Image Therm Engineering
Solutions for science and industry

Image Therm Engineering, Inc.
142 North Road, Suite R
Sudbury, MA 01776 USA

Tel: (978) 371-8822
Fax: (978) 371-8942
www.imagetherm.com

To: Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

From: Dino J. Farina

Date: 3 July, 2003

Re: Comments related to Docket No. 99D-1738, Guidance for Industry: "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", dated April 3, 2003.

The comments contained in this document reflect the collective thoughts of Image Therm Engineering, Inc. and some of its customers who are involved in characterizing the performance of nasal spray and nasal aerosol drug products primarily for spray pattern, plume geometry and drop size distribution by laser diffraction. Our comments here are intended solely to help clarify the issues discussed in the FDA draft guidance document and to hopefully improve the interpretation and understanding of the FDA's new requirements. Our comments are as follows:

1. Allowance for different T and R pumps with different actuation settings.	
Document Reference: Lines: 390-393 Page: 11.	***"We recommend you validate all in vitro tests for accuracy and precision prior to the study. For applicable studies, instrument settings established during prestudy validation would be used in the study. For comparative studies, use of the same settings will ensure that T and R are studied under the same instrumental conditions."***
Comments	Does "same instrumental conditions" mean that T and R need to be studied with identical actuation settings? We understand the need for using the same settings for analysis and experimental setup conditions. We bring this up because in our experience with nasal spray products, it is likely that T and R products will use different physical pumps. We've found that this situation can arise because the pump used in the reference product may not be available to anyone but the reference manufacturer, leaving the test product manufacturer no choice but to use a substitute pump with different performance properties. Recent work by our staff here with a sensor capable of recording the performance of hand actuation has shown that the different pumps will likely be actuated differently by trained patients (e.g. different actuation velocity and/or acceleration) even though they can produce the same delivered dose of drug.
Recommendations	Add clarifying language here to allow the use of different pumps between T and R with different actuation settings. However, the different settings must be justified based on exploratory studies in which the relevant parameters are varied to simulate in vitro performance upon hand actuation as suggested in footnote 10 on

	page 11, and the pumps must produce the same delivered dose of drug.

2. Clarification of Spray Pattern equivalence criteria.	
Document Reference: Lines: 680-686 Page: 18.	***"Comparative visual inspection for shape. For the automated analyses, the true shapes identified by the software serve as the basis of comparison (qualitative). Establishment of qualitative sameness of T and R spray pattern shapes is a prerequisite to the quantitative analyses in the following two bullets.*** • ***Equivalent area within the perimeter of the true shape for automated analysis, or equivalent Dmax for manual analysis (quantitative)*** • ***Equivalent ovality (ellipticity) ratio (quantitative)"***
Comments	What is the definition of "equivalent"? Will this be defined mathematically in the upcoming Appendices to this document?
Recommendations	Define "equivalen(ce)t in a mathematically meaningful way, including appropriate tolerance intervals in the Appendices to the guidance document.

3. Spray Pattern perimeter definition.	
Document Reference: Lines: 693, 722 Pages: 18, 19.	***"…to include a high proportion, e.g., 95% of the total pattern…"***
Comments	The words "total pattern" seem vague here. For instance, should stray particles/droplets be included in the "total pattern"?
Recommendations	Define "total pattern" as follows: "largest contiguous grouping of droplets/particles representing a level of intensity sufficiently above the background to allow reliable detection".

4. Inclusion of system settings in addition to software settings.	
Document Reference: Lines: 697-698 Pages: 18.	***"Software settings can be established during prestudy validation and the settings should be used consistently in the study."***
Comments	We believe that in addition to software settings, overall system settings should be established for T and R during prestudy validation and that the overall settings should be used consistently in the study.
Recommendations	Broaden the language to read "measurement system settings (including software and hardware) can be established during prestudy validation for T and R and these settings should be used consistently in the study".

5. Spray Pattern distance from actuator orifice range.	
Document Reference: Lines: 748-751 Pages: 19.	• ***"Two distances from the actuator orifice, which allow discriminatory capability between individual pump units and between T and R products. For nasal sprays, these distances are recommended to be at least 3 cm apart within the range of 3 to 7 cm."***
Comments	With the above recommendation, the two distance pairs that can be used are 3-4 cm paired with 6-7 cm and the range between 5-6 cm cannot be achieved. In our experience testing many nasal spray products with nonimpaction Spray Pattern

	measurement systems, a 6 cm or greater distance produces sparse Spray Pattern images (low droplet concentration) that are prone to high variability. This behavior is due to the flow dynamics in nonimpaction systems that allows the spray plume to develop naturally and therefore have wider plume angles (>60° in some cases). As described in the guidance under plume geometry (lines 778-780, page 20) most nasal sprays produce a relatively small and stable conical plume (linear cone defined by a constant plume angle). Beyond the conical region, the spray is heavily influenced by ambient conditions such as cross flow and room air entrainment which lead to turbulence (hence chaotic behavior). Due to this behavior, we believe that consistent Spray Pattern measurements can only be made in the conical region of the spray. Further, confirmation that the selected spray pattern distance range is within the conical region can be done during Plume Geometry testing, further complementing the two tests. See Comment 6, below. Additionally, many nasal sprays can exhibit good Spray Pattern measurement performance around 5 cm from the actuator orifice.
Recommendations	Define the range as follows: "For nasal sprays, these distances are recommended to be at least 2 cm apart within the range of 2 to 7 cm and the selected region should be verified to be within the conical region of the spray plume by plume geometry characterization." Also, make this same recommendation for Droplet Size Distribution by Laser Diffraction measurements (line 520, page 14). This range would allow Spray Pattern measurements to be made at a minimum of 2 and 4 cm, which are far more likely to be within the conical region of the spray plume. We believe that this wider range and smaller separation distance would provide finer control of where to measure spray pattern while maintaining discriminatory capability between individual pump units and between T and R products. Additionally, we believe that this range would still produce good results with impaction Spray Pattern methods and with DSD by Laser Diffraction systems despite the higher droplet concentration levels present closer to the actuator orifice.

6. Plume geometry.	
Document Reference: Lines: 774 Pages: 20.	***"For this guidance, the recommended plume width would be the width at a distance equal to the greater of the two distances selected for characterization of the spray pattern. Plume width data would thus complementary to spray pattern data obtained at the same distance."***
Comments	Our experience shows that measurements of the plume width at the greater of the two spray pattern distances are prone to high variability, especially if the greater distance selected is beyond the conical region of the spray as described in Comment 5, above. This is due primarily to the reasons described in Comment 5, above, but also because the edge of the plume becomes more difficult to reliably identify outside of the conical region. However, we do agree strongly with making spray pattern and plume geometry data more complementary.
Recommendations	Define the plume width as follows: "For this guidance, the recommended plume width would be the width at the distance equal to the greater of the two distances selected for characterization of spray pattern, and within the conical region of the plume."

7. Plume height.	
Document Reference: Lines: 790-791 Pages: 20.	***"Plume height would be the distance from the actuator orifice (sprays) or end of the inhaler tube (aerosols) to the leading edge of the plume."***
Comments	In our experience reliably determining the "leading edge of the plume" for nasal sprays and nasal aerosols is nearly impossible, and even it were possible we question what value it brings in determining equivalency of T and R products. In addition, many nasal sprays including many that are currently marketed in the US, produce plumes that are quite large (>100 cm). Further compounding the problem is the fact the leading edge of the plume moves with time as the plume grows and this makes determining what instance in time to use for the leading edge subjective. With these issues and the comments mentioned in Comments 5 and 6 above, we feel that a more meaningful metric here would be plume "length" (height connotes vertical orientation which may or may not be intended here) defined as the length of the conical region of the plume. Defined in this way, plume length would be statistically meaningful as described in the guidance (lines 809-814, pages 20-21) and help correlate the equivalence between T and R better. Additionally, this definition makes the measurement essentially time independent and therefore more deterministic for the analyst.
Recommendations	Define the plume length or height as follows: "Plume length (height) would be the distance from the actuator orifice (sprays) or end of the inhaler tube (aerosols) to the end of the conical region of the plume."

We hope that these comments are helpful to the FDA with respect to the guidance document. Finally, we feel that this draft is a significant improvement over the previous version issued in June 1999, especially with regard to spray pattern and plume geometry characterization.

Sincerely,

Digitally signed by Dino J Farina
cn=Dino J Farina, o=Image Therm Engineering, Inc., c=US
Date: 2003.07.03 15:42:00 -05'00'
Reason: I am the author of this document
Sudbury, MA

Dino J. Farina, President