FDA Overview On Nasal Drug Products: Recommendations For Improving Quality Of Nasal Product ANDA Submissions

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Generic nasal and inhalation product development

Generic nasal products

Generic inhalation products
ANDA applications of generic inhalation products are incoming!

What are the practical issues expected in the incoming ANDA submissions of inhalation products?

how do we prepare ourselves to solve these issues?
Outline

• History of FDA guidance development on bioequivalence (BE) of nasal drug products
• Common issues observed in nasal product ANDA submissions
• FDA’s recommendations for improving application quality
History of FDA guidance development on bioequivalence of nasal drug products
Milestones for Generic Nasal Spray (NS)

1978: FDA received the first nasal spray ANDA.
1999: The first draft nasal BA/BE guidance (later withdrawn) & Statistical guidance published.
2001: FDA decided not to pursue dose-response recommendation for locally acting drug products for allergic rhinitis.
2003: The second draft nasal BA/BE guidance published.
2010: Standardization of NS review and publication of CTD tables, significant improvement of review efficiency.
FDA BE recommendations for locally acting nasal products: “weight-of-evidence approach”
FDA BE recommendations for locally acting nasal suspension: weight-of-evidence approach

### Device and Formulation Similarity

- Valve, pump, and actuator designs be as close as possible in all critical dimensions
- Metering chamber volumes and actuator orifice diameters be the same
- Formulation: Q1/Q2 the same

### Equivalent In Vitro Performance

1. Single Actuation Contents Through Container Life (SAC)
2. Droplet Size Distribution by Laser Diffraction
3. Drug in Small Particles/Droplet Size Distribution by Cascade Impactor
4. Spray Pattern
5. Plume Geometry
6. Priming and Repriming

### Equivalent Systemic Exposure

- Based on PK (AUC and Cmax) data (For nasal suspensions)

### Equivalent Local Delivery

- Based on clinical endpoints (For nasal suspensions)
Scientific rationale for weight-of-evidence approach

- Equivalent in vitro Performance
- Device Similarity
- Equivalent Efficacy
- Systemic Toxicity
- Equivalent Safety
- Local Toxicity
- Equivalent Local Delivery: Clinical Endpoint
- Equivalent Systemic Exposure
- Formulation Q1/Q2 Sameness

confirmatory
Statistics on nasal product submissions to FDA
From 1987 to 2013, FDA has received eighty five (85) nasal spray drug product ANDAs

The average of nasal spray ANDA applications FDA received in the past 10 years (2003-2013) is six applications/year
Status of nasal drug product ANDAs received by FDA

<table>
<thead>
<tr>
<th>Status</th>
<th># of ANDAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>27</td>
</tr>
<tr>
<td>Pending review</td>
<td>22</td>
</tr>
<tr>
<td>Refused to receive</td>
<td>4</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>32</td>
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</tbody>
</table>

Data collected up to Dec. 2013
# Nasal drug products approved by FDA

<table>
<thead>
<tr>
<th>Drug Product Name</th>
<th># of Applications Approved</th>
</tr>
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<tbody>
<tr>
<td>Azelastine Nasal Spray</td>
<td>3</td>
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<tr>
<td>Butorphanol Tartrate Nasal Spray</td>
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</tr>
<tr>
<td>Desmopressin</td>
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<tr>
<td>Flunisolide</td>
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<tr>
<td>Fluticasone Propionate Nasal Spray</td>
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<tr>
<td>Ipratropium Bromide Nasal Spray</td>
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<tr>
<td>Triamcinolone Hydrochloride Nasal Spray</td>
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<tr>
<td>Tetrahydrozoline Nasal Spray</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27</strong></td>
</tr>
</tbody>
</table>

Data collected up to Dec. 2013
Common issues observed in nasal product ANDA submissions and FDA’s recommendations for improving application quality

- General issues
- Examples of commonly seen deficiencies
- Frequently asked questions
General issues - ANDA organization issues

- BE reviewers take a long time to complete reviews of NS ANDA that are poorly organized
  - Average time for completing a BE review of a NS product was about 5-6 weeks

- We recommend that the sponsors submit applications in CTD format that is published on the FDA public website on 2010:

- Standardized CTD format submission facilitates quick review
  - Average review time of a NS product BE review has been reduced from 5-6 weeks to 2-3 weeks
General issues - Electronic table issues

• Not prepared properly
  – File created by scanning tables rather than by creating a PDF file

• Not submitted in both Word and PDF formats
General issues - SAS® file issues

- SAS file not submitted in proper format
  - Data should be in .xpt file
- Data in SAS file does not match data presented in study report
General issues - commonly missing information

- Missing Certificate of Analysis (COA) for the reference listed drug product
- Missing protocols/SOPs for the in vitro test method
- Missing analytical SOP (Procedural SOP and Method Validation SOP) for the in vitro test
- FDA recommends 20% Chromatograms for Drug in Small Particles/Droplets by Cascade Impactor. This data are often missing
- FDA recommends complete (100%) raw numerical data for all of the in vitro and in vivo tests. This data are often missing
General issues causing refuse-to-file ANDAs

Two Major Reasons:

- The test formulation is not Q1/Q2 the same as the RLD formulation

- Unacceptable clinical endpoint study
Examples of commonly seen deficiencies

Case #1: Multiple actuations were used in the spray pattern test and the average of multiple actuations was used to conduct PBE analysis.

Recommendation: As per the Draft Nasal BA/BE Guidance, **one single spray** should be used for the spray pattern test.
Examples of commonly seen deficiencies

• Case #2: The sponsor used test product to conduct the pre-study validations for BE in vitro tests

• Recommendation: The Agency recommends the use of reference drug product to conduct the pre-study validations for BE in vitro tests
Examples of commonly seen deficiencies

Case #3: Insufficient sample size was used in the BE in vitro tests: the sponsor used two (2) batches of RLD product in the in vitro studies

Recommendation: The agency recommends 3 or more batches of the test product and RLD each for the in vitro BE test
Q 1: How many retention samples should be reserved for each site of in vivo and in vitro BE studies of NS?

A:

- If the BE studies are conducted at one site: at least 50 units for each batch of test and reference products, including placebos (if applicable), must be retained for BE studies;
- If the BE studies are conducted at multiple sites: at least 50 units for each batch of test and reference products, including placebos (if applicable), with not less than 10 units per each batch per site, be retained for the BE studies.

An example: if a BE study is conducted at 6 sites, using 1 batch of T and R, the total number of reserve samples to be retained for T and R must be at least 60, with at least 10 units per each batch per site (10 units/batch/site X 1 batch/product X 6 sites = at least 60 units/product).

- Please refer to Drug Specific BE Guidance for Budesonide Inhalation Suspension for details.
Q 2: What are FDA’s expectations for plume height?

A: Currently, plume height data is submitted as supporting evidence only. FDA does not set specific criteria for plume height evaluation.
Frequently asked questions

Q 3: FDA follows the weight-of-evidence approach. What happens when all parameters pass in vitro BE except one parameter?

A: All parameters in the in vitro tests should pass their respective BE criteria to be able to conclude BE. If one of the parameters failed, the sponsor will be advised to repeat that particular test. The BE study is considered acceptable when the repeated test meets the BE criterion, together with adequate justifications.
Frequently asked questions

Q 4: Is spray pattern analysis using TLC plates acceptable to FDA?

A: Yes, it is acceptable.
Frequently asked questions

Q 5: Can Population Bioequivalence (PBE) be performed with more than 3 lots; for example with 4 lots of T versus 4 lots of RLD. Alternatively, can PBE be performed with more than 10 units per batch; for example 12 units of Test and Reference?

A: Yes. PBE can be performed with more than 3 lots; PBE can be performed with more than 10 units per batch.
Q 6: Various changes may take place in nasal spray product development. These changes can occur at the developmental stage, i.e., after the product passed BE tests yet pending approval, or after drug product has been approved. Does FDA recommend a full package BE tests for these changes?

A: In general, an abbreviated package including some in vitro tests are recommended to demonstrate BE of these changed products. Currently, OGD handles this case-by-case. The sponsors are encouraged to consult the OGD for the specific recommendations based on their respective changes.
Summary and conclusions

- FDA received an average of 6 nasal spray ANDA applications per year in the past 10 years
- FDA has approved 27 generic nasal spray drug products up to the end of 2013
- FDA recommends weight-of-evidence approach for BE demonstration of locally acting nasal spray products
- Avoiding common errors in BE submissions will help speed up ANDA review
References

– Bioequivalence Summary Tables For Aqueous Nasal Spray Products
  SAS Data Tables for Aqueous Nasal Spray Product In Vitro Bioequivalence Study Data Submission:

– Bioequivalence Recommendations for Specific Products - Budesonide Inhalation Suspension:
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081288.htm
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Thank you for your attention!