Available online on 15 Mar, 2023 at https://ijdra.com/index.php/journal
International Journal of Drug Regulatory Affairs
Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with RAPS & Delhi Pharmaceutical Sciences & Research University

Review Article

Open Access

A Comparative Study of Regulations of Nasal Products in the US and EU

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Abstract

A study relating to the regulation for nasal products has been conducted for the current review. The analysis emphasized the significance of classifying nasal products. Nasal products are challenging to manufacture in India due to regulatory and logistical issues. In addition to the production guidelines established by the USFDA and EU, the study analyses the prospects for nasal products in the future. Some common policies held by the 2 major international agencies have been shown in this review.

The current evaluation focuses on how nasal product production should be done in conjunction with other product production and will examine the fundamental recommendations made by the USFDA and EU, as well as whether or not there is a specific category of recommendations for nasal products.

Conclusions

The article demonstrates the USFDA and EU guidelines, and it was found that there were not major differences between the guidelines of the two. Instead, there are only minor differences between the infrastructures of the two agencies related to nasal products.

Keywords: Regulations, Nasal Products, nasal sprays, Dry Powder Inhalers (DPIs), USFDA, EU

Article Info: Received 23 Jan 2023; Review Completed 27 Feb 2023; Accepted 06 Mar 2023

Cite this article as:
Jaiswal S, Sharma P, Qureshi H. A Comparative Study of Regulations of Nasal Products in the US and EU. Int J Drug Reg Affairs [Internet]. 2023 Mar 15 [cited 2023 Mar 15]; 11(1):15-23. Available from: http://ijdra.com/index.php/journal/article/view/573

DOI: 10.22270/ijdra.v11i1.573
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1. Introduction

As the name implies, nasal products are used to provide drugs through the nasal cavities. They are used topically to treat problems including allergic rhinitis and nasal congestion. These products are chosen in some circumstances as an alternative to injection or tablets when the requirement is to administer medication quickly and directly through the nose. Numerous pharmaceuticals are available as nasal sprays to administer via the nose like sedative-analgesics, treatments for migraine, osteoporosis and nausea. Nasal hormone replacement therapy is used to treat Parkinson disease. For systemically active medications, the nasal route is being more thoroughly studied, investigated, and used as an alternative to oral or parenteral delivery. Compared to the oral and parenteral routes, the nasal route offers more benefits and produces better outcomes. Below are mentioned some of the factors that need to be taken care of during the production of the nasal products. (1) There are two types of nasal sprays most commonly available in market

- Saline nasal sprays.
- Decongestant nasal sprays

Saline nasal sprays: In the winters when the air around us cold then the most commonly used spray to avoid bacteria and the germs is used the saline nasal spray. These sprays avoid bacteria germs and reduce the inflammation. Furthermore, if any individual or patient has a sensitive nose then use of nasal spray without preservative is preferred. If any patient is suffering from thick, nasal congestion, saline nasal sprays can help to loosen and thin out the mucus.

Decongestant nasal sprays: While saline nasal sprays can be used regularly without issues, decongestant nasal sprays use should be avoided for more than 3 days regularly. It is important to use these as directed by the doctor overuse of these sprays may lead to the chronic nasal disorder, as long term use of these sprays should be avoided otherwise steroidal sprays are employed to treat the problems caused by the overuse. (2)

Table 1. Important factors need to be taken care during the production of nasal products (3)

Drug	Device	Carrier
Potency	Single dose	Viscosity
Molecular size	Multi dose	pH
Chirality	Sophisticated	Solubility
Chemical structure	Simple	Emulsion

2. Guidelines of USFDA

2.1 Nasal sprays

For medication items that are applied through nasal spray, the following tests criteria are advised. Each test parameter should have appropriate acceptance criteria and verified test methodologies implemented. Generally these standards reflect the critical information required from the submitted batches. Release testing can be replaced, if necessary, by certain manufacturing related tests (such as pH, osmolality, viscosity, and net content). However, the acceptability criteria should still be included in the drug product specification. (4)

Description: The formulation's color and clarity, the size and shape of the pump's parts and the texture of the container's inside should all match with the description mentioned on the outside and interior of the container, respectively, which reflects as an indicator of the drug product's integrity. A quantitative test with appropriate acceptance criteria should be developed for the drug product, if the formulation contains any color (either naturally occurring or as a result of deteriorative processes that take place throughout the period of the medicine's shelf life).

Identification: A specialized identification test must be used in order to confirm the identity of the drug in the drug product. It is believed that multiple chromatographic methods are necessary for accurate identification. Therefore, it is advised to use two chromatographic procedures such as HPLC/MS, or to combine tests into a single process (such as UV-spectroscopy and IR). If the therapeutic ingredient is a salt, a counter ion identification test should be provided.

Assay: Analysis of active pharmaceutical drug in the packed container ought to be done using a stability indicating method, unless other method is justified. The concentration and net content can be determined. A suitable test procedure must address issues related to solvent evaporation and/or leakage, drug substance degradation and its adherence to the container and closure components, other stability issues.

Impurities and Degradation: Quantities of contaminants and degraded products must be analyzed using validated analytical technique / processes. Establishing acceptable standards for degradation products and contaminants, both individually and collectively, is crucial. Any related contaminants that shows quantities up to 0.1 percent or higher, issue must be taken into account.

Preservatives and Stabilizing Excipients: If preservatives, antioxidants, chelating agents, or other stabilizing excipients (such as benzalkonium chloride, phenyl ethyl alcohol, or edetate) are added in the formulation, specific test for these related compounds along with acceptability criteria must be conducted.

Pump Delivery: It is advised to do a test so as to evaluate the delivery of the pump and to assess how well the medicine items perform from pump. To ensure proper operation, the pump's manufacturer should build the pump with components that are precisely the right size. The delivery of the pump spray should be confirmed by the applicant for the pharmaceutical product. (5)

Content uniformity of spray: This test is designed to demonstrate whether the product meets SCU acceptance standards and delivers the stated number of complete medicine sprays for the course of the nasal spray unit's shelf life. The test entails calculating the SCU for an adequate number of containers at the label claim number of sprays per container (n = 5 is recommended). (5)

Spray Pattern and Plume Geometry: Characterization of spray pattern and plume geometry is important for evaluating the performances of the pump and the nozzle. Various factors can affect the spray pattern and plume geometry, including the size and shape of the nozzle, the design of the pump, the size of the metering chamber, and the characteristics of the formulation. Spray pattern testing should be performed on a routine basis as a quality control for release of the drug product. However, the characterization of plume geometry should typically be established during the characterization of the product and is not necessarily tested routinely thereafter. The proposed test procedure for spray pattern, including analytical sampling plans, should be provided in detail to allow duplication by agency laboratories. (6)

Droplet Size Distribution: For both suspension and solution nasal sprays, the specifications should include an appropriate control for the droplet size distribution (e.g., 3 to 4 cut-off values) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions. Appropriate and validated dynamic plume droplet size, analytical procedures should be described in sufficient detail to allow accurate assessment by agency laboratories (e.g., apparatus and accessories, software version and calculation algorithms, sample placement, laser trigger condition, measurement range, beam width). (7)

Particle Size Distribution (Suspensions): For suspension nasal sprays, the specification should include controls for the particle size distribution of the drug substance particles in the formulation. This quantitative procedure should be appropriately

validated in terms of its sensitivity and ability to detect shifts that may occur in the distribution. The acceptance criteria should control the complete distribution and should reflect the data obtained for the submitted batches (e.g., clinical, preclinical, biobatch, primary stability, production).

Particulate Matter: For both solution and suspension nasal sprays, there should be validated testing and associated acceptability standards for particulate matter. Particulate matter can come from the manufacturing procedure, formulation ingredients, and components of the container and closure. The drug particle matter content may increase with the use of heat, and stress. Batch should be released only if stability statistics supporting the application demonstrate that particulate matter levels do not increase over time.

Microbial Limits: The appropriate tests and acceptance criteria should regulate the total aerobic count, the total yeast and mould count. The medication shouldn't promote the growth of microorganisms, and appropriate testing should show that this is the case throughout the expiration date.

Net Content: Formulation net content in the container should meet acceptable requirements for medications used for nasal spraying. The net content of each test container shall conform to the release standard. Items intended for nasal spray medication must meet acceptable standards for stability and weight loss. Since the orientation of the medical product during storage impacts how well the container closing mechanism seals, weight loss for products stored upright and horizontally or upright and inverted should be measured.

2.2 Regulatory Considerations for Generic Inhalers

Dry powder inhalers devices in the US market could differ significantly in terms of their internal makeup, physical design, and operational principles. Therefore, it is crucial to take into account certain factors like how different design elements, such as the energy source, the metering principle, and dose, the outer working principle, shape, and size, affect. The active pharmaceutical ingredient (API) is either used alone or it must be combined along with carrier. Another option is to use additional inactive ingredients like magnesium stearate. The type of inactive ingredient(s) utilized in the formulation also have a significant impact on the effectiveness and safety of the medication (e.g., irritation cause in respiratory tract).Therefore, inactive ingredient(s) in a test product is crucial for establishing bioequivalence to the Reference/standard dry powder inhalers and safety. The test product must be qualitatively (Q1) be same as that of Reference dry powder inhalers due to the aforementioned reasons, which means it must contain the same inactive ingredient(s).

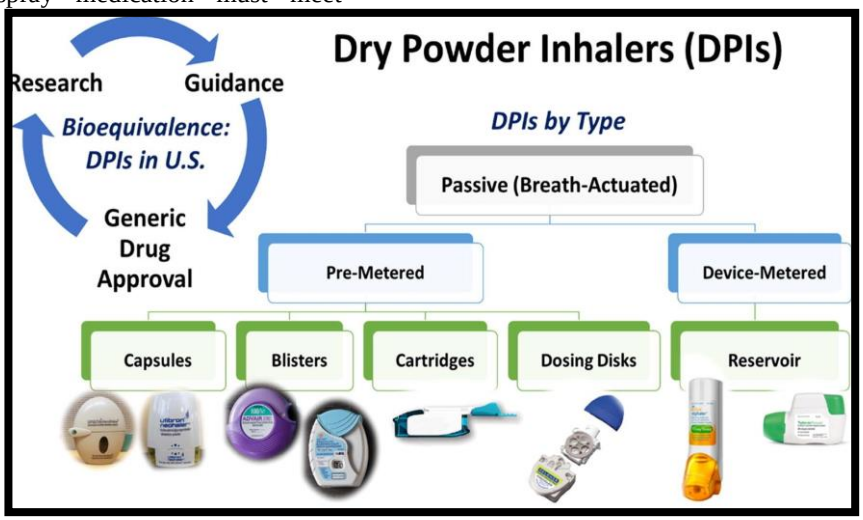

Figure 1. Bioequivalence of Dry Powder Inhalers (DPIs) in US (8)

2.3 Regulatory consideration for Inhalers

Data supporting the proposed generic product's pharmacological and bioequivalence to the designated RLD in accordance with 21 CFR 320.1 (c) and (e), respectively, must be included in the Drug Application (ANDA) sent to the US FDA office of Generic Drugs (OGD). For the majority of orally administered drugs that go to their site(s) of action via the systemic circulation, BE is established based on the drug concentration in a biologic fluid (e.g., plasma or blood). However, this strategy is less effective because the drug's intended action and method of distribution in the lung do not rely on the systemic circulation. However, this approach is currently viewed as insufficient in the US to establish BE of inhalation products intended for local action, such as MDIs and dry powder inhalers that are used to treat lung diseases (such as asthma and COPD). Therefore, it is challenging to show BE for these locally acting pharmaceuticals. To address this issue, the FDA developed aggregate weight-of-evidence approach, which determines the BE of inhalation agents using 1) in vitro research, 2) pharmacokinetic studies, and 3) pharmacodynamic or clinical endpoint studies. (9)

In April and September 2013, respectively, the FDA issued its first recommendations for MDI and dry powder inhalers that were product-specific. A scientific framework for the aggregate weight-of-evidence method

is also covered in this section along with the formulation and device challenges pertaining to developing generic inhalation drugs for the US market. DRY POWDER inhalers, including long acting agonists and corticosteroids, are some of the examples used to illustrate the basic ideas. The increasing hypothesis that PK may be related to the bioavailability of poorly soluble orally breathed medications accumulating in the lungs served as the foundation for this work (e.g., FP).If the weight-of-evidence approach is successful, the class of poorly soluble orally inhaled medications may not need the CE study. (7-8)

Requirement for BE Studies

The *in vitro* & *in vivo* performance for inhalation products is still not fully understood. However, because they are often less variable and more sensitive than *in vivo* tests in finding variations in product performance, *in vitro* investigations are regarded as helpful in the BE assessment. Aerodynamic particle size distribution and single actuation content (SAC) are the two primary *in vitro* experiments required for BE evaluation of dry powder inhalers (APSD). The formulation for the majority of dry powder inhalers are either housed in single-dose blisters with pre-metered doses or in reservoir compartments inside of the devices. The qualities of the material used for device and formulation vary between the Test and Reference items, which may have an impact on how well the dry powder inhalers performs. Therefore, it's crucial to show that SAC and APSD are equivalent over a range of product life phases, including the start, middle (for ED only), and finish. Additionally, flow rates might affect the in vitro efficacy of passive dry powder inhalers. Therefore, it's crucial to show that SAC and APSD are equivalent at various flow rates (a minimum of three flow rates). It is preferred that the device resistance of a Test dry powder inhalers be comparable to that of a Reference dry powder inhalers in order to guarantee that the targeted patients can use the Test dry powder inhalers device effectively and receive the proper medication without experiencing any appreciable changes compared to use of the Reference/Standard dry powder inhalers.

PK studies

OIDPs designed to transport drugs to the lung's sites of action, but instead, the drugs are deposited in the lung's target area. Currently, a thorough knowledge of the connection between local drug delivery in the lung and this downstream mechanism (i.e., medication entering via inhalation route into blood) is inadequate. However, due to potential systemic adverse effects of orally inhaled medicines, examining drug concentration in the blood is important.

Single dosage is typically administered to healthy volunteers for such a research work. It is anticipated that the PK BE study done in healthy persons will offer accurate result for identifying variations in drug product properties that could impact the BE of the Test and Reference inhalation products. Regulatory Considerations for Generic Inhalers 1287 are the basis of the equivalence Test and Reference inhalation products' systemic exposure on the natural log-transformed data. Peak concentration (Cmax) and area under the curve (AUC) values using the average BE method. In general, both the products are thought to be PK-equivalent if its geometric mean ratios for AUC and Cmax lie within the range of 80.00- 125.00% for the 90% confidence intervals. However, many unanswered questions about the adequacy of data for establishing bioequivalence because of limited understanding of how results from these BE studies relate to drug concentrations at the local site(s) of action in the lung. Therefore, it is currently believed that a further clinical investigation is required to justify BE of these locally acting pharmacological compounds. When appropriately constructed, models based on functioning of lung tests provide an adequate dose-response relationship for short acting agonists (SABAs). For long acting agonists like salmeterol xinafoate and inhaled corticosteroids (ICS) like fluticasone propionate no models are there that could establish relationship between dose and response. (10)

2.4. Guidelines on Nasal spray and spray drug products

Suspensions and Inhalation Solutions

Aqueous solutions are often the foundation of drug formulations for suspension and inhalation formulations that might include comprise therapeutically active ingredients and other excipients. The oral inhalation suspension and aqueous-based solutions must be sterile (21 CFR 200.51). To prevent microbiological contamination while using these pharmaceutical drugs, unit-dose administration is suggested. The container, the closure, and potentially supplementary protective packaging like foil overwrap make up the container closure system for these medicinal goods. Suggestions for overwrapping inhalation medicine products that are sealed with semi permeable container closure methods are provided in Section III.G.5

Inhalation sprays

Orally, the dose of inhalation sprays given to the lungs is intended to produce local or systemic effects. Sprays intended for oral inhalation that have an aqueous base must be sterile (21 CFR 200.51). In addition to therapeutically useful chemicals, the products also contain excipients. The formulation may be administered in a single dose or in a number of doses. To ensure the safety and tolerability of the drug product, some excipients must be evaluated before being included in a formulation. When a patient activates a device-metered unit, a reservoir filled with formulation enough for many doses is released, allowing the device to dispense the medication as metered sprays. Many of the distinctive qualities stated in section II.A for nasal sprays apply to medication preparations for inhalation spray as well. The most important features, regardless of the design, are the repeatability of the dosage, the spray plume, and the particle/droplet4 size distribution, since these factors might influence the drug substance's delivery to the desired biological target. Maintaining the repeatability

of these parameters through the expiry date and making sure the device's sterility and functioning (such as its spray mechanism, electrical components, and sensors) are intact for the duration of its usage by patients. (11)

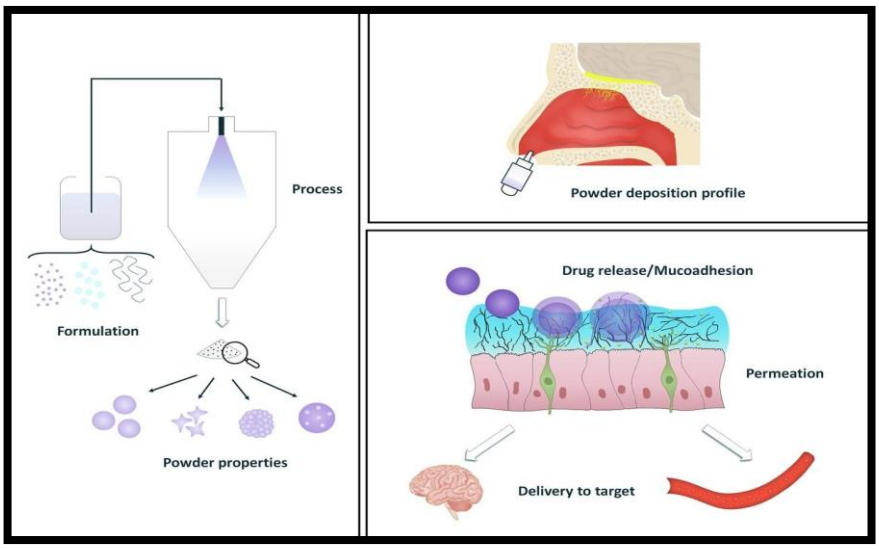

Figure 2. Inhalers functioning (11)

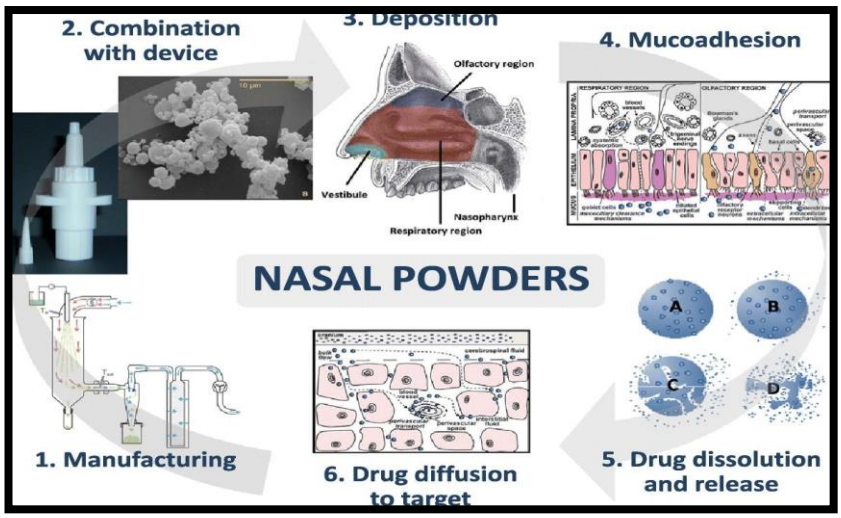

Figure 3. Spray dried powders for Nasal delivery; process and formulation considerations (12)

3. Guidelines of European Union

The law of European Union (EU) on the evaluation and authorization of medicinal products establishes only when a product poses a substantial risk to the public's health may it be rejected. If the proof of equivalence for a product fails, such as a generic or hybrid product that makes a similar claim to standard product may be a danger to the public's health. However, because it is a subject of national competence or something that must be resolved by national authorities of several European nations, a product's substitute is outside the purview of EU regulation. If the product has favorable benefit-risk relationship, approval may be given. Once these generic products in the EU are not needed to be identical to the Reference product in every way, but Pharmacokinetic (PK) bioavailability studies are required to show that they are bioequivalent to the Reference product, or they must be exempt from this PK demonstration. Hybrid products are defined as those that could demonstrate equivalency using pharmacodynamic endpoints for example orally inhaled drug products (OIDPs), which operate locally. This categorization places more emphasis on the method used to demonstrate therapeutic equivalence than it does on the product's interchangeability. However, pharmacokinetics results of some locally acting drugs shown that *in vitro* data or PK data are being employed in place of PD data. Regulatory Considerations for Generic Inhalers 1289, strictly speaking, there are no generic OIDPs in the EU; rather, all of them fall under hybrid OIDPs. (13)

Description: Where relevant, a description of the formulation and the entire delivery system (including the actuator) should be included.

Assay: The quantity of drug material in multi-dose products should be calculated per weight unit or per volume unit, as appropriate. The test for single-dose items should be expressed in terms of mass per dosage unit. The typical assay limits for pharmaceuticals are in effect.

Moisture Content: Based on the findings of stability investigations, the moisture content limit should be set. If the results are consistent over the course of the product's shelf life or if any variations in moisture content do not affect any other metrics.

Delivered Dose Uniformity: A established pharmacopoeia approach must be used for the delivered dosage uniformity test. Limits should be applied in accordance with the pharmacopoeia, with adaptations as needed to assess device variability both within and between devices. (13)

Content Uniformity / Uniformity of Dosage Units: As per the guidelines given to consumers and healthcare experts, content consistency should be examined on samples taken from the containers. Acceptance limitations ought to be defended in light of pharmacopoeia criteria.

Leak Rate: A leak rate test and limits should be included in the specification.

Microbial / Microbiological Limits: A recognized pharmacopoeia test should be used for microbiological quality testing, or the Reason of Specification(s) section should provide justification for its exclusion.

Sterility: Sterility testing should be conducted according to an accepted pharmacopoeia test. (14)

Drug substance specification: If the drug substance is found in any inhalation or nasal products at any time during their production, storage, or use, a warning must be included in the drug substance specification. Sizing guidelines and tests for particles, the ideal approach is to employ a tried-and-true particle sizing technique (such laser diffraction) with acceptance criteria outlined at various points throughout the size distribution. Acceptance criteria have to ensure a stable particle size distribution in terms of the proportion of all particles that fall within a specified size range. The median, upper, and/or lower particle size limitations should be precisely established. The observed range of variance should be used to set acceptance criteria, and it should be taken into mind that batches with acceptable in vivo performance will be used. (15)

Stability tests: The stability-indicating tests must be passed by all inhalation and nasal medications. The drug product specification includes information on compliance with the pertinent guideline documents. Weight loss should be monitored as well, if necessary If product performance is anticipated to be affected by storage orientation, containers should be stored in various orientations during the research to examine the influence of orientation (for pressurized metered dosage inhalers, for example). Data for each direction should be given separately. If the product has secondary packaging to shield it from light and/or humidity, the length of time it may be used after the protective packing has been removed should be supported by stability (for example, a dry powder inhaler under a foil overwrap). (15)

3.1 Bioequivalence Requirements

In the European Union, a step-by-step method used for systemically acting drugs is used for locally acting products. When proving therapeutic equivalence, an *in vitro* method may be sufficient in some circumstances (e.g., solutions used for nebulization having same composition). If this particular method is not employed, than assays based on PK to evaluate its systemic safety and lung deposition can be used. Moreover, if bioequivalence cannot be proven in this second step, then the third phase, based on clinical outcome, may be carried out to get a marketing authorization.

Step 1

In the past, systemic safety has not been considered as reliable criteria of the bioequivalence of locally acting drugs contrast with drugs that are delivered to the site of action through blood. Concentrations at the target site will be same if the amounts in the plasma are the same. Therefore, it was necessary to establish therapeutic equivalency for locally acting medicines utilizing clinical outcomes. Slight variations are occasionally approved without any need for in vivo results. It is hard to explain equivalence between two batches of the standard product, a 15% in vitro acceptable range has been proposed. For these reasons, a significant number of samples should be evaluated (possibly more than three), according to several EU regulators. (16)

Table 2. In vitro comparison of studies in steps (16)

Steps	Systematically acting drugs	Locally acting drugs	Weight evidence approach
Step 1	Based on BCS and dosage form	In vitro comparison	In vitro comparison
Step 2	PD, BA and BE	For safety	For systematic safety
Step 3	PD & clinical endpoints	Relative potency	Relative potency

Step 2

When the contribution of the swallowed portion is little, PK bioequivalence studies are recognized as a crucial component to evaluate the inhaled amount of drug deposited in lungs and its pattern of deposition. Efficacy profile may be regarded as equivalent if the lung deposition is shown to be equal. Area Under Curve (AUC) equivalence is not a guarantee. A PK research with active charcoal is required to determine

effectiveness in medications with a sizable oral bioavailability (such as budesonide), whereas a trial without charcoal is performed to determine safety. Verifying the charcoal barrier is necessary. (16)

Step 3

The broncho-provocation and broncho-dilation models whereas for Salmeterol would require a few minor modifications to the broncho-provocation protocol recognized for short-acting medications it seems to apply to bronchodilators. Salmeterol, however, does not exhibit assay sensitivity within the therapeutic dose range, making PD studies unable of differentiating between various inhalation products. Corticosteroids also appear to lack assay sensitivity. Therefore, any PD or clinical outcome with an appropriately steep dose-response curve would be appreciated. The PD endpoint/marker should ideally represent inflammation. The literature-reported methods for measuring methacholine PD20, exhaled NO, sputum eosinophilia, and even non-specific FEV1 are acceptable in the EU. Limited evidence suggests that the methacholine PD20 model may be used if people are selected who can respond differently to the two dosage levels of the medicine. Relative potency is a component of both the dose-scale analysis and the Regulatory Considerations for Generic Inhalers 1291 response. Scale analysis is mandated by the EMA guideline. Last but not least, equivalence for the other strengths of multi- strength medications must be proven using in vitro data (step 1) or PK data (step 2). (16)

3.2 Challenges faced in the EU Regulatory

Several unanswered scientific questions and unsolved methodological disagreements among European regulators, for instance:

Stage pooling is acceptable for comparing APSDs according to the European standard, although given that IVIVC is still developing, some nations may opt to compare each stage separately rather than pooling stages.A visual examination of a flow rate dependence plot for both Test and Reference products, presently the sole method used to compare the flow rate dependency of dry powder inhalers and some nations may even disregard this criterion. It might be essential to compare all of the strengths of the Test and Reference products in order to get to the conclusion that they display proportionate APSD. It may not be possible to demonstrate PK bioequivalence based on the OIDP guideline To find representative batches (within 15% of their respective median), several regulators advise testing multiple batches of both the Test and Reference products prior to the in vitro comparison. If pre-specified in the protocol, the usage of distinct batches for each active component may be necessary in the event of fixed combinations. To adjust the PK research results to the in vitro specifications' mean values and construct product specifications that may guarantee APSD equivalency throughout the whole range shown for the Reference product, it may be helpful to develop an IVIVC. Additionally, although it is frequently believed that a low oral bioavailability suffices to demonstrate a little GI contribution, the GI contribution for inhaled medications also depends on the inhaled portion. If just a small portion of the entire dosage is inhaled (say, 10%), even if the lung bioavailability is assumed to be 100%, a 1% GI bioavailability of the remaining 90% of the given dose, which is ingested, corresponds to 8.26% of the total systemic exposure (10% lungs plus 0.9% GI). The primary difficulty faced in EU is educating evaluators about the limitations of the traditional approach of comparing the generics, as the results offered by the response-scale is insufficient so, at least two dosage levels need to be examined to detect a 2-fold or 4-fold difference. Only displaying equivalent in the response scale analysis does not guarantee equivalence.

Table 3. Comparison between EU and USFDA guidelines for Nasal products (17)

Requirements	USFDA	EU
CRO (Audits)	Audited by FDA	By MHRA
Reserve sample	5 times the sample required for analysis	No such requirement
Fasted	Must be of OSD recommendation	No much requirement
Reserve of samples	5 years	No much requirement
BE study for generic drugs	Against US RLD in any country	Against EU reference product
Quality control	In the US, the Quality Control Unit is responsible for conducting a production record review according to CFR Part211.192 and for ensuring contractors meet GMPs (211.22 a).	In the EU, a named Qualified Person (QP) must certify the GMP compliance for each batch of a drug product, either commercial or investigational (IMPs). The responsibilities of the Qualified Person are defined in Annex 16 to the EU-GMP Guidelines. If commercial products or IMPs are manufactured or packaged in the US and then imported into the EU, additional analytical testing in the EU is needed. Additionally a successful supplier qualification is needed including initial and periodic compliance audits which

		are conducted according to the respective EU-GMP Guidance. These audits are performed by the QP or on behalf of the QP. An inspection by a competent authority does not replace the need for an audit. So US companies will still need to face EU audits, even after full implementation of the MRA.
Production and GMP	FDA lacks these guidelines in the production of the inhalation products and the guidelines related to the GMP of the inhalation products, Contamination Control, Supply Chain Traceability, GMP for Excipients	Contamination Control Supply Chain Traceability GMP for Excipients EU has guidelines related to the same

4. Conclusion

The article demonstrates that there are some significant differences between the testing requirements of the two agencies, and if we consider a common guideline for the same, then it's important to overlook all the necessary considerations. As in this article, we studied the guidelines of the USFDA and EU, and we found that there are not major differences between the guidelines of the two. Instead, there are only minor differences between the infrastructures of the two agencies related to nasal products.

Acknowledgements

We would like to express our sincere gratitude to IJDRA Journal for publishing our work.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article

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