigh their known risks.

Dr. Throckmorton received his medical degree from the University of Nebraska Medical School and completed his residency and fellowship at Case Western Reserve University and Yale University, respectively. Prior to coming to the FDA in 1997, he conducted basic science research and practiced medicine at the Medical College of Georgia, Augusta, Georgia and Augusta Veterans Administration Hospital. He is a board-certified physician.



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