

WHITE PAPER

COMPLEX GENERICS: MAXIMIZING FDA APPROVAL PROSPECTS

Aloka Srinivasan, Ph.D., Principal Consultant at PAREXEL, and former Team Leader at the FDA, answers common questions about complex generics and more efficient, cost-effective pursuit of U.S. Food & Drug Administration (FDA) regulatory approvals.

Q What are Complex Generics and why are they in the limelight these days?

A While there is no official definition of “complex” generics, one can broadly define complex generics as generic drugs for which it is particularly difficult to establish therapeutic equivalence as defined in the *Orange Book*.

As it states in the Preface of the *FDA's Orange Book*, “Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.” Complex generics have always existed, but we hear a lot more about them of late. This can be ascribed to the fact that innovators are developing more and more complex products these days, and with the increasing complexity

in the reference listed drugs (RLDs), the complexity of the generic drugs are increasing.

Each complex generic is “complex” in its own way. Some of them present significant challenges in establishing pharmaceutical equivalence due to problems related to physiochemical characterization and, for some, a simple bioequivalence study is not enough to establish that they will have the same clinical and safety profile as the reference listed drug.

For many of these products, complexity may be in the realm of the active pharmaceutical ingredients (APIs), for others, it is in the formulations, and/or within the inclusion of a device for drug delivery. The following are some examples of complex generics; the list continues to grow as more products are being added in this category everyday:

- Complex Active Pharmaceutical Ingredients (APIs), examples being Enoxaparin, Low Molecular Weight Heparin, Glatiramoids, Iron Carbohydrate Complexes etc.

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Preface of the *FDA's Orange Book*

- Complex Formulations, examples being Liposomes, abuse-deterrent generics, parenteral microspheres.
- Complex Route of Delivery, such as topical ointments and locally-acting GI drugs.
- Complex Drug-Device Combinations, such as DPI, MDI, nasal sprays, and transdermal systems.

Today, approximate 86%* of traditional prescriptions in the US are generics, and complex generics are expected to eventually own a significant percentage of this market. Thus, it is imperative that the pharmaceutical industry understands the need to evolve in a manner through which they can meet the American public's need for affordable, yet safe and efficacious generic versions of complex drugs. Obviously, the better they know the territory, the more opportunities they can successfully develop.

Q What are the biggest challenges with Complex Generics?

A At present, the road to development and marketing of complex generics may be construed as a rocky one. There are challenges for the industry as well as for the FDA.

For the industry, one of the biggest challenges involves those put forward by the innovators of these products, including patent challenges and citizen petitions. Also, the costly and time consuming development for complex generics requires significant commitment from the sponsor. Another challenging aspect is the major difference in submission criteria between various

international health agencies, which makes it difficult to develop the same product for distribution in different parts of the world. Also, the review process that is traditionally employed for generic drug approvals in the FDA's Office of Generic Drugs (OGD), do not work well for complex generics. Thus, if a sponsor submits an abbreviated new drug application (ANDA) for a complex generic drug via traditional processes to OGD, they face high risk of being rejected outright due to lack of adequate information related to "sameness" to the RLD, or due to the need for repeating significant studies, including clinical studies.

In addition to the challenges within the industry, complex generic related submissions also present a significant challenge to the OGD. Some of these products may be so complex, that it's an arduous task for the OGD to establish clearly defined pathways for them. Also, the pathway may differ significantly from product to product. The GDUFA (Generic Drug User Fee Act)[3], unlike its new drug counterpart PDUFA (Prescription Drug User Fee Act)[4], does not have a provision for regular pre-ANDA meetings or for submission of INDs, except under very special circumstances. Thus, each submission needs to be managed by the OGD on a case-by-case basis. However, the OGD has interacted with industry through face-to-face meetings and controlled correspondences and approved many complex generics. Currently, the OGD is working diligently toward laying down a path for review and approval of more complex generics within the GDUFA framework. For the sponsors, the challenges related to regulatory submissions for complex generics can be overcome or minimized by understanding the alternative submission processes necessary for these drugs and following through accordingly.

*Source: IMS Institute for Healthcare Informatics report, "Generic Drug Savings in the U.S., Sixth Annual Edition: 2014."

Q What are the best ways for a developer of complex generics to move forward with the FDA?

A Above all, developers of complex generic products need to be prepared for a different style of interaction with the FDA.

For example, unlike in traditional ANDA submissions, companies who develop only generic products may want to meet or speak with the OGD at the beginning of the development process and maintain a dialogue with them throughout development. Getting the OGD's advice – preferably in face-to-face meetings or through several controlled correspondences – will not only increase the likelihood of approval, but can also help the developer contain costs and reduce time-to-market delays.

Innovators, who would like to develop complex generics, need to understand that there is no IND submission at the OGD for most of these products and the possibility and level of interaction with OGD is significantly less, compared to that at other offices at FDA. The volume of applications and high workload of the OGD staff can make frequent interactions with them difficult to achieve, but it is essential to involve them early enough in the development process to let them guide the sponsor through the development process.

Q So what is the best way to communicate with the OGD regarding a complex generic product?

A Based on recent communications from the OGD, it is apparent that they are in the process of developing a pathway for the review and approval of complex generics.

The OGD now has provisions to grant pre-ANDA meetings for complex generics. However, only a small percentage of the meeting requests are being granted and are usually limited to products for which there are no generics on the market, or a product with unique regulatory or scientific issues. The meeting request should be supported with data (pilot studies, pharmaceutical development) which would demonstrate to the OGD the commitment of the sponsor to developing the product. Requesting meetings with non-specific questions or looking for solutions from the FDA will most likely lead to a refusal.

Q What kind of preparation is needed for a meeting with the FDA regarding a complex product that does not have any generics in the market?

A We recommend that every sponsor does their homework to make sure they understand the innovator product prior to requesting a meeting with the OGD or even sending controlled correspondences.

One way to start understanding a complex product is by reading the label of the RLD, browsing the Drugs@FDA site (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?CFID=7047809&CFTOKEN=33b2ebba69903f61-8F502B17-5056-994B-8A1B0C23C497AA27>) to collect as much information

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on the product as possible and understand the critical quality attributes of the drug as well as know the clinical development. It may also be wise to perform some pharmaceutical development at laboratory scale and some pilot clinical or BA/BE studies to have better understanding of the product. Based on such findings, a clear pathway to development should be mapped out and presented to the OGD in the meeting request. Submission of information on developmental batches, and also pilot studies, provides the OGD with assurance regarding the intent of the sponsor to move forward with the product, which in turn increases the chance of them granting a pre-ANDA meeting.

Q Do all complex generics need clinical trials?

A This is decided on a case by case basis. Some complex generics may be approved with no clinical trials but extensive physicochemical characterization to establish the “sameness” with the RLD.

There are others which may require complex bioequivalence studies; the iron carbohydrate complexes fall in this category. And, a significant number of complex generics also need clinical end point bioequivalence studies. However, there are significant challenges in the clinical development of complex generics, including need for a large therapeutic equivalence studies, choice of patient population and defining clinical conditions of use – all important parameters on which sponsors need to pay attention while designing specific clinical trials. In these cases, PAREXEL can support with clinical study design, development of the study protocol and also conduct the studies themselves.

Q Can you recommend other resources, case studies, or guidance for the FDA approvals process for complex generics?

A There are several presentations and also case studies published by the staff of the OGD regarding approval of complex generics, provided in the reference section of this paper.

However, the OGD is still in the process of defining the development requirements of these drugs, so the path is likely to vary on a case by case basis. Obviously, it is always best to have someone with you who knows the road ahead when you're on a journey as complicated as keeping complex generics on the proper regulatory path.

Based on our extensive regulatory experience with this class of products in PAREXEL, we use many tools to help our clients develop their complex generics, communicate with the agency regarding these products and also answer the agencies queries, which in turn can significantly increase the chance of approval of the ANDA and reduce the time to market. Additionally, PAREXEL's clinical experience in developing a variety of generic drugs across many therapeutic areas will ensure that the development path for your generic product will be successful and acceptable to the FDA.

We are always available for a conversation.

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- FDA's two Refuse-to-Receive (RTR) guidance documents issued in September of 2014 addressing overall ANDA submission standards and specific ANDA RTR impurity limits.
 1. <http://www.gpo.gov/fdsys/pkg/FR-2014-09-17/pdf/2014-22068.pdf>
 2. <http://www.gpo.gov/fdsys/pkg/FR-2014-09-17/pdf/2014-22110.pdf>
- FDA provides Q&A Guide on ANDAs and Stability Testing of Drug Substances and Products. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm366082.pdf>
- Guidance on Controlled Correspondence Related to Generic Drug Development issued by FDA <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm411478.pdf>

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