The AAPS Journal (2019) 21: 14
DOI: 10.1208/s12248-018-0283-9

Regulatory Note

Scientific Considerations for the Review and Approval of First Generic Mometasone Furoate Nasal Suspension Spray in the United States from the Bioequivalence Perspective

Qing Liu,[1] Mohammad Absar,[1,2] Bhawana Saluja,[1,2] Changning Guo,[3] Badrul Chowdhury,[4,5] Robert Lionberger,[1] Dale P. Conner,[1] and Bing V. Li[1,6]

Received 11 September 2018; accepted 6 December 2018; published online 7 January 2019

Abstract. In 2016, the US Food and Drug Administration (FDA) approved the first Abbreviated New Drug Application for Mometasone Furoate Nasal Suspension Spray. To establish the bioequivalence of this generic nasal suspension spray with the reference listed drug product (RLD), Nasonex®, a "weight-of-evidence" approach was utilized by the applicant that included formulation and device similarities, equivalent *in vitro* performance, equivalent systemic exposure, and equivalent local delivery. In addition to these testing for comprehensive evaluation of the drug product, FDA also considered supportive data generated by a novel *in vitro* method, Morphologically-Directed Raman Spectroscopy (MDRS), to characterize the particle size distribution (PSD) of active pharmaceutical ingredient (API) in the drug product. In this case, MDRS data eliminated the need for a comparative clinical endpoint bioequivalence study. The approval of the first generic Mometasone Furoate Nasal Suspension Spray is precedent-setting and paves a new pathway to establish bioequivalence for generic nasal suspension sprays. This approval also exemplifies FDA's commitment to advance regulatory science for evaluation of generic drug products.

KEY WORDS: bioequivalence; weight-of-evidence; nasal suspension spray; particle size distribution.

INTRODUCTION

Nasonex® (mometasone furoate) Nasal Spray contains a suspension of an anti-inflammatory corticosteroid and is indicated for the treatment of seasonal and perennial allergic rhinitis symptoms in patients 2 years of age and older. The global sale of Nasonex® topped $1.3 billion in 2012. FDA approved the first generic Mometasone Furoate Nasal Spray from Apotex in March 2016.

The first generic Mometasone Furoate Nasal Suspension Spray was approved based, in part, on being bioequivalent to the RLD product, Nasonex®. As defined in the Code of Federal Regulations (CFR) at 21 CFR 320.23(b)(1), "[*t*] *wo drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose*". 21 CFR 320.23(a)(1) further states that "[*f*]*or drug product that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action*".(2).

Mometasone Furoate Nasal Suspension Spray is a locally-acting drug product that is complex because it contains drug in suspension and also integrates a delivery device. Based on the definition in CFR, determination of bioequivalence is based on comparison of bioavailability for mometasone furoate at the site of action, the nasal passage.

Qing Liu and Mohammad Absar contributed equally to this work.

[1] Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.
[2] *Present Address:* Office of Translational Research, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.
[3] Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.
[4] Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.
[5] *Present Address:* Respiratory, Inflammation and Autoimmunity, Medimmune, AstraZeneca Pharmaceuticals, Gaithersburg, Maryland, USA.
[6] To whom correspondence should be addressed. (e–mail: bing.li@fda.hhs.gov)

Establishing bioequivalence of locally-acting drugs can be a challenging task. Unlike the systemically-acting drugs, for which the rate and extent of drug absorption are reflected by the drug concentrations in systemic circulation, locally-acting drugs exert their therapeutic effects through directly reaching the sites of action. Subsequently, they may or may not reach the systemic circulation through a downstream process following appearance at the sites of drug action; therefore, using the traditional pharmacokinetic study results as pivotal evidence to support bioequivalence for the systemically-acting drugs is not applicable to the locally-acting drugs. Furthermore, aerosolized nasal drug products are also integrated with a device; therefore, the interaction between the drug formulation and the delivery device also plays a role in ensuring bioequivalence.

The FDA recommends bioequivalence of generic locally-acting nasal drug products be demonstrated through a battery of evidence, commonly described as a "weight-of-evidence" approach, including comparative evaluation of the formulation and device, equivalent *in vitro* performance (demonstrated through comparative *in vitro* studies), equivalent systemic exposure (demonstrated through comparative pharmacokinetic studies), as well as equivalent local delivery (demonstrated through comparative clinical endpoint studies) (3). The "weight-of-evidence" approach as outlined in Fig. 1 is applied, and the components within this approach are designed to provide thorough evidence to establish bioequivalence of generic and RLD nasal suspension sprays (4).

Formulation and Device Similarities

FDA recommends that the formulation of the generic Mometasone Furoate Nasal Suspension Spray be qualitatively (Q1) the same and quantitatively (Q2) the same as that of the RLD (5). Q1 sameness means that the test product should contain the same excipients as the RLD. Q2 sameness means the excipients in the test product should not differ by greater than 5% of the concentration or the amount in the RLD (3). When the formulations are the same, the risk of difference in local irritation and adverse events are minimized. Comparable devices support interchangeability of the generic and brand name nasal sprays in patient's hands.

Nasonex® is an aqueous suspension of mometasone furoate monohydrate, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80 (6), in which the API, mometasone furoate monohydrate, and one of the excipients, microcrystalline cellulose (7), are insoluble and hence are suspended particles in the aqueous formulation.

Equivalent *In Vitro* Performance

Six *in vitro* studies are recommended to ensure demonstration of bioequivalence of generic Mometasone Furoate Nasal Suspension Spray, which include single actuation content, priming/repriming, droplet size distribution, drug in small particles, spray pattern and plume geometry. The *in vitro* study results for the generic and brand name drug products are considered comparable if the criteria, as defined in the FDA guidance 2003, are met (5). Comparable *in vitro* results between the generic and RLD products from these six studies should lead to comparable deposition location and patterns at the site of action, to ensure similar absorption from the nasal passages and regions of the airways beyond the nose into the systemic circulation. Similar local deposition and systemic circulation are likely to result in comparable local bioavailability and systemic adverse events from the generic and RLD drug products.

The *in vitro* studies are cost-effective, reproducible, and sensitive to detect difference between generic and RLD products (8); however, the correlation of the difference detected by the *in vitro* studies with clinical difference has not been clearly established (9). In addition, some of the *in vitro* studies, such as droplet size distribution, spray pattern, and plume geometry, influence the deposition profiles of both excipients and API. Since particles of API are not the only suspended particles in the formulation of Mometasone Furoate Nasal Suspension Spray, the results from *in vitro* studies may not truly reflect the particle size distribution profile for the API. Bioavailability of mometasone furoate to the local site of action in the nose is impacted by the API particle size and distribution patterns, local dissolution of API from the formulation, absorption of API across the nasal mucosa, and rate of mucociliary clearance in the nose; therefore, local bioavailability and dissolution of API cannot be ensured solely on the basis of equivalent results from the *in vitro* studies. To supplement the limitations of the *in vitro* studies, *in vivo* pharmacokinetic and comparative clinical endpoint studies are recommended. According to the FDA

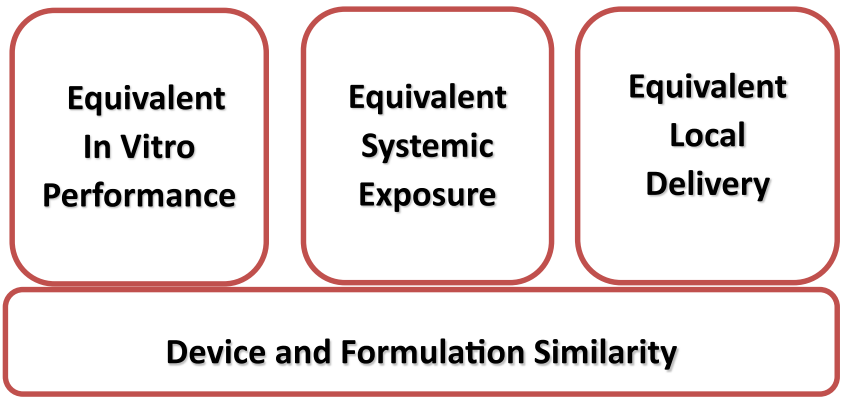

Fig. 1. The weight-of-evidence approach

Draft Guidance for Nasal Aerosols and Sprays (2003), "*in vivo studies are recommended because of an inability at the present time to adequately characterize drug particle size distribution (PSD) in aerosols and sprays. Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to the systemic circulation*" (3).

Equivalent Systemic Exposure

Systemic exposure from the nasal suspension spray results from drug absorption from the nasal mucosa, and gastrointestinal tract by ingestion. Since it was documented that Mometasone Furoate Nasal Suspension Spray produces measurable plasma concentration of mometasone furoate at therapeutic dose (10), the product-specific guidance for this drug product recommends a two-way crossover pharmacokinetic study to compare the systemic exposure of generic and RLD products (5). Comparable systemic exposure ensures comparable systemic adverse events of the two drug products, and provides indirect evidence to support equivalence in local delivery of the two products.

Equivalent Local Delivery

The formulation sameness, *in vitro* studies, and pharmacokinetic studies do not directly demonstrate comparable local availability of the generic and RLD Mometasone Furoate Nasal Suspension Spray. A comparative clinical endpoint study is recommended to confirm the lack of clinical difference between generic and RLD products. A comparative clinical endpoint study often expects enrollment of a large number of subjects due to high variability in the primary comparative clinical endpoint, which is both time- and resource-consuming. In addition, results from clinical endpoint study for allergic rhinitis are relatively insensitive to reflect dose differences (11) and therefore, insensitive to detect formulation differences between the generic and RLD products. The lack of dose-response in the comparative clinical endpoint BE study at therapeutic doses may be attributed partly to non-discriminative feature of the primary endpoint, total nasal symptom score with the approved doses of some drug products being at the upper plateau portion of the dose-response curve.

Given the limitation and reason to conduct the comparative clinical endpoint study, an *in vitro* approach utilizing MDRS to adequately characterize API particle size distribution in the drug product as an alternative of comparative clinical endpoint study was considered as supportive evidence for approval of the first generic of Mometasone Furoate Nasal Suspension Spray.

MDRS METHOD INTRODUCTION

The MDRS is an integrated method that measures particle morphological characteristics (size and shape) using its microscopic component, and performs chemical identification by analyzing Raman spectra. The observed particles in a given sample can be classified based on morphology and/or Raman spectra. The selected particles are then characterized for size distribution using microscopic technique. Hence, MDRS method can potentially be utilized for ingredient (API)-specific particle size measurement in a sample containing both API and excipient particles (12). The basic operating steps in MDRS include:

- Creation of a Raman spectra reference of all possible chemical identities (particles) in the sample
- Morphological measurement of particles using microscope imaging analysis
- Selection of particles exhibiting specific characteristics via morphology filters integrated in the instrument
- Conduct of Raman analysis on selected particles, and classify a sub-population (*e.g.*, API) by spectral correlation to the reference spectra
- Size characterization of the selected population

Briefly, a Raman spectral library is first created for the suspended particles in the sample, *e.g.*, mometasone furoate and cellulose particles in case of Mometasone Furoate Nasal Suspension Spray. This reference library is later used to identify the particles of interest. From the drug product, samples are prepared on a microscopic slide to visually observe in the MDRS instrument. Multiple morphology filters are integrated in the software, *e.g.*, elongation, circularity, and convexity, which can be applied to classify mometasone furoate particles from the cellulose particles based upon the difference in particle shape. Such classification would allow exclusion of large number of cellulose particles from further assessment; however, due to overlapping morphological features that might exist between mometasone furoate and some cellulose particles, the classified particle population may still contain some cellulose particles. The chemical identification using Raman spectra allows identification of particles despite having morphological similarity, and thus can minimize any error in selecting particles solely based on morphology filters. The instrument records the Raman spectra of the classified particles and compares the spectra with that of the reference library. Since Raman spectra is specific for mometasone furoate and cellulose, the spectral correlation can identify the mometasone furoate particles for subsequent size measurement. Figure 2 provides a schematic diagram for particle size measurement using MDRS.

MDRS Method Optimization and Validation

Like any other analytical method, MDRS should be adequately optimized and validated to generate reliable particle size data. The optimization/validation process starts with sample preparation since a distorted sample will provide misleading data. Ideally, the sample should represent pre- and post-spray conditions of the mometasone furoate nasal spray product. The user should ensure that sample concentration is neither too high to cause many touching/aggregated particles, nor too low to result in insufficient number of particles for size measurement. Particles should not also be damaged during sample preparation. If surfactants are used during sample preparation, solubility of suspended particles in the surfactant should be adequately assessed. Surfactants that are likely to solubilize API should be avoided. Sample volume, particle settling time, and batch-to-batch variability should also be optimized.

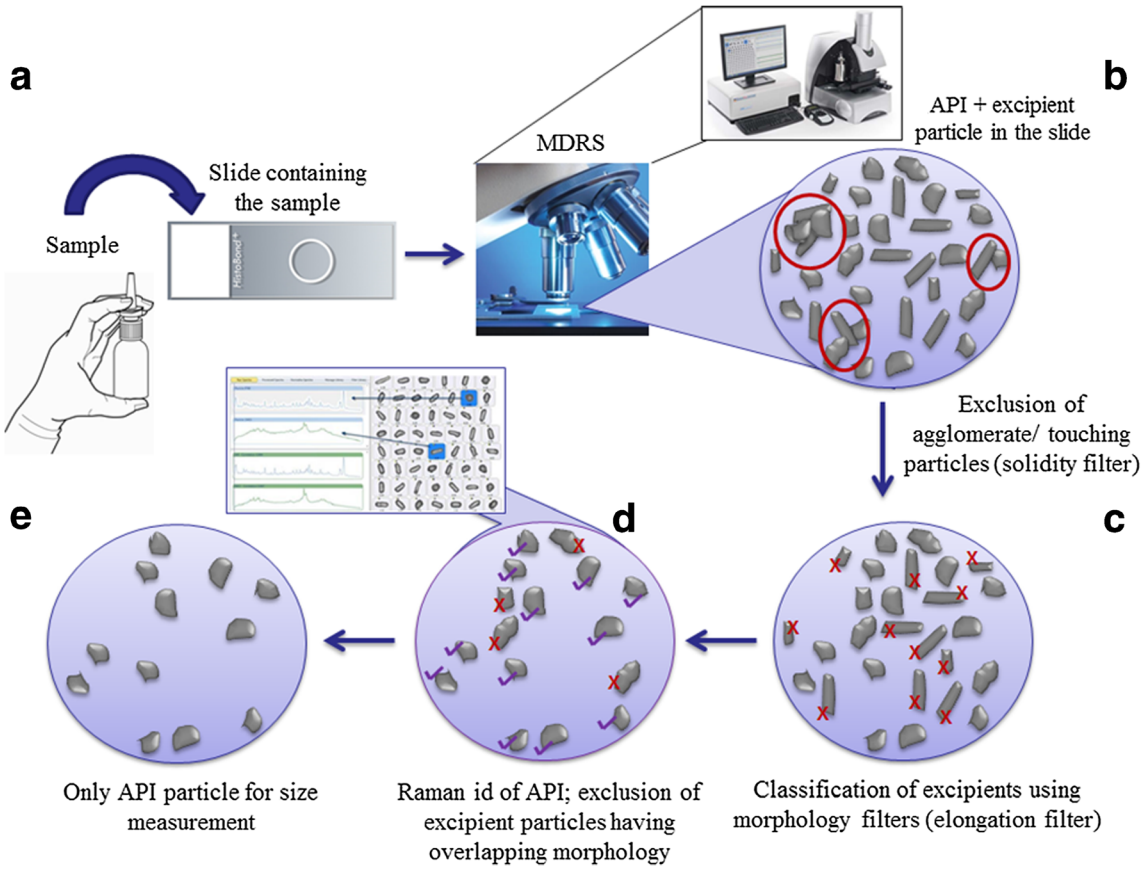

Fig. 2. Basic operating steps of MDRS. **a** Sample preparation; **b** morphological measurement of particles in the sample, exclusion of aggregates, and touching particles; **c** selection of particle of interest using morphology filters; **d** identification of particles using Raman spectra; **e** size measurement of the particle of interest

During microscopic assessment, the magnification and threshold values should be optimized for proper visualization of particles. Application of convexity filter is one way of identifying aggregated/touching particles. Since aggregated and/or touching particles may result in misleading data, all such particles should be excluded from measurement; however, if large amount of aggregates (API/API, API/excipient) are observed, the formulation needs to be further investigated for potential stability issue. In addition, the extent to which aggregates were present in the test and reference products should also be investigated, and differences, if any, should be adequately justified to avoid bias in particle size measurement. The number of particles for size measurement should be properly optimized to have robust particle size data. In addition, reproducibility, accuracy, and robustness of the method should be validated.

While classifying the API particles, morphology filters should be carefully selected to ensure that no API particles are excluded from further assessment. In reality, API particles may cover a broad morphology range and there may be a small amount of API particles that cannot be separated from excipient particles by morphology. In that case, morphology filters need to be carefully selected to ensure that a minimum number of particles are excluded from further assessment, and the selection of the filters need to be validated during method development phase to justify that excluding those API particles will not influence the API PSD result. The steps for selection of morphology filters will depend on the morphology of the particles of interest and the extent to which the morphology features overlap between the particle species, and hence will generally be determined on a case-by-case basis. Figure 3 illustrates the general steps for selecting a morphology filter.

Morphology filter parameters should be optimized for both test and reference products since the particle morphology might vary between the products. For chemical identification using Raman spectra, the correlation score should also to be optimized.

DISCUSSION

The regulatory recommendations to demonstrate bioequivalence of generic nasal suspension drug products to the corresponding RLD include comparative *in vitro*, *in vivo* pharmacokinetic, and clinical endpoint bioequivalence studies. Based on FDA Guidance of 2003 (3), the comparative clinical endpoint bioequivalence study is recommended despite its insensitivity to detect formulation change and the high cost associated with its conduct. The recommendation was based on limitation of analytical assay to measure PSD of API in the drug products, in which both API and excipient(s) are suspended particles. In contrast, for another similar drug

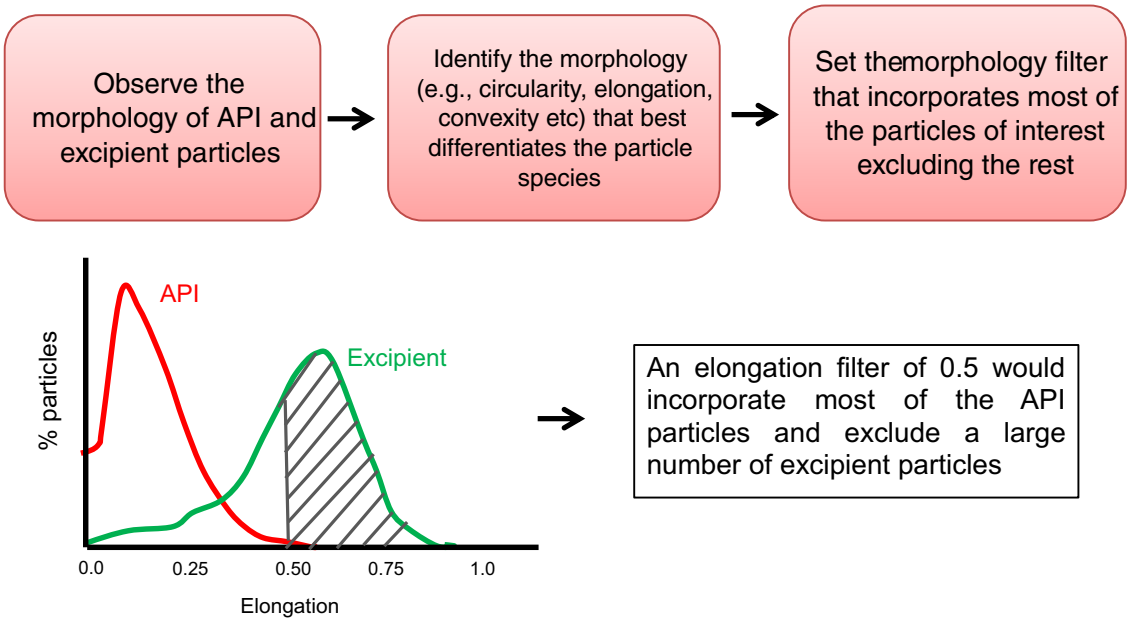

Fig. 3. General steps for selection of morphology filters in MDRS for particles with different elongation ratios. Note that the steps may vary depending on the morphology of particles of interest, and hence should be determined on a case-by-case basis

product, Budesonide Inhalation Suspension, in which the API is the only suspended particles in the formulation (13), measuring drug particle and agglomerate PSD together with a series of *in vitro* studies together with formulation Q1/Q2 can be used as the sole approaches to establish bioequivalence of a generic drug and the RLD, in lieu of the weight-of-evidence approach (14); therefore, a novel technology that can distinguish API from the suspended excipient particles and measure API PSD was the missing piece in moving toward an *in vitro* bioequivalence method in lieu of clinical endpoint bioequivalence study for the Mometasone Furoate Nasal Spray.

With the development of technology in the recent years, MDRS was utilized to fill in the gap of the analytical method for API PSD. Based on published literature (12) and proprietary data submitted by the sponsor, this technique appears to be a sensitive method in detecting particle size of mometasone furoate in the nasal spray suspension product. Data generated from this method were used as supportive evidence for approval of first generic of Mometasone Furoate Nasal Suspension Spray. To establish this method, adequate method optimization and validation ensures that the selected particle population represents the API, and the reported particle size data are robust. During MDRS method validation process, the study samples were optimally prepared to minimize the number of touching/aggregated particles. By using morphology filters, the aggregated particles were excluded from PSD analysis. For a microscopic technique, the number of particles analyzed for PSD can influence the result, particularly for a polydispersed sample. To ensure that optimum number of particles were analyzed, the relative standard deviation (%RSD) of the measured PSD was compared by analyzing different numbers of particles; no variation of %RSD confirmed that the selected number of particles represent the particle population. One potential challenge in this method is to optimize the morphology filters to classify API particles in a way that excluded particle population does not contain the API. To address this, particles classified as API using the morphology filters were compared with that of corresponding API batch, and a similar PSD was observed. In addition, because of potential difference in shape of API between generic and RLD products, further consideration is warranted before applying the morphology filters (optimized with the test product) to classify RLD's API. Note that optimizing the morphology filters for the reference product could often be challenging due to lack of availability of reference API drug substance. To confirm that the morphology filters used for the test product do not exclude any mometasone furoate particles from the measurement of the RLD sample, Raman spectral correlation was used to ensure that there are minimal mometasone furoate particles present in the particle population classified as "excipient" (based on morphology filters of test product). Ideally, excipient particles that are classified based on morphology filters should not correlate with the Raman spectra of API (at the selected correlation score).

One major limitation of the MDRS method is its inability to measure particle size below 1 μm. Hence, while applying MDRS method, users may need to use orthogonal methods to assess the submicron API particles. In case of Mometasone Furoate Nasal Suspension Spray, the Morphologi G3 instrument, which lacks the Raman component, but is able to measure particle size up to 0.5 μm was used as one of the orthogonal methods. In addition, % particles below 0.5 μm, as determined by laser diffraction technique, was < 1% for both generic and RLD products. Hence, with the totality of evidence, the MDRS method was deemed acceptable to compare the API PSD between test and RLD Mometasone Furoate Nasal Suspension Spray products; however, in cases where there are significant number of particles that fall in the range of < 1 μm, and/or the % of API particles < 1 μm varies between generic and RLD products, additional

considerations for characterization of API PSD would be warranted. If a suitable orthogonal method cannot adequately characterize the particles < 1 μm, use of MDRS in such case could be challenging. In addition, if the morphological features of the API and excipient particles significantly overlap, the morphology filters may not be able to classify particles. In such cases, users need to carefully investigate the API and excipient particle characteristics in the product, and may consider directly applying Raman identification to classify suspended particles. The Office of Generic Drugs is currently investigating the method validation and optimization strategies for MDRS for future applications.

Approval of this product paved a new regulatory pathway for FDA to use a validated, simple, sensitive, and accurate *in vitro* method instead of a much expensive and time-consuming comparative clinical endpoint study, in demonstrating bioequivalence of locally-acting nasal suspension spray drug products. Based on the knowledge gained during review and approval of first generic Mometasone Furoate Nasal Suspension Spray, the Office of Generic Drugs published product-specific guidance for Triamcinolone Acetonide Nasal Suspension Spray with suggestion for "alternate approach to the comparative clinical endpoint study" in October 2016 (15).

CONCLUSION

The deployment of *in vitro* methods for demonstrating bioequivalence will tremendously expedite the development and reduce the cost for developing generic locally-acting drug products. It signifies a major advancement in the US regulatory science and has significant impact on other complex drugs. The outcome is that the American public may have remarkably faster access to generic locally-acting drug products.

COMPLIANCE WITH ETHICAL STANDARDS

Disclaimer This article reflects the views of the author and should not be construed to represent the Food and Drug Administration's view or policies.

REFERENCES

1. https://www.fiercepharma.com/special-report/nasonex-merck
2. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.23. Last assessed 07/08/2018.
3. FDA. US. FDA Draft Guidance for Industry. Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action. 2003. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070111.pdf.
4. Li BV, et al. Bioequivalence for locally acting nasal spray and nasal aerosol products: standard development and generic approval. AAPS J. 2013;15(3):875–83.
5. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461141.pdf (Recommended September 2015).
6. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=12df48a0-fd2e-4e1c-b135-e616a1f31f42 (Updated December 19, 2017).
7. https://www.chemicalbook.com/ChemicalProductProperty_EN_CB4217972.htm
8. Suman JD, Laube BL, Lin TC, Brouet G, Dalby R. Relevance of in vitro tests of nasal solutions to predict *in vivo* deposition. Pharm Res. 2002;19:1–6.
9. Suman JD, Laube BL, Dalby R. Validity of in vitro tests on aqueous spray pumps as surrogates for nasal deposition, absorption, and biologic response. J Aerosol Med. 2006;19(4):510–21.
10. Daley-Yates P, Kunka RL, Yin Y, Andrews SM, Callejas S, Ng C. Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. Eur J Clin Pharmacol. 2004;60(4):265–8.
11. Advisory Committee for Pharmaceutical Science, 07/17/2001.
12. Shur J, Farias G, Huck-Jones D, O'Grady C, Saluja B, Price R. Characterizing nasal suspensions for regulatory and scientific purposes. Respiratory Drug Delivery 2016.
13. Budesonide Inhalation Suspension Drug Label Information. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c52c5382-1400-44b9-95be-a30e1cf706da. (Updated December 11, 2018).
14. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf (Recommended September 2012).
15. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520271.pdf (Recommended October 2016).