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FDA Embraces Emerging Technology for Bioequivalence Evaluation of Locally Acting Nasal Sprays

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1. [FY 2016 Regulatory Science Initiatives Part 15 Public Meeting](#) – May 20th – Silver Spring MD
2. CDER SBIA Webinar – CDER Direct Product Reporting (*pre-recorded, to be announced...*)
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4. Public Meeting: [Over-the-Counter Monograph User Fees](#) – June 10th – Silver Spring MD

The Office of Generic Drugs (OGD) recently supported approval of the first-generic nasal spray containing mometasone furoate, manufactured by Apotex. To learn more about why this approval was so noteworthy, we spoke with Dr. Bing Li, acting director for the OGD Office of Bioequivalence I, who has been working on this application since it arrived in 2008. In this interview, Dr. Li discusses the challenges OGD faced with this application, the emerging technology used in this approval, and how this approval may inform future generic drug review.

How long did it take for FDA to approve the ANDA for mometasone furoate nasal spray?

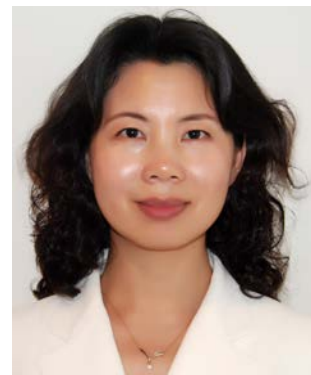
This application was submitted in December 2008 and was approved in March 2016 - about 8 years of work! The application history included a refuse-to-accept determination, a dispute resolution, and a significant number of amendments...a long way to reach its approval! Nevertheless, this approval is a great example of commitment and collaboration between CDER staff and industry to overcome challenges and embrace new technology in bringing a generic product to the American public.

Can you provide some background on the bioequivalence of locally acting nasal sprays?

Mometasone nasal spray is a locally acting nasal product. Bioequivalence (BE) evaluation of locally acting drugs is a very challenging task.

For systemically acting drugs, the rate and extent of drug absorption—the basis for evaluating BE - are reflected by the drug concentrations in blood circulation. However, locally acting drugs exert their therapeutic effect directly at the site of action, so they may or may not reach systemic circulation. Therefore, traditional pharmacokinetic (PK) approaches to the determination of BE are not applicable.

Furthermore, aerosolized nasal drug products are complex dosage forms that integrate a drug with a device, so that product performance depends on the interaction between the formulation and the delivery device.



Dr. Bing Li



Because of the unique routes of administration and the complexity of the dosage form of locally acting nasal sprays, FDA recommends a battery of evidence to demonstrate the BE of aerosolized locally acting nasal products. This evidence includes:

- Similarities in device and formulation
- Equivalent in vitro performance
- Equivalent PK studies
- Equivalent local delivery through pharmacodynamic (PD) or clinical studies.

This approach is called a “weight-of-evidence” approach, since no single study alone could adequately demonstrate the equivalence of these products. The weight-of-evidence approach to support a generic for mometasone furoate nasal spray is described in FDA’s [Draft Guidance on Bioequivalence Recommendation for Mometasone Furoate Nasal Spray](#).

What makes this generic approval so special?

Well, there are many highlights associated with this application:

- This is the first generic mometasone nasal spray made available in the US market.
- The review was extremely complicated and involved many amendments, many internal and external meetings, and a formal dispute resolution.
- The review of this application involved a coordinated and collaborative effort of disciplines within OGD, the Office of Pharmaceutical Quality, and the Office of New Drugs.
- This was a very timely approval – during allergy season.

What was the emerging technology used in this application and why was it pivotal to the approval of this drug?

Apotex used data from an in vitro approach utilizing innovative technology in lieu of the clinical endpoint study, which was deemed unacceptable by FDA.

The in vitro approach used is called Morphologically-Directed Raman Spectroscopy (MDRS). This particle-sizing technology first became available in 2012. It measures morphological characteristics (size and shape) using its microscopic component, and performs chemical identification by Raman spectra. This technology enables a comparison of the particle size of active pharmaceutical ingredient (API) in the generic and innovator drug products.

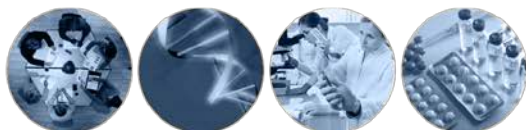
Successful use of this technology sets a precedent to accept an in vitro approach in lieu of a clinical endpoint BE study. It opens the possibility to change the FDA’s historical paradigm for the BE evaluation of locally acting nasal suspension products (the weight-of-evidence approach).

FDA is very happy to have approved an application that included this innovative technology just four years after it became available. This shows our inclination to embrace emerging technology.

What were some of the specific challenges encountered along the way?

There were many technical challenges along the way. For example:

- The clinical endpoint BE study was unacceptable to FDA because it used API manufactured from a site that was not intended for the manufacture of the commercial batch. The two API batches showed a certain level of difference in terms of their particle size distribution.
- The PK endpoint BE studies were challenging, as they always are with locally acting drugs. As I mentioned earlier, locally acting drugs lead to a low systemic drug concentrations in the blood and therefore require a sensitive analytical method. The PK endpoint BE study is one of the elements of the weight-of-evidence approach and demonstrates the comparative systemic exposure of the drug. It is considered a critical element for the overall BE evaluation.



- In vitro BE studies were also challenging and were repeated multiple times. There are a total of six in vitro BE tests recommended for this drug product. The firm first conducted all six tests using API manufactured by a single site. As the firm later switched to API manufactured by a second site (for batches intended for commercial use), they had to repeat some of these in vitro studies.
- The generic used an anhydrous API, whereas the innovator used a monohydrate API. Anhydrous and monohydrate drug substance have different hydration levels. Typically, a generic firm uses the same form as that of RLD. In this case, Apotex chose to use a different form. Since the anhydrous form of the API and the monohydrate form may undergo inter-conversion, we required adequate evidence to demonstrate that the final drug formulation remain anhydrous throughout the shelf life.

Did the FDA review of this product differ from prior ANDA reviews in the same class?

In the past, FDA has approved ANDAs for other locally acting nasal sprays, but none were as complex as the ANDA for mometasone nasal spray. The regulatory standard and scientific principles which FDA employed to review this drug product were essentially the same as used to review other generic locally acting nasal sprays. However, since this particular application presented many unique challenges, the review was more challenging. FDA scientists worked diligently to resolve the scientific challenges and come to an approval decision.

You mentioned that the use of new technology sets a precedent for change. What does this mean for future approvals of the same class?

FDA accepted the in vitro particle size data from MDRS in lieu of the clinical endpoint BE study, deemed unacceptable due to its API manufacturing site issue. This is a first in OGD history. Clinical BE determinations are expensive and time-consuming. Pharmaceutical companies face huge challenges with recruiting patients, and the results are unpredictable in many cases. Simple, accurate in vitro studies can therefore greatly enhance ANDA reviews. This application opened the possibility for in vitro appraisals of BE to be used in the review of future ANDAs submitted to the FDA.

Thank you so much for speaking with us Dr. Li. Is there anything else you would like to add?

This application is one of the most challenging that I have encountered in my 12 year professional career at the FDA! Not only did this application overcome so many scientific challenges and barriers, but it also exemplified FDA's commitment to review strategies that involve innovative technology. In particular, the new technology in this instance opened a new paradigm for a regulatory pathway in the context of a complex dosage form.

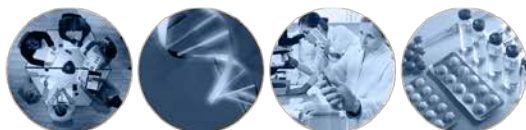
The thing that strikes me the most is that it changed my perspective on how to review a submission. On a late Saturday evening, the moment I finished my last edits for ANDA 91161 with a long relaxing exhale, a very special feeling emerged. I felt like this ANDA submission was a fresh, living thing with its own story. It was such a strange feeling - perhaps because I have been accompanying this ANDA for its long journey: from its first filing review in 2009, to the last submitted piece in 2016, to closing in an approval. This application presented so many challenges, from the refuse-to-accept determination, to the multiple BE amendments, to the formal dispute resolution, to the API particle size distribution and the introduction of the MDRS method. No application I have reviewed has gone through such a difficult and long journey.

In the words of Dr. Kathleen Uhl, Director of OGD: "Many reviewers and other staff have worked closely with Apotex to resolve scientific issues and get this application in a state in which it could be approved". Together, we were able to work through challenges presented in this long journey to make this generic drug available to the American public - and that too, during allergy season!

Cheers,
Renu Lal, Pharm.D.
CDER Small Business and Industry Assistance

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