NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

1197 '03 JUL -1 A9:08

June 27, 2003

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

Dear Sir/Madam:

Re: Comments on Docket No. 99D-1738
Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

The Apotex Group of Companies appreciates the opportunity to comment on this proposed rule. Please see the comments provided below.

1. Lines 199-200 recommend that we use the same particle size distribution in the test products as in the reference product. If there is no technology available to determine the particle size distribution in suspension, how can we be certain that we are using the same particle size as the reference in our ANDA test product?

2. Lines 251-254 recommend that the formulations (test and reference) be Q_1 the same and Q_2 essentially the same. However, we don't always have the formulation of the reference product when we develop a generic. There are times when there is a combination of cellulosic materials in the formula to keep the drug in suspension, but it may not be possible to determine the exact amounts and grades of these materials in the reference. How can we be certain that we are Q_2 essentially the same if we can't determine how much is in the reference? If all in-vitro and in-vivo test results are equivalent, shouldn't this be acceptable for approval of a generic product even if we are outside ±5%?

3. Lines 382 and 383 point out the requirement for Spray Pattern and Plume Geometry. Since we're spraying the product into a confined space (the nasal cavity), how important are these tests? In addition, line 810 states that the comparative plume geometry data are merely supportive for BE studies. Therefore, why should we be required to spend the time and money on these tests?

99D-1738

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REGISTERED COMPANY ISO 9002 SGS

4. Drug Particle Size Distribution By Microscopy, lines 634-658: We found that sometimes it is very hard to distinguish drug particles from excipients under a light microscope, resulting in a lot of subjectivity when testing drug particle size for suspensions. The requirement for light microscopy testing should be eliminated from this guidance until there is a validated technique available.

5. From lines 712-713 in the Guidance, the manual analysis of spray pattern for impaction systems (e.g., TLC) recommends that the approximate COM be identified and the Dmax and Dmin be drawn through this center for each spray pattern. The determination of an estimated COM should be defined in the Guidance for the manual quantitation of a spray pattern, especially if the pattern is star-shaped or horseshoe-shaped.

6. From lines 698-700 and lines 716-717 in the Guidance, the statistical analysis for non-impaction systems (e.g., SprayVIEW) is based on equivalence of area within the perimeter and ovality whereas the statistical analysis for impaction systems (e.g., TLC) is based on equivalence of Dmax and ovality. The statistical analysis for equivalence in spray pattern should be the same regardless of using a non-impaction or impaction systems, analyzing Dmax and ovality for both systems.

7. Lines 906-907 specify a two-week efficacy trial. Is this the minimum that we can run our study, or the maximum length of the study. [Canada is requiring three weeks. In order to run studies that are suitable for both US and Canada, we'd like to be able to run a three week study for both countries.]

8. The FDA is asking for a PK study to show systemic equivalence. However, "if a sponsor has convincing data based on unsuccessful attempts to conduct the PK study a PD or clinical study for systemic absorption could be used" (lines 1023-1024). What does the agency consider to be "convincing"? Is a pilot study with the lowest available LOQ by standard methods sufficient?

9. Line 950 recommends that the study be multicenter. It is not necessary to perform the clinical BE study in multiple centers because the efficacy endpoint is patient self-rated TNSS. That is, there is very little subjective evaluation involved with the investigations.

10. On Line 961, for the evaluable population, the requirement of having no protocol violations is too tight. It should be changed to having no SIGNIFICANT protocol violations.

11. Lines 967-970 indicate that a Bio-IND is recommended for a BE study with a clinical endpoint. However, lines 874-875 state that for an ANDA a Bio-IND is required.

12. In lines 938-941, FDA is requesting that the baseline TNSS be calculated based on the last 3 days of the placebo run-in (AM and PM TNSS) as well as the AM for day

1 of randomization. It is my understanding, from talking with an allergist, that the AM and PM scores can be quite different. Since we're only using 7 values to calculate the baseline, aren't we skewing the average by including the extra AM score?

13. Lines 1066-1070 refer to a multiple dose PK study. The Guidance implies that multiple dose studies would be dosed every 12 or 24 hours, depending on the drug product labeling. Wouldn't it be acceptable to dose, for example, every 30 minutes so that the drug levels can be built up yet the volume administered at any dose wouldn't be too large? Assuming this is found to be safe by the IRB

14. On Line 1125, it is not necessary to do the clinical study for systemic exposure in allergic rhinitis patients because of the presence of placebo and active control, which can be used for checking subject compliance in the study. The evaluation of efficacy is a duplication of what would be found in the clinical BE study.

15. On Line 1180, without knowing the criteria for equivalence, it is difficult to estimate the sample size. Nevertheless, the criteria should not be so stringent that more subjects will be needed in the clinical exposure study than in the clinical BE study.

16. Lines 783-784 in the plume geometry section state "The applicant would provide documentation that the plume is fully developed at the selected delay time."

    We recommend that a standardized procedure be used to determine when the plume is fully developed by the addition of the following statement: "If the same automated actuation station is used for plume geometry and droplet size by laser diffraction, the delay time of the fully developed phase of the plume can be identified by the obscuration profile on droplet size distribution by laser diffraction where obscuration reaches its plateau values."

    The rationale behind this proposed change was determined by various plume geometry and droplet size distribution by laser diffraction testing on aqueous nasal sprays and suspension nasal sprays. The SprayVIEW NSx actuation station was used for all testing.

    Please note, the Table and Figures referred to in the text below have been appended to this letter.

    Aqueous Nasal Spray:

    Using the SprayVIEW Spray Characterization system supplied by Image Therm Engineering to determine the plume geometry of a spray, a single snapshot at a delay time in the fully formed region of the plume must be analyzed. Using the average image intensity profile, a snapshot of the plume is taken at a delay time representative of the fully formed plume. Figure 1 depicts the average image

intensity profile of the Novex product and the Innovator product. In each case, the profile does not show a distinct plateau region and thus, it is difficult to identify the time where the plume is fully formed. The delay time chosen in Figure 1 is 50msec. This time should be within the region of the fully developed plume but is on the upslope of the average image intensity profile. If there is a plateau, it may not start until a delay time of 80msec.which is unreasonable. Therefore, a plateau region in the image intensity profile for plume geometry cannot be used to identify the region of the fully developed plume.

Using the Malvern SprayTEC RT Sizer to determine the droplet size by laser diffraction, a Time History plot of Time vs. % Transmission is used to determine the fully formed region of the plume. In this case, the fully formed plume is defined by the attainment of a plateau (as per FDA guidance). Figure 2 depicts the Time History plot of the Novex product and Innovator product. The plateau region of the spray was easier to identify which represented the region of the fully formed plume at reasonable delay times. (eg. starting around 20msec)

Thus, the plateau region from image intensity profile in plume geometry should not be used to determine the fully formed plume region of the spray. The plateau region from the time history plot in droplet size distribution should be used to determine the fully formed plume for the spray. The single snapshot used for plume geometry at a delay time where the plume is fully formed will be determined from the plateau range established in the Time History plot for droplet size distribution by laser diffraction as long as the same actuation station is used.

Suspension Nasal Spray:

Using the SprayVIEW Spray Characterization system, Figure 3 depicts the average image intensity profile of the Novex product and the Innovator product. In each case, the profile does not show a distinct plateau region and thus, it is difficult to identify the time where the plume is fully formed. The delay time chosen in Figure 3 is 40msec. This time should be within the region of the fully developed plume but is on the upslope of the average image intensity profile. If there is a plateau, it may not start until a delay time of 60msec.which is unreasonable. Therefore, a plateau region in the image intensity profile for plume geometry cannot be used to identify the region of the fully developed plume.

Using the Malvern SprayTEC RT Sizer, Figure 4 depicts the Time History plot of the Novex product and Innovator product. The plateau region of the spray was easier to identify which represented the region of the fully formed plume at reasonable delay times. (eg. starting around 20msec).

Thus, the plateau region from image intensity profile in plume geometry should not be used to determine the fully formed plume region of the spray. The plateau region from the time history plot in droplet size distribution should be used to determine the fully formed plume for the spray. The single snapshot used for plume geometry

at a delay time where the plume is fully formed will be determined from the plateau range established in the Time History plot for droplet size distribution by laser diffraction as long as the same actuation station is used.

Differences in Actuation Stations:

A study was performed to determine any differences in droplet size distribution and Time History Plots using the same Malvern RT Sizer with different automated actuation stations, the SprayVIEW NSx and the Innova. One distance was measured at 3cm for both the Novex and Innovator nasal spray product in aqueous and suspension forms.

There were significant variations in the delay time and the droplet size distribution using the SprayVIEW NSx and Innova systems for each of the nasal sprays tested. (Table 1)

For the suspension nasal spray, the droplet size distribution was significantly larger when using the SprayVIEW NSx compared to when the Innova was used. The duration of the fully formed plume was also longer using the SprayVIEW NSx. (Figures 2-5)

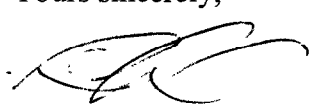
For the aqueous nasal spray, the droplet size distribution was significantly larger when using the SprayVIEW NSx compared to when the Innova was used. The duration of the fully formed plume was also longer using the SprayVIEW NSx. (Figures 3-6)

Conclusion:

It is possible to correlate the fully formed plume region determined from the Time History Plot for droplet size distribution by laser diffraction and the fully formed plume region from the average image intensity profile for plume geometry. However, there are major differences in results when performing the tests with 2 different automated actuation stations. If the droplet size distribution Time History plot is to be utilized to determine the delay time on the average image intensity profile used for plume geometry measurements, then the same automated actuation station MUST be used for both tests.

Should you have any questions regarding the above, please do not hesitate to contact me directly at (905) 508-2445, or FAX your questions to (905) 884-0357.

Yours sincerely,



Gina Sirianni, M.Sc.
Manager, US Regulatory Affairs

Fig. 1 AQUEOUS NASAL SPRAYS – PLUME GEOMETRY

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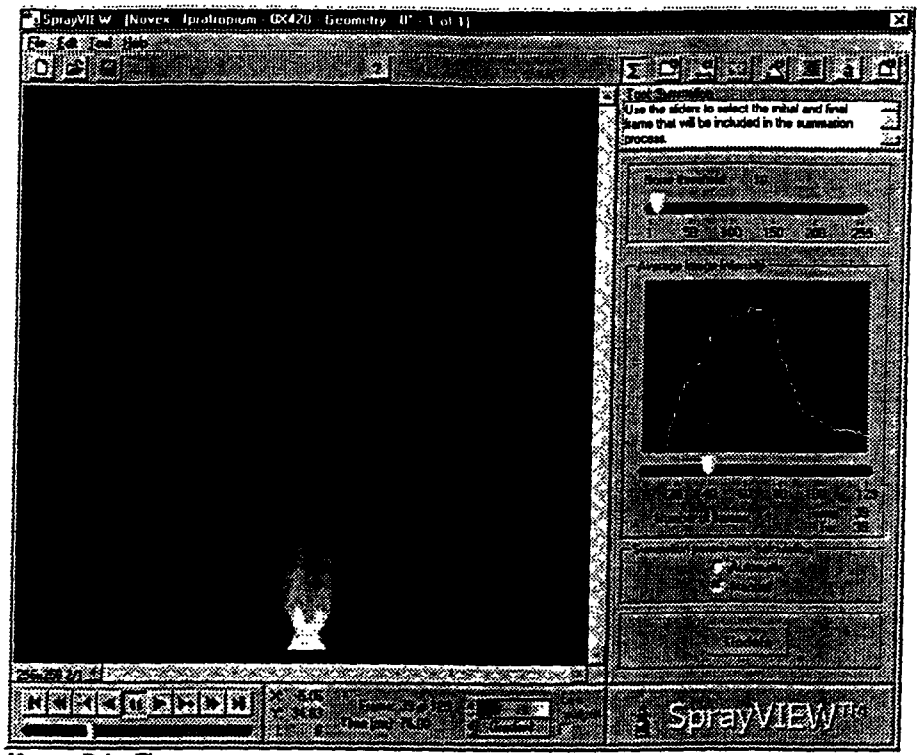
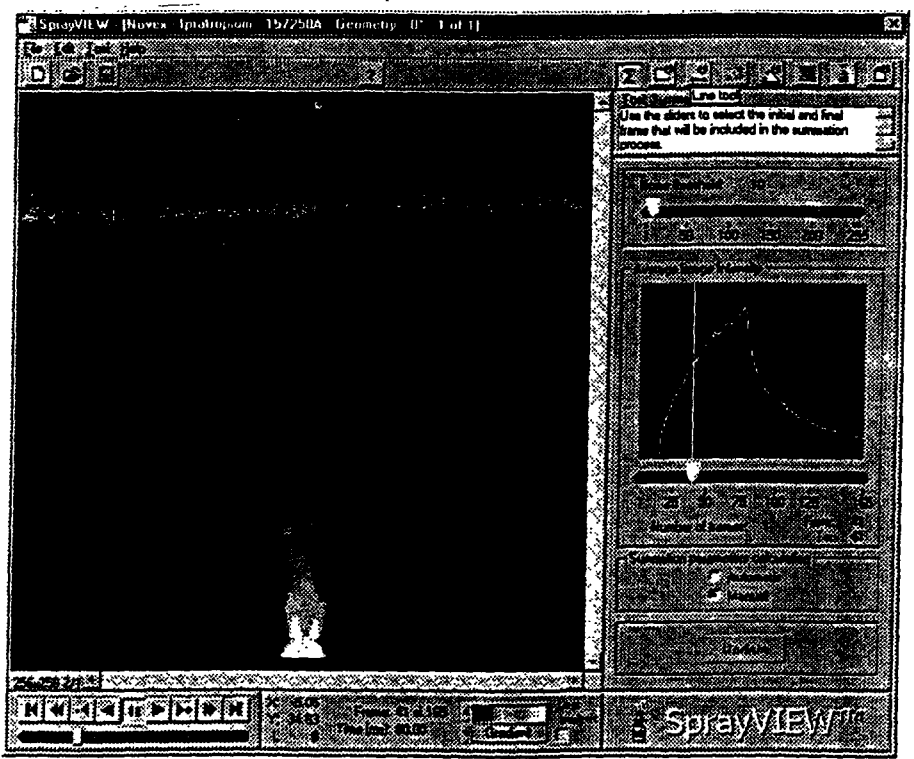


50 msec. Delay Time

INNOVATOR



50 msec. Delay Time

Fig. 2 AQUEOUS NASAL SPRAYS – DROPLET SIZE BY LASER DIFFRACTION

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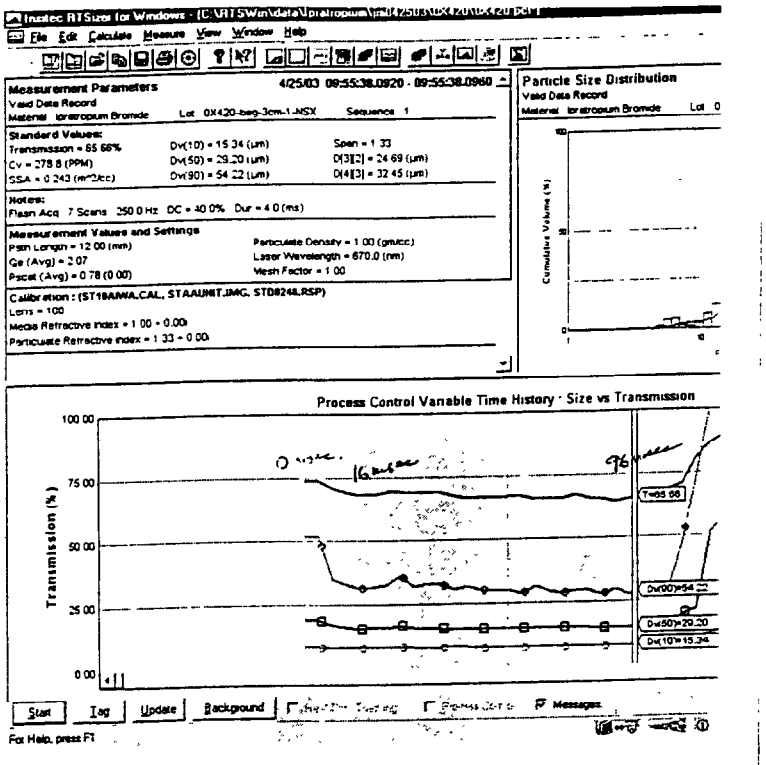

INNOVATOR

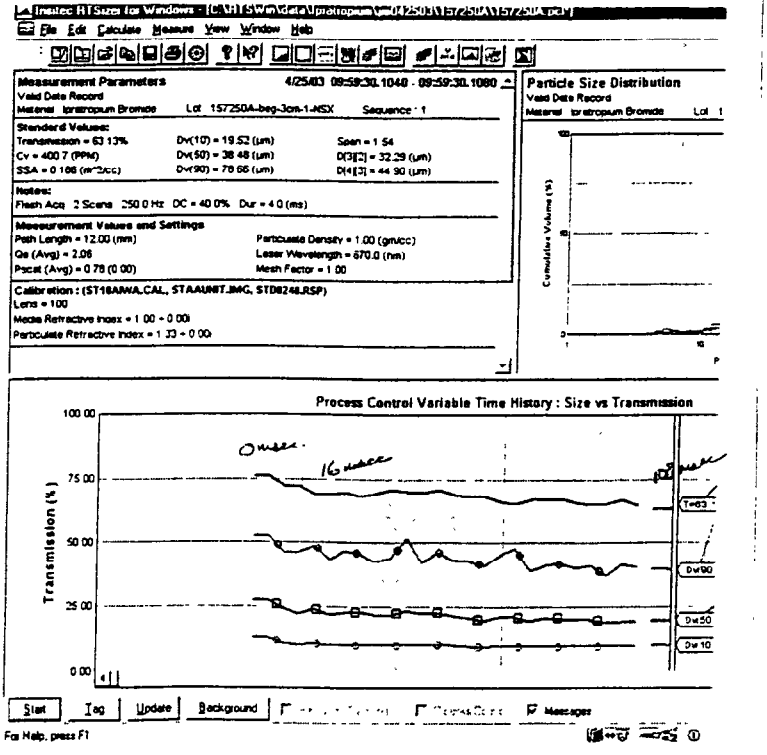

Fig. 3 SUSPENSION NASAL SPRAYS – PLUME GEOMETRY

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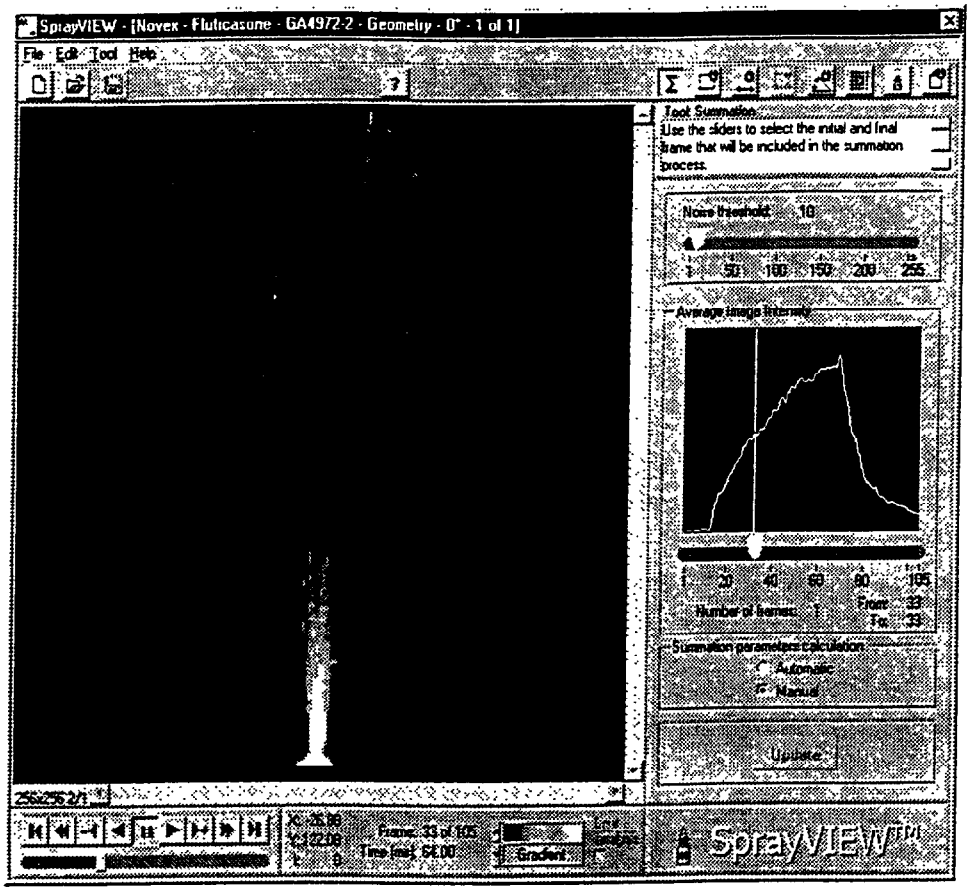
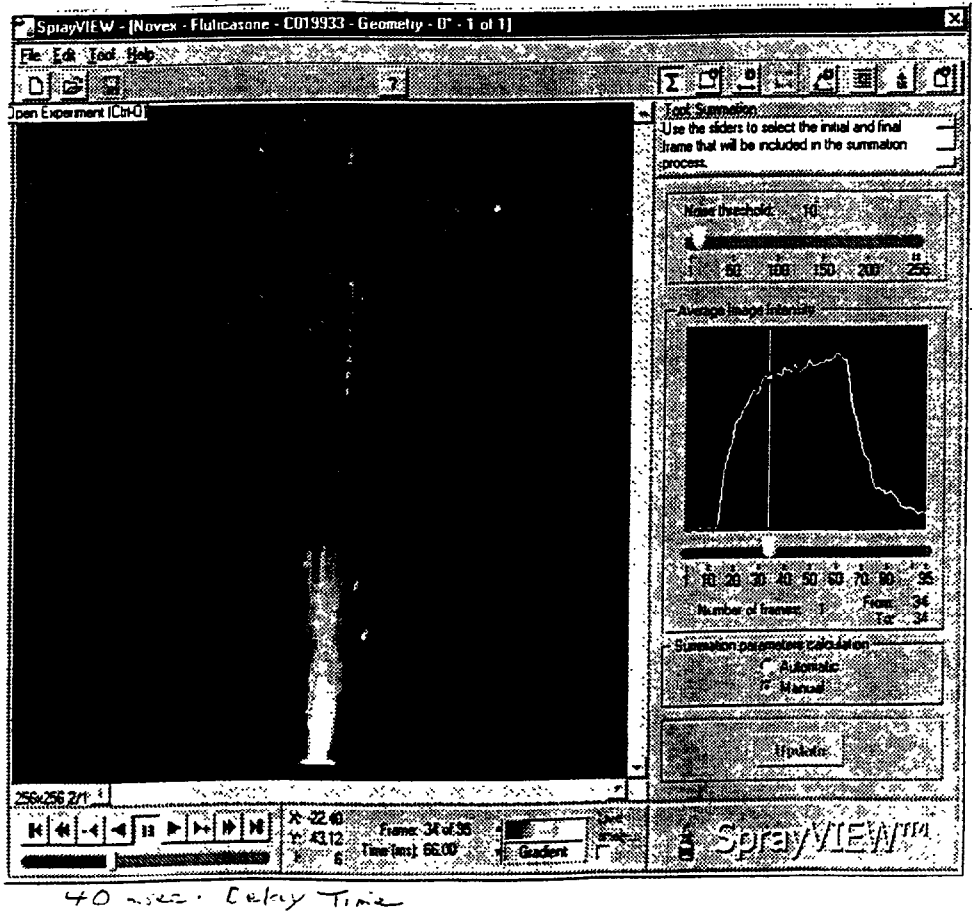


40 msec Delay Time

INNOVATOR



40 msec Delay Time

Fig. 4 SUSPENSION NASAL SPRAYS–DROPLET SIZE BY LASER DIFFRACTION

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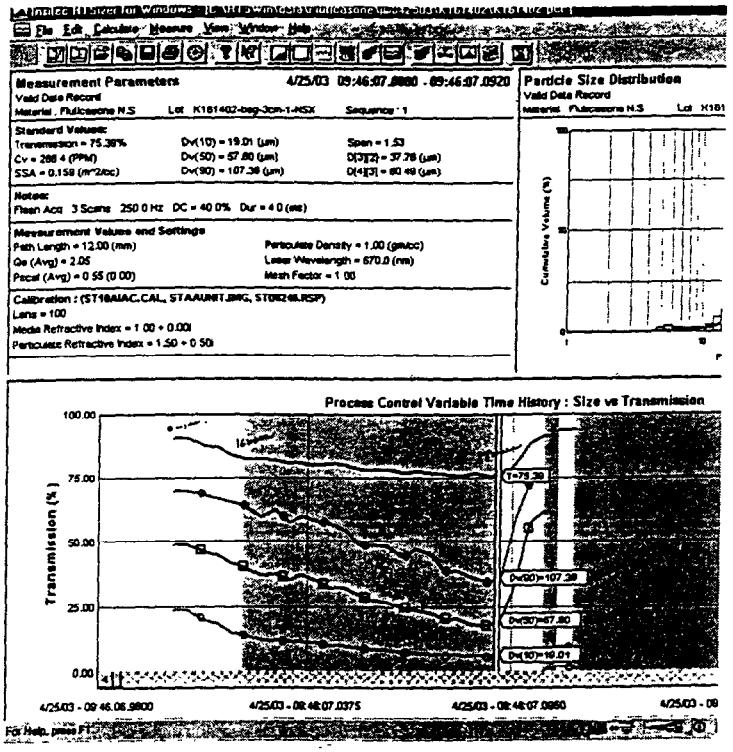

INNOVATOR

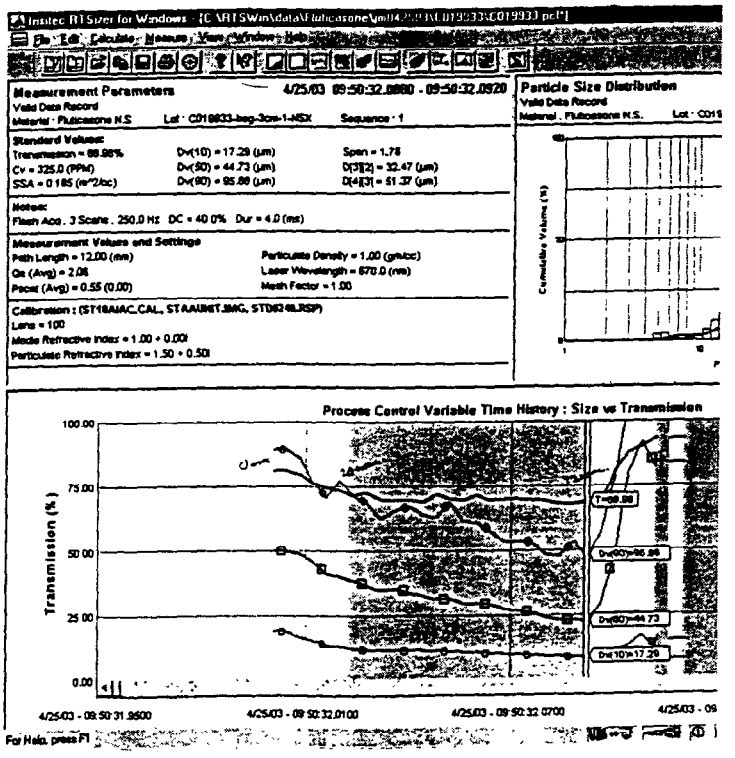

Fig. 5 AQUEOUS NASAL SPRAY – DROPLET SIZE USING INNOVA

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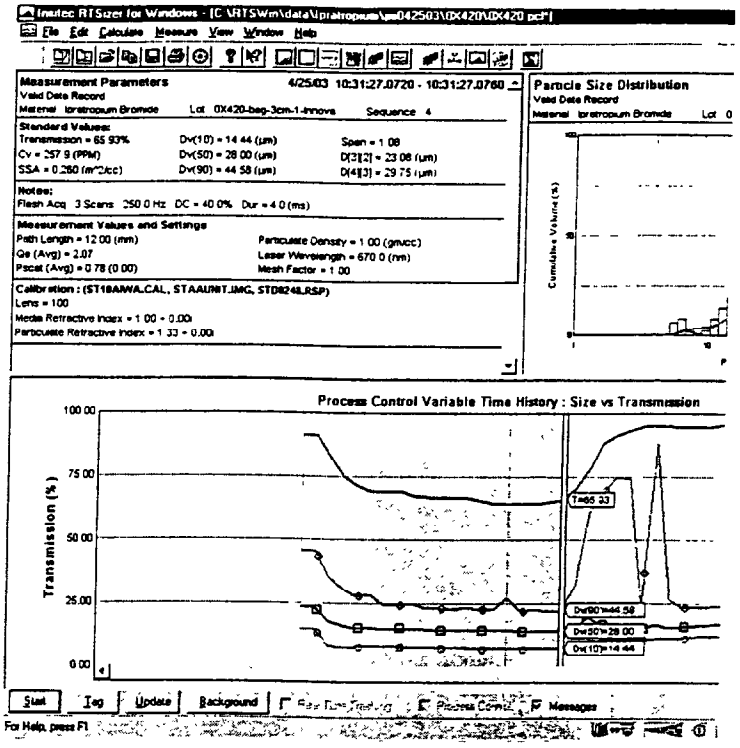

INNOVATOR

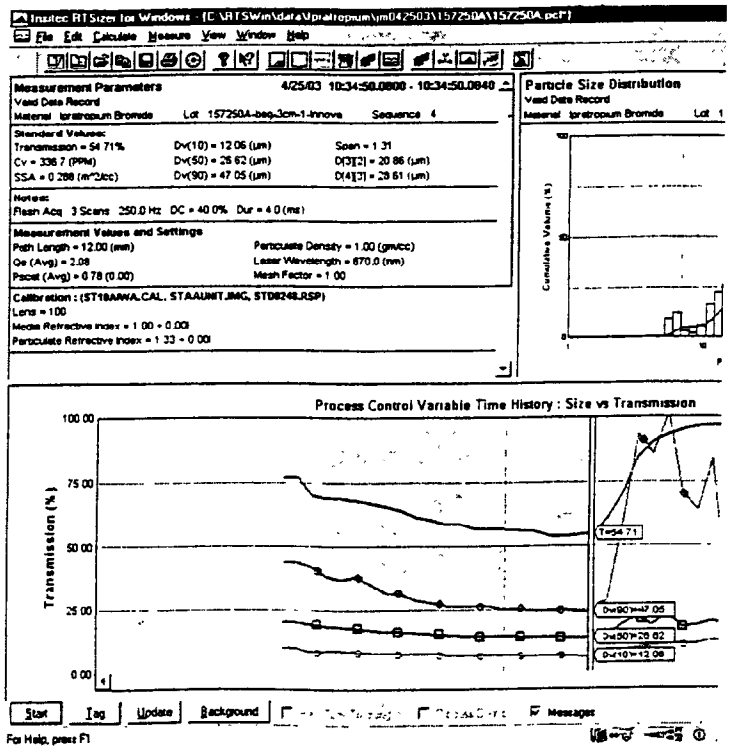

Fig. 6 SUSPENSION NASAL SPRAY – DROPLET SIZE USING INNOVA

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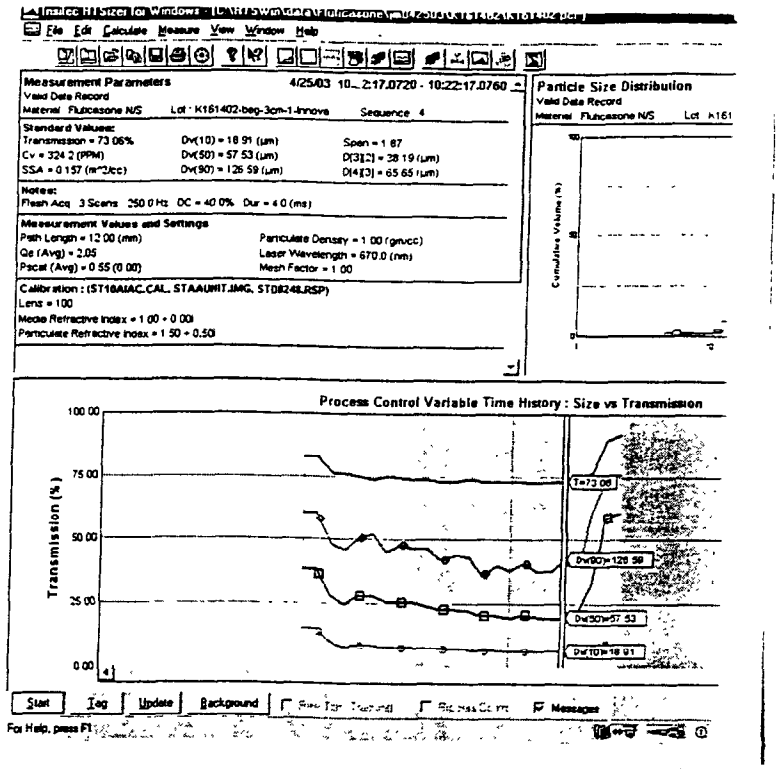

INNOVATOR

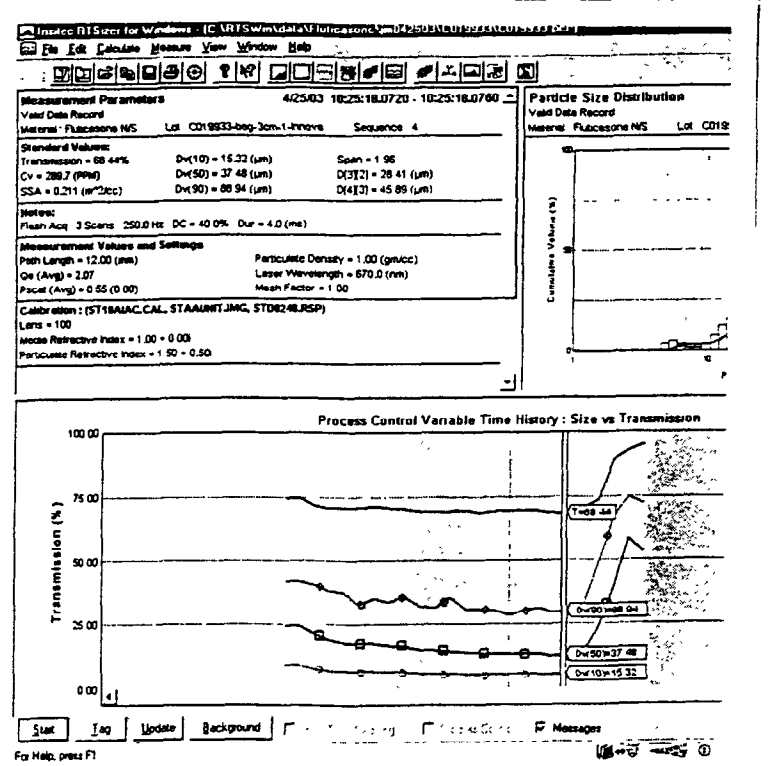

Table 1 COMPARISON OF SPRAYVIEW NSX VS. INNOVA ACTUATION STATIONS TESTING DROPLET SIZE BY LASER DIFFRACTION

Investigation of Different Actuation Stations Used for Droplet Size with the SprayTEC RT Sizer For Nasal Sprays

Apr.25/03

Product Type	Supplier	Vertical Distance	Actuation Station	Spray #	Intermediate Plume						
					D10	D50	D90	Span	Start Time (msec)	End Time (msec)	Duration (msec)
Suspension	Novex	3cm	SprayVIEW NSx	1	25.71	87.75	161.41	1.55	16	88	72
				2	25.93	87.19	162.69	1.57	16	88	72
				3	26.06	87.68	159.80	1.53	16	88	72
		3cm	Innova	1	20.81	64.83	125.23	1.61	24	76	52
				2	20.41	64.79	126.59	1.64	28	80	52
				3	21.46	64.47	122.97	1.57	28	80	52
				Mean	**23.40**	**76.12**	**143.12**	**1.58**	**21**	**83**	**62**
				CV	**11.8**	**16.4**	**14.0**	**2.5**	**28.2**	**6.4**	**17.7**
Suspension	Innovator	3cm	SprayVIEW NSx	1	21.14	60.39	121.98	1.67	20	92	72
				2	21.11	60.71	120.62	1.64	20	88	68
				3	20.85	57.31	118.76	1.71	24	92	68
		3cm	Innova	1	17.16	43.76	95.99	1.80	16	72	56
				2	17.14	41.93	96.01	1.88	12	76	64
				3	17.16	42.28	95.84	1.86	20	76	56
				Mean	**19.09**	**51.06**	**108.20**	**1.76**	**19**	**83**	**64**
				CV	**11.1**	**18.2**	**12.4**	**5.7**	**22.1**	**10.9**	**10.5**
Aqueous	Novex	3cm	SprayVIEW NSx	1	15.45	30.43	60.80	1.49	16	96	80
				2	16.59	32.27	62.97	1.44	16	108	92
				3	16.65	31.20	59.53	1.37	12	108	96
		3cm	Innova	1	14.91	28.71	46.70	1.11	16	76	60
				2	14.30	26.95	44.89	1.13	16	76	60
				3	13.99	27.49	45.69	1.15	20	72	52
				Mean	**15.32**	**29.51**	**53.43**	**1.28**	**16**	**89**	**73**
				CV	**7.4**	**7.2**	**15.9**	**13.3**	**15.8**	**18.7**	**25.3**
Aqueous	Innovator	3cm	SprayVIEW NSx	1	19.33	41.32	85.15	1.59	16	108	92
				2	18.83	41.24	87.00	1.65	8	112	104
				3	19.01	42.29	85.95	1.58	12	108	96
		3cm	Innova	1	13.95	29.92	57.52	1.46	8	84	76
				2	13.87	30.09	60.79	1.56	8	84	76
				3	13.72	29.06	56.67	1.48	12	84	72
				Mean	**16.45**	**35.65**	**72.18**	**1.55**	**11**	**97**	**86**
				CV	**17.4**	**18.4**	**21.1**	**4.6**	**30.6**	**14.4**	**15.2**