University of Groningen

Performance of PARI eFlow (R) Response

Rottier, Bart L.; de Boer, Anne H.

Published in:

Journal of aerosol medicine and pulmonary drug delivery

DOI:

[10.1089/jamp.2009.Cor3](https://doi.org/10.1089/jamp.2009.Cor3)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Rottier, B. L., & de Boer, A. H. (2010). Performance of PARI eFlow (R) Response. *Journal of aerosol medicine and pulmonary drug delivery*, 23(2), 114-118. <https://doi.org/10.1089/jamp.2009.Cor3>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

pulmonary delivery of inhaled tobramycin for pseudomonas infection in cystic fibrosis. *Pediatr Pulmonol*. 2008;43:753–759.

6. Fischer R, et al.: Inhalation with the PARI eFlow rapid reduces treatment time burden significantly in adult CF patients without altering lung function. Poster presentation at the ECFC conference in Belek, 2008. [Abstract in *J Cyst Fibrosis*. 6(Suppl 1):S41.]
7. Miltz S, et al.: E-Flow rapid: improved lung function and patient satisfaction with more volume delivered to the lungs during inhalation therapy in cystic fibrosis. Poster presented at the ECFC conference in Prague, 2008. [Abstract in *J Cyst Fibrosis*. 7(Suppl. 2):S67.]
8. Bakuridze L, Andrieu V, Dupont C, and Dubus JC: Does repeated disinfection of the e-Flow rapid[®] nebulizer affect in vitro performance? *J Cystic Fibrosis*. 2007;6:309–310.
9. Perkins WR, et al.: Aerosolization of liposomal amikacin (Arikace[™]) using different nebulizers: selection of the eFlow[®] nebulizer. Poster presented at the NACF conference in Anaheim, 2007. [Abstract in *Pediatric Pulmonology*, 2007; 42(Suppl. 30):356.]

DOI: 10.1089/jamp.2009.Cor2

To the Editor:

I am somewhat disturbed by the methodology in the recent publication by Rottier et al.⁽¹⁾ discussing the performance of the PARI eFlow Rapid and the PARI LC Plus. For example, they used laser diffraction with the Fraunhofer theory for particle sizing and found the differences between their results and other previously published results “cannot be explained easily.” I would beg to differ. The Fraunhofer theory is very appropriate for opaque particles such as coal dust but not for transparent spheres or droplets. Jolyon Mitchell, in his extensive (as one would expect from Jolyon) and excellent review of laser diffraction particle sizing,⁽²⁾ points out that the correct theory for transparent spheres is the Mie theory. If Rottier and colleagues recalculate their data using the Mie theory, I am fairly certain that they will find similar results for MMD as have been found by others.

The other issue is that the manufacturers of most reusable respiratory equipment have specific cleaning and maintenance instructions, and PARI is no exception. The physiotherapist in our cystic fibrosis (CF) clinic spends much of her time instructing and then reminding patients of the appropriate cleaning instructions for their equipment. No where in the Rottier article is there reference to whether or not the patients were told to follow the manufacturer’s instructions with regard to maintaining the equipment and what efforts were made in their CF clinic to see if such instructions were followed. In other words, suggesting that equipment that may well have been mistreated is not doing what is expected is not a fair scientific claim. In fact, others have drawn quite different conclusions⁽³⁾ with regard to eFlow Rapid. What would have been much more of interest to the clinician would have been the combination of device performance and the degree of bacterial contamination that might have been present when the equipment was maintained as suggested by the manufacturer. Cleaning and disinfection issues has been a problem with the reuse of disposable equipment in CF clinics.⁽⁴⁾

In summary, I do not think that the quality of science in the manuscript by Rottier and colleagues is of the caliber that I would expect in our Journal. Furthermore, it gives a misleading impression of device particles sizes and performance that may be misinterpreted by clinicians.

Author Disclosure Statement

Dr. Allan Coates has received research support from Axentix Pharma, Novartis Pharmaceuticals, PARI, and MAP Pharmaceuticals over the past year.

Dr. Alan L. Coates
Department of Respiratory Medicine
The Hospital for Sick Children
Toronto, Ontario, Canada

References

1. Rottier BL, van Erp CJP, Sluyter TS, Heijerman HGM, Frijlink HW, and de Boer AH: Changes in performance of the pari eFlow[®] rapid and pari LC plus[™] during 6 months use by CF patients. *J Aerosol Med Pulm Drug Deliv*. 2009;22:1–7
2. Mitchell JP, Nagel MW, Nichols S, and Nerbrink O: Laser diffractometry as a technique for rapid assessment of aerosol particle size from inhalers. *J Aerosol Med*. 2006;19:409–433.
3. Bakuridze L, Andrieu V, Dupont C, and Dubus JC: Does repeated disinfection of the e-Flow rapid nebulizer affect in vitro performance? *J Cyst Fibros*. 2007;6:309–10.
4. Rosenfeld M, Emerson J, Astley S, Joy P, Williams-Warren J, Standaert TA, Yim DL, Crist D, Thykkuttatihil M-J, Torrence M, FitzSimmons SC, and Ramsey BW: Home nebulizer use among patients with cystic fibrosis. *J Pediatr*. 1998;132:125–131.

DOI: 10.1089/jamp.2009.Cor3

Authors’ Responses

We would like to thank Mr. Perkins for his comments on the “eFlow study.”⁽¹⁾

He adds references^(2–8) to discuss aspects of this article, which partly give additional data, but do not contradict ours, as our eFlow study is designed to investigate changes in performance after 6 months of daily clinical practice. From that study it is obvious that people use different drugs in the same device (based on questionnaire data), although instructed not to do so. Nor do they clean their devices according to manufacturer’s instructions. As explained in our article, we had to extend the study with a second series of used devices after it became clear that the devices in the first series were not maintained properly. This conclusion was based on checking the nebulizers upon pollution with drug residues. For the second series we put extra emphasis on correct cleaning and handling. Yet, the condition of the returned devices was practically the same as that of the first series. This confirms, as anticipated, that daily use at home is different from testing in a well-controlled environment like a laboratory or a clinic. Furthermore, at the time when the eFlows were used by the patients, the PARI Easy Care system was not yet available. The patients were supplied with an alternative disinfection and cleaning device (Petra) by

Novartis (Basel, Switzerland), but in only rare cases they made the effort of using this device, as we learned from the questionnaire. Moreover, we were informed by PARI (personal communication) that the Easy Care system should be used scarcely, as it also changes the performance of the mesh in the long term. So, although we fully agree with Mr. Perkins that specific cleaning and maintenance instructions are required to be followed, in daily practice compliance with these instructions appears to be very poor, and therefore, the conclusions of our study are still valid.

The results of the studies in references 2–8 are in a study setting in which a higher compliance can be expected (better cleaning, no mixing of drugs). Reference⁽²⁾ does not take the eFlow into account, but the Aerodose 5.5. in comparison with PARI LC Plus. The full article of reference⁽³⁾ was not published at the time of publication of our article; the nebulizer is used for a month only, and the authors do not look for changes in performance regarding particle size. Reference⁽⁴⁾ by Mitchell is a review on laser diffraction analysis and does not relate to specific nebulizers. The Coates⁽⁵⁾ radionuclide deposition study shows data in favor of eFlow to LC Plus but does not include results after use over time. The mentioned poster abstracts were not considered to refer to. Indeed, referral to Bakuridze et al.⁽⁹⁾ would have been informative, although, again, this is a laboratory study with followed cleaning procedures and use of one drug per device.

The author gives the general result (without specific data) of his own study with liposomal amikacin in a laboratory setting with a double cleaning procedure (daily and weekly).⁽¹⁰⁾

In summary, this letter does not contradict the eFlow article, but adds some more perspective to the conclusion in the eFlow article that cleaning procedures of the eFlow are important, and timely replacement of the mesh is mandatory.

We very much appreciate the efforts of Dr. Coates to maintain a high scientific level of the articles in the *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. Dr. Coates disagrees with the methods and conclusions of our study,⁽¹⁾ and he addresses three aspects in particular: the use of the Fraunhofer theory, the difference in mass median diameters (MMDs) for the PARI LC Plus and eFlow between our study and PARI's (as presented in their information leaflet for the eFlow), and a lack of good cleaning instructions for the eFlow. We would like to reply to these issues immediately below and present more technical details in the Appendix after the references.

With regard to the choice between Mie and Fraunhofer, we fully agree with Dr. Coates that Mie is theoretically the better theory as it takes account of all optical effects, including diffraction, absorption, reflection, and refraction. Ignoring the effect of refraction may result in an overestimation of the finest particles, although opposite effects have been reported also.⁽¹¹⁾ However, making a proper choice is not as simple as Dr. Coates presumes. For a correct use of the Mie theory the precise optical parameters (refractive index n and absorption coefficient k) have to be known because a minor change in the complex refractive index ($\text{CRI} = n - i^*k$) may result in a considerable shift of the size distribution. In practice, often the refractive index of water ($n = 1.333$) is used for various drug solutions, but this is likely to yield incorrect values. Considering that the drug concentration increases

during the nebulization process (particularly for a classic jet nebulizer like the LC Plus, which served as reference for the eFlow in our study), CRI is theoretically a variable parameter. Moreover, the absorption coefficient k is frequently not known (although this coefficient mostly approaches zero). Therefore, Fraunhofer may produce more reliable results. Of course we checked this for a number of different experiments before making the decision of which theory to use for the study, as explained and shown for one example in the Appendix. Additionally, we controlled all individual data by looking at the shape of the distribution curve. Whether an overestimation of fines has been calculated with Fraunhofer or not can mostly directly be concluded from deviations at the fine particle side. We also gave an example for that in the Appendix.

The second issue Dr. Coates addresses is our statement that differences between our data and data from PARI cannot be explained easily. He suggests that recalculation with the Mie theory will yield similar results, as have been found by others. As we show in the Appendix, this is not true. For the single measurement given in the Appendix, which we selected as a representative example for the eFlow with TOBI, the MMD (X_{50} -value) obtained with the Fraunhofer computation is $3.6\ \mu\text{m}$, whereas MMD from the Mie calculation is $3.7\ \mu\text{m}$ for the optical model of TOBI ($n = 1.349$; $k = 0$). So, the Mie calculation with the correct optical model gives nearly the same median diameter as the Fraunhofer approximation for the eFlow with TOBI at 30 L/min; the difference is only 0.1 micron.

In our article we referred to the PARI product information leaflet for the eFlow, which presents a mass median aerodynamic diameter (MMAD) of 3.95 microns (for TOBI) measured with the Andersen impactor at 28.3 L/min. PARI presented posters on various conferences in which MMDs (also for TOBI) are mentioned of $3.6\ \mu\text{m}$ ^(12,13) to $3.8\ \mu\text{m}$ ⁽¹⁴⁾ when measured with the Malvern MasterSizer X (without reference to the diffraction theory used). This is the same range as we calculated with Sympatec (using different diffraction models), and this seems to reduce the discussion to the basic differences between cascade impactor and laser diffraction technique. Because a discussion between these two different sizing principles is outside the scope of our reply and involves many aspects to be considered (including the effects of droplet evaporation, as has been investigated by Dr. Coates himself⁽¹⁶⁾), we would like to adhere to our statement that it is difficult to explain differences between results from different studies, particularly when different techniques are used and not all conditions are given.

Although different measuring principles may produce different MMDs, this is not really relevant to our study in which we compare the performance of the eFlow before and after use in daily practice as well as with that of the LC Plus (also before and after use). This is a comparative evaluation, and there are no arguments to believe that the conclusions would have been different when a different sizing technique was used.

Thirdly, Dr. Coates raises the question of cleaning instructions and compliance with them. We apologize if our explanation that "patients were given appropriate instructions on cleaning and were provided with a disinfection device" is not detailed enough. Before the start of our eFlow evaluation study, a representative from the PARI company

gave instructions for use, cleaning, and disinfection of the eFlow to the cystic fibrosis (CF) nurses of the participating CF centers. The CF nurses instructed the patients accordingly, and handed out the compliance survey protocol with the instructions and additional information about the study objectives. Patients received a questionnaire to complete with questions about cleaning and disinfection. They were invited to make notes on their experience with nebulizing, as well as cleaning and maintenance of their eFlow. All patients received a Petra disinfection device (Henrotech, Belgium) with written instructions on how to use this device for their eFlow nebulizer. At the time our eFlow study was started, the PARI Easycare cleaning aid for the aerosol head was not yet available.

From the answers in the questionnaire regarding cleaning and disinfection we learned that partial compliance appears to be the standard. The need for good cleaning is better understood than the need for disinfection. More than 90% of the patients cleaned their eFlow twice daily, but less than 50% used the Petra device with the same frequency. Twenty percent disinfected only once daily, and more than 30% considered a lower frequency sufficient. One patient used the Petra device only at the start of the study, one patient only three times in total (during three cycles of 28 days), and one patient did not use it at all. Reasons given were that the Petra device is inconvenient to travel with, and that disinfection takes too much time. In practice, and in disagreement with the instructions, also different rinsing procedures were used, such as nebulization of demineralized water with the eFlow, rinsing with hot water or a lukewarm soap solution. We expect that particularly the last cleaning and disinfection step at the end of the month using TOBI (as TOBI is usually, but not always, used in an alternate month schedule) may be crucial to the performance of the eFlow. When the device is put at rest for several weeks, clogging of membrane orifices may become irreversible. Additionally, patients used the eFlow, although strongly advised not to do so, for the administration of other drugs used in CF therapy. The list of drug solutions included salbutamol, colistin, Pulmozyme, Mucomyst, Mucomyst plus Atrovent, Bricanyl, and 0.9% saline.

To exclude that poor patient compliance with the cleaning instructions determines the outcome of our study, we asked the same patients to continue to participate in the study with new devices after even more emphasis was put the relevance of good cleaning and maintenance of their devices. Much to our surprise, the difference in performance between used devices in the first and second series was small, as shown and discussed in our article.

Our findings with the eFlow do not exclude successful use of this device for the administration of TOBI and other drug solutions. However, our study confirms that when vulnerable techniques, such as vibrating meshes, are used, a strict compliance with instructions for use and cleaning is needed. Otherwise, clogging of orifices can result. In daily life this may be difficult, as our study clearly demonstrates.

In summary, we have explained the scientific basis for using the Fraunhofer theory in our experiments. Recalculation with the Mie theory does not change our conclusions nor does it explain the differences with the PARI-sponsored studies. Not surprisingly, regimes that are time consuming and difficult to adhere to such as cleaning and disinfection

procedures may result in differences between laboratory experiments, drug studies with intense monitoring, and daily life, for which our study was designed.

Author Disclosure Statement

Both authors equally contributed to discussing the Letter to the Editor and writing the response. Neither of the authors has a conflicting interest in nebulizer equipment. Anne H. de Boer has designed and patented a Dry Powder Inhaler (Twincer), which is not the subject of the Letter.

Bart L. Rottier, M.D.¹ and Anne H. de Boer, Ph.D.²

¹Beatrix Children's Hospital
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

²Department of Pharmaceutical Technology and Biopharmacy
University of Groningen
Groningen, The Netherlands

References

1. Rottier BL, van Erp CJ, Sluyter TS, Heijerman HG, Frijlink HW, Boer AH: Changes in performance of the Pari eFlow rapid and Pari LC Plus during 6 months use by CF patients. *J Aerosol Med Pulm Drug Deliv.* 2009;22:263–269.
2. Geller DE, Margaret Rosenfeld, David A. Waltz, Robert W. Wilmott, and the AeroDose TOBI Study Group: Efficiency of pulmonary administration of tobramycin solution for inhalation in cystic fibrosis using an improved drug delivery system. *Chest.* 2003;123:28–36.
3. Hubert D, et al.: Pharmacokinetic comparison of inhaled tobramycin (TOBI) via PARI eFlow[®] rapid or PARI LC[®] Plus nebulizers in cystic fibrosis patients. Poster presentation at the ECFC conference in Belek, 2007. [Abstract in *J Cyst Fibrosis.* 6(Suppl. 1):S12. The full paper: Pharmacokinetics and safety of tobramycin administered by the PARI eFlow[®] rapid nebulizer in cystic fibrosis has recently been published in *J Cyst Fibrosis.* 2009;6:332–337.]
4. Mitchell JP, Nagel MW, Nichols S, and Nerbrink O: Laser diffractometry as a technique for rapid assessment of aerosol particle size from inhalers. *J Aerosol Med.* 2006;19:409–433.
5. Coates AL, Green M, Leung K, Louca E, Tservistas M, Chan J, Ribeiro N, Charron M: The challenges of quantitative measurement of lung deposition using ⁹⁹Tc-DTPA from delivery systems with very different delivery times. *J Aerosol Med* 2007;20:320–329.
6. Coates AL, Green M, Leung K, Chan J, Ribeiro N, Louca E, Ratjen F, Charron M, Tservistas M, and Keller M: Rapid pulmonary delivery of inhaled tobramycin for pseudomonas infection in cystic fibrosis. *Pediatr Pulmonol.* 2008;43:753–759.
7. Fischer R, et al.: Inhalation with the PARI eFlow rapid reduces treatment time burden significantly in adult CF patients without altering lung function. Poster presentation at the ECFC conference in Belek, 2008. [Abstract in *J Cyst Fibrosis.* 6(Suppl 1):S41.]
8. Militz S, et al.: E-Flow rapid: improved lung function and patient satisfaction with more volume delivered to the lungs during inhalation therapy in cystic fibrosis. Poster presented at the ECFC conference in Prague, 2008. [Abstract in *J Cyst Fibrosis.* 7(Suppl. 2):S67.]

9. Bakuridze L, Andrieu V, Dupond C, and Dubus JC: Does repeated disinfection of the e-Flow rapid[®] nebulizer affect in vitro performance? *J Cystic Fibrosis*. 2007;6:309–310.
10. Perkins WR, et al.: Aerosolization of liposomal amikacin (Arikace[™]) using different nebulizers: selection of the eFlow[®] nebulizer. Poster presented at the NACF conference in Anaheim, 2007. [Abstract in *Pediatric Pulmonology*, 2007;42(Suppl. 30):356.]
11. Müller RH, and Schuhmann R: *Teilchengrössenmessung in der Laborpraxis*. Wissenschaftliche Verlagsgesellschaft, Stuttgart; pp. 65–70, 1996.
12. Stangl R, Waldner R, Seemann S, and Knoch M: In-vitro characterization of the eFlow[™] electronic inhaler. *Poster 194, 14th Congress of the International Society for Aerosols in Medicine*, Baltimore; 2003.
13. Keller M, Balcke A, Tservistas M, Bucholski A, Stempfle P, Stangl R, and Knoch M: Reduced treatment time for tobramycin application by device and formulation customization. *Poster 329, 17th Annual North American Cystic Fibrosis Conference*, Anaheim; 2003.
14. Friedrichs F, Keller M, Döhmen H, Pfannenstiel C, and Ledermüller R: Comparison of tobramycin serum plasma levels in 5 CF patients after inhalation via a PARI LC Plus[®] nebuliser and via a eFlow[®], a novel electronic inhaler. *Poster P245, 27th European Cystic Fibrosis Conference*, Birmingham; 2004.
15. Kwong WT, Ho SL, and Coates AL: Comparison of nebulized particle size distribution with Malvern laser diffraction analyzer versus Andersen cascade impactor and low-flow Marple personal cascade impactor. *J Aerosol Med*. 2000;13: 303–314.

Appendix

As a standard routine for laser diffraction characterization of wet aerosols, we do preliminary investigations to optimize the measuring conditions. We measure the size distribution from the aerosol generation device(s) for water and the drug solution(s) under the same conditions as applied for the study, including the suction flow rate(s) and relative humidity value(s) of the air. We compute the size distribution(s) with the Fraunhofer theory and also with the Mie theory, using the optical models for water (refractive index: n is 1.333; absorption coefficient: $k = 1.5 \times 10^{-8} \approx 0$) and for the drug solution (refractive index measured with a refractometer RL, Varimex, Poland). The laser diffraction apparatus used for our studies is either the Sympatec Compact KA, the HELOS BF/MAGIC, or the HELOS BF-OM; all devices are operated with the latest WINDOX software versions. The Sympatec software offers the possibility to do Fraunhofer calculations in the LD or HLD mode. We make use of the LD mode because the HLD mode involves more smoothing of the computed distribution curves. Aerosols are measured with a 100-mm lens and start and stop of the measurement is triggered on a threshold value for the optical signal of 0.2% on the channel receiving the highest signal, which in practice for aerosols is mostly channel 30. Triggering on the optical signal on one of the channels for fine particles (instead of triggering on the optical concentration, which is a measure for the extinction and which is much less sensitive) prevents the fact that we miss part of the aerosol at the start of nebulization. If there is any doubt about missing larger droplets that are re-

leased by the aerosol generation device first before the finer aerosol particles are produced, we perform a timesliced measurement to check this. To control the suction flow rate through the aerosol generation device, we use an INHALER 2000 adapter (Sympatec) or one of our home-constructed prototype adapters for this interface accessory. We tilt the adapter to make a perfect alignment between the adapter body and the angled mouthpiece of the nebulizer and to keep the nebulizer cup in a perfectly horizontal position. We use a short front cylinder for this adapter to assure that the distance between the exit of the mouthpiece and the laser beam is within the range from 1.5 to 2 mm, which prevents droplets from evaporating and that particles pass the laser beam outside the measuring volume for the 100-mm lens. Also, as a standard routine we check droplet evaporation at the same conditions for the relative air humidity and suction flow rate by using a longer front cylinder, which increases the distance between the mouthpiece end and the laser beam. We also test different amounts of counterflow, and if necessary additional sheath flow, through the adapter to keep the windows free from adhering particles. From these checks we make a choice for the diffraction theory and the other settings and conditions to be used for the study itself. We normally do not present all these details of the testing program in our article, but confine ourselves to the final settings and conditions.

Whether Fraunhofer or Mie is the better theory does not only depend on the type of particle dispersion to be measured. Differences between both theories include differences in the algorithms and smoothing techniques used to produce a size distribution curve from the complex diffraction pattern. Generally, Fraunhofer gives a good result for solid (nontransparent) particles in air, but this may be different when these particles are suspended in a liquid. The opaque nature of crystals is frequently a property of the crystal surface (cracks and lattice discontinuities), and such particles can become very transparent after filling these pores with liquid. It then depends on the difference in refractive index between the suspension liquid and the solid material whether Mie or Fraunhofer is the better theory. The errors obtained with the Fraunhofer approximation depend on the particle size distribution (psd) and also the optical concentration in the aerosol. There may be a great difference between pure water and a drug solution. As an example, we would like to show the psd of the aerosol from the Boehringer Respimat (with water) at a suction flow rate of 60 L/min (Fig. 1). The optical concentration in the cloud from this device at this flow rate is around 11% and the median diameters are 4.83 μm when computed with Fraunhofer and 5.04 μm obtained with the Mie theory (optical model for water: $n = 1.333$). Despite the relative small difference in MMD (X_{50} -value), there is a considerable difference in the fine particle fractions. This is due to neglecting the effect of refraction (with Fraunhofer), which for these conditions appears to be rather extreme.

For the TOBI study with the PARI LC Plus and the eFlow, we performed all the checks described in this Appendix. We found that the differences between Fraunhofer and Mie computation are very small, particularly when the optical model for a tobramycin solution is used. For a typical example of the eFlow, the cumulative volume distribution curves are shown in Figure 2 in comparison with the Andersen impactor

FIG. 1. Cumulative volume distribution curves as a function of the particle diameter for the Boehringer Respimat (with water) computed with two different diffraction theories.

FIG. 2. Cumulative volume distribution curves as function of the particle diameter for TOBI from the eFlow, computed with Fraunhofer and Mie for two different optical models (CRI 1.333 is for water and CRI 1.349 is for TOBI).

data (at 28.3 L/min) presented by PARI in their information leaflet for the eFlow.

The difference in effect between Figures 1 and 2 may be the result of differences in the optical concentration (20% for TOBI from the eFlow vs. 11% for water from the Respimat at 30 L/min), the optical properties of the solution (tobramycin solution plus additives vs. pure water) and the size distribution (X_{50} is 3.6 μm for TOBI from the eFlow vs. 4.8 μm for water from the Respimat, both from the Fraunhofer approximation). We experienced from extensive characterization with the laser diffraction technique of fine aerosols generated with Rayleigh breakup, that minor shifts in the optical concentration and psd may have a great effect on the difference obtained between the Fraunhofer and Mie computation (for water and 0.9% saline).

Figure 2 shows that the distribution curves for Fraunhofer and Mie with the optical model for a tobramycin solution are almost the same (X_{50} is 3.6 and 3.7 μm , respectively), and for that reason it was decided to use the Fraunhofer theory for the eFlow evaluation study.

The difference between the distribution curves from the (Andersen) cascade impactor and the laser diffraction apparatus (Fig. 2) can have different explanations, which for this application we did not study. The optical concentrations reached a value that seems to exclude an effect of obscuration (double refraction). The argument of measuring different diameters with both techniques (geometric vs. aero-

dynamic) is irrelevant because aerosol droplets of aqueous drug solutions are spherical and approach unit density. Laser diffraction technique assumes sphericity for the particles measured, and therefore, deviations as can be expected for solid particles are excluded also. The algorithms used in the laser diffraction technique may give rise to deviations from the real particle size distribution; however, because there is a tendency to twist skewed particle size distributions into log-normal ones (although the "real" particle size distribution does not exist, because each size distribution is inherent in the principle used for measurement). Size distributions from cascade impactors may be influenced by various effects also. For wet aerosols such effects are particularly droplet evaporation and coalescence. Droplets do not only travel a long distance between the mouthpiece of the aerosol generator and the final stages of the impactor, they also have to follow a tortuous pathway. Considering the high particle concentration in the aerosol from the eFlow it seems inevitable that some particles collide and merge together. Furthermore, considering the inaccuracies and uncertainties involved in cascade impactor analysis, one must be dissuaded to consider this technique as a perfect reference for laser diffraction measurement. The fact that the Mie curves in Figure 2 approach the distribution curve obtained with the Andersen cascade impactor more than the Fraunhofer curve is therefore not an argument for the selection of the diffraction theory.