IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Horst OLSCHEWSKI et al.

Title: TREPROSTINIL ADMINISTRATION BY INHALATION

Appl. No.: 12/591,200

Filing Date: 11/12/2009

Examiner: Sara Elizabeth Townsley

Art Unit: 1629

Confirmation Number: 4093

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. EDMUND J. ELDER, JR.

I, Dr. Edmund J. Elder, Jr., hereby declare:

1. I hold a Ph.D. in Pharmaceutical Sciences and a B.S. in Pharmacy from the Medical University of South Carolina. I currently serve as the Director of Zeeh Pharmaceutical Experiment Station and a lecturer in both the School of Pharmacy and the School of Medicine and Public Health at the University of Wisconsin-Madison. *See* EXHIBIT 1.
2. My work focuses on drug development, including formulation and physiochemical characterization of compounds. My CV, which is attached as EXHIBIT 1, lists my publications.
3. I am a paid consultant for United Therapeutics, the assignee of the above-identified patent application, in connection with this matter. My compensation is in no way dependent on the content of my opinions or the disposition of this application.

4. To the best of my knowledge, I have not received any prior research funding or other compensation from United Therapeutics.

I. The Cited References

5. I am familiar with the Office Action dated October 10, 2014 in U.S. Patent Application No. 12/591,200, as well as the disclosure and claims of the subject application. I am also familiar with the references cited in the Office Action and the response filed November 9, 2015.

6. I understand the claims of U.S. Patent Application No. 12/591,200 are directed to a method of treating pulmonary hypertension comprising: administering by inhalation to a human in need thereof a therapeutically effective single event dose of an inhalable formulation with a pulsed ultrasonic nebulizer, wherein said therapeutically effective single event dose comprises from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof, said therapeutically effective single event dose is inhaled in 18 or less breaths by the human.

7. I have reviewed US 2004/0265238 (Chaudry) and U.S. Patent No. 6,357,671 (Cewers) cited in the Office Action, in addition to further references pertinent in the art – specifically those references mentioned below and attached as EXHIBITS 2-6.

II. Single Event Dose

8. At the time the '200 application was filed, the "single event dose" featured in the pending claims is recognized as depending on two parameters: (1) the concentration of the treprostinil inhalation formulation prior to aerosolization; and (2) the total amount (weight or volume) of the formulation delivered through the single inhalation event ("delivered weight" or "delivered volume"). *See, e.g.*, "Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation" (Exhibit 2) on page 38, stating that:

> The medication dose delivered to the patient should be expressed by a statement in this section, such as: Each spray delivers 'x' mcg of drug

substance in 'w' mg of suspension or solution equivalent to 'y' mcg of drug substance base (if applicable) from the nasal actuator or mouthpiece. The term approximately should not be used to modify the medication dose delivered.

9. According to the Office Action, the guidance allegedly provided by Chaudry regarding single event dose is found in prophetic example 4, reproduced below in its entirety:

> Example 4
> [0097]
> 5 Treprostinil sodium 0.1-10.0 mg/ml Sodium Chloride 2.0-10.0 mg/ml Sodium Hydroxide q.s. Citric Acid q.s. Water q.s.
> [0098] Example 4 is a prophetic example of a formulation comprising the vasodilator epoprostenol [sic: treprostinil]. Sodium chloride may be added to the solution to adjust tonicity, and sodium hydroxide and citric acid are added to adjust the pH of the solution. The solution of Example 4 may be made by methods known to those of ordinary skill in the art.

10. This prophetic example gives a range of treprostinil concentration that varies 100-fold with the lowest concentration set at 0.1 mg/mL, *i.e.* 100 µg/mL, and increasing to 10 mg/mL. Such a wide dosing range is consistent with the prophetic nature of the example, and does little to provide guidance to one of skill in the art if attempting to determine a "single event dose" for the treprostinil formulation in Example 4.

11. With respect to the total amount (weight or volume) of the formulation delivered through the single event ("delivered weight" or "delivered volume"), the "delivered volume" of an inhalable formulation delivered through a single inhalation event by a nebulizer system is recognized as depending on a number of factors. Those factors include the initial volume of the formulation, *i.e.*, the "fill volume," and the residual volume of the formulation that cannot be further delivered through the nebulizer, *i.e.*, the "dead volume" (or "residual volume"). *See, e.g.* "European Respiratory Society Guidelines on the use of nebulizers: Guidelines prepared by a European Respiratory Society Task Force on the use of nebulizers" (Exhibit 3) in the paragraph bridging pages 230-231, stating that:

> Important factors influencing the total dose delivered to a patient's airways include the initial volume fill, the efficiency by which nebulized aerosol is made available for patient inhalation, and the amount of residual or "dead"

> volume left in the nebulizer on cessation of operation. . . Nebulization therapy usually continues until the volume left in the nebulizer is so low that the nebulizer ceases to function continuously and begins to "sputter". This volume is typically ~1 mL, but may be as low as 0.5 mL or as high as 1.5 mL. The amount left is very high compared to a typical volume fill (e.g. 2.5 mL).

12. Accordingly, the "delivered volume" corresponds to the difference between the "dead volume" and the "fill volume". In other words, both the "dead volume" and the "fill volume" are needed to assess the volume of the formulation delivered through a single event inhalation.

13. Turning to Chaudry's specification, paragraph [0001]-[0059] and paragraphs [0067]-[0099] of Chaudry do not describe "dead volume" or "fill volume."

14. Chaudry's paragraph [0060] describes "fill volume" in the form of a laundry list containing alternative ranges or values ("In another alternative embodiment, the system of the present invention comprises one or more dispensing containers prefilled with about 0.1 to about 5.0 ml, or about 0.5 ml to about 5.0 ml, or about 1.0 ml to about 5.0 ml; or about 0.1 ml to about 3.0 ml, or about 0.1 ml to about 2.0 ml, or about 0.5 ml to about 2.0 ml, or about 1 ml, or about 1.5 ml, or about 2.0 ml, or about 2.5 ml, or about 3.0 ml, or about 3.5 ml, or about 4.0 ml, or about 4.5 ml, or about 5.0 ml, or about 0.1 ml to about 2.25 ml, or about 1.0 ml to about 2.0 ml, or about 2.0 ml to about 2.4 ml of a premixed, premeasured, aqueous inhalation solution comprising a single unit dose of a therapeutically effective amount of one or more pulmonary hypertension reducing agents"). Nothing in Chaudry's paragraph [0060] describes the corresponding "dead volume" of any of the alternative ranges or values of the "fill volume."

15. Chaudry's paragraph [0062] also describes "fill volume" in the form of a laundry list containing alternative ranges or values ("In one alternative embodiment, the volume of the one or more pulmonary hypertension reducing agents inhalation solutions of the present invention is about 0.1 ml to about 2.25 ml, or about 0.1 ml to about 2 ml, or about 1 ml to about 2 ml, or about 1.5 ml to about 2 ml, preferably about 1 ml, about 1.5 ml, about 2.0 ml, or about 2.25 ml"). Nothing in Chaudry's paragraph [0062] describes the

corresponding "dead volume" of any of the alternative ranges or values of the "fill volume."

16. Chaudry's paragraph [0066] describes "fill volume" in the form of a broad hypothetical range (emphasis supplied): ". . . It is believed that administering about 0.1 ml to about 2.0 ml fill volume of an inhalation solution into a nebulizer, for example, will optimize the therapeutic effect of the individual's deep inspiration efforts during treatment, and will optimize the therapeutic effect of the individual's breath-holding efforts as well." Nothing in Chaudry's paragraph [0066] describes the corresponding "dead volume" of the broad hypothetical range of "fill volume."

17. Chaudry's paragraph [0065] describes "dead volume" also in the form of a laundry list of alternative ranges (emphasis supplied): ". . . Less solution remaining in the nebulizer system means more medication (e.g., one or more pulmonary hypertension reducing agents) administered to the individual during each treatment. In one alternative embodiment, the amount of solution remaining in the nebulizer system after each treatment **may be** less than 0.50 ml, or less than 0.30 ml, or less than 0.20 ml or less than 0.10 ml or less than 0.05 ml of the one or more pulmonary hypertension reducing agents inhalation solutions of the present invention, e.g. an inhalation solution comprising 2.5 mg albuterol and 0.5 mg ipratropium bromide." Nothing in Chaudry's paragraph [0065] describes the corresponding "fill volume" of any of the alternative hypothetical ranges of the "dead volume." Chaudry's description of the "fill volume" in paragraphs [0060], [0062], and [0066], and Chaudry's description of the "dead volume" in paragraph [0065], are insufficient to allow reasonable assessment of the "delivered volume" of the formulation in a single event inhalation, especially in light of the many alternative ranges provided in those disconnected paragraphs. Indeed, the combination of certain values selected from the "fill volume" and "dead volume" paragraphs results in a negative volume, which would be undeliverable.

18. Paragraph [0064] of Chaudry specifically describes both "dead volume" and "fill volume" of the nebulizing device:

> For example, when nebulizing an inhalation solution comprising 2.5 ml or more, about 0.7 ml of the solution remains in the nebulizer system after treatment, though the amount may vary depending on the model of the nebulizer used. In these instances, the individual is not receiving the prescribed dosage or optimum dosage of inhalation medication.

19. Chaudry's paragraph [0064] describes a problem of nebulizing devices in general – insufficient delivery of formulation per inhalation event because of the dead volume. Moreover, one of ordinary skill in the art would understand from paragraph [0064] that a delivery volume of 1.8 mL (2.5 mL fill volume – 0.7 mL dead volume) would lead to the individual "not receiving the prescribed dosage or optimum dosage of inhalation medication," including its exemplary formulations (*e.g.*, prophetic example 4) containing at least 0.1 mg/mL, *i.e.* 100 μg/mL, of treprostinil.

20. The insufficiency or inadequacy of 1.8 mL delivery volume is reconfirmed by Chaudry toward the end of paragraph [0064], stating that (emphasis supplied):

> For example, in one day, due to the residual medication remaining in the nebulizer system after each treatment, an individual fails to receive approximately 2.1 ml, or more of the prescribed daily amount of medication.

21. Chaudry purportedly solves the problem by adjusting filling volume to reduce the dead volume with the ultimate effect of delivering more drug than conventional nebulizers, stating in paragraph [0065] that (emphasis supplied):

> It is believed that the fill volumes of the one or more pulmonary hypertension reducing agents inhalation solutions of the present invention will result in lesser amounts of solution remaining in the nebulizer system after treatment, when compared to conventional inhalation solutions (e.g. 2.5 ml or 3 ml fill volume). Less solution remaining in the nebulizer system means more medication (e.g., one or more pulmonary hypertension reducing agents) administered to the individual during each treatment.

22. Taken together, Chaudry specifically teaches the amount of medication delivered per nebulizing event as being greater than a conventional nebulizer, *e.g.* at least greater than the 1.8 mL delivery volume described in paragraph [0064]. With the lower limit of treprostinil concentration in Chaudry being 100 μg/mL, the single event dose in Chaudry

would be at least 180 μg of treprostinil, which is at least two times the upper limit of the single event dose featured in the pending claims, "from 15 μg to 90 μg" in claim 18.

III. "18 or less breaths"

23. The "18 or less breaths" featured in the pending claims corresponds to an inhalation time of at least less than a few minutes. *See, e.g.* "Ganong's Review of Medical Physiology – 23rd Ed" (Exhibit 4) on page 600, describing 30 breaths per minute as "rapid shallow breathing" and 10 breaths per minute as "slow deep breathing."

TABLE 35–3 Effect of variations in respiratory rate and depth on alveolar ventilation.

Respiratory rate	30/min	10/min
Tidal volume	200 mL	600 mL
Minute volume	6 L	6 L
Alveolar ventilation	(200 – 150) × 30 = 1500 mL	(600 – 150) × 10 = 4500 mL

that is, the amount of air reaching the alveoli per minute, is less than the respiratory minute volume. Note in addition that because of the dead space, rapid shallow breathing produces much less alveolar ventilation than slow deep breathing at the same respiratory minute volume (Table 35–3).

24. Turning to Chaudry's specification, paragraphs [0001]-[0062] and paragraphs [0068]-[0099] of Chaudry do not describe the duration of a single inhalation event.

25. According to the outstanding Office Action, the guidance allegedly provided by Chaudry regarding the single event inhalation time is found in paragraph [0063], stating that:

> In one alternative embodiment, the above fill volumes of the present invention may reduce the time of each nebulization treatment by at least 20%, 30%, 40%, 50%, 60%, 70% or 80% or more over conventional nebulizer treatments (e.g. 2.5 ml or 3 ml fill volume). In another alternative embodiment, the fill volumes of the present invention may reduce each nebulization treatment to about 12, 10, 9, 8, 6, 5, 4, 3 minutes, or less over conventional nebulizer treatments (e.g. 2.5 ml or 3.0

ml fill volume). Reducing the amount of time to complete the treatment means individuals will be more likely to comply with the prescribed dosing regimen and achieve optimal benefit from the medication prescribed.

26. The first sentence of Chaudry's paragraph [0063] describes percentage reduction of inhalation time compared to that of a conventional nebulization treatment. Without knowing the value of the duration of conventional inhalation time or which of the various concentrations, fill volumes, dead volumes are to be used, one of ordinary skill in the art would not be able to assess the actual reduced inhalation time described in the first sentence of paragraph [0063]. Chaudry, thus, offers a possible outcome – reduction of inhalation time – without guidance on which variables need to be adjusted to achieve the result. Instead, Chaudry provides a variety of possible permutations and combinations of variables, leaving one of ordinary skill in the art with no starting point from which to determine how to achieve a specific outcome.

27. In my opinion, the second sentence of Chaudry's paragraph [0063] refers to the following two alternative embodiments: (1) reduce each nebulization treatment to "about 12, 10, 9, 8, 6, 5, 4, 3 minutes", or (2) reduce each nebulization treatment to "less over conventional nebulizer treatments." This interpretation is consistent with the rest of Chaudry's disclosure of regarding treatment time. *See, e.g.*, Chaudry's paragraph [0067], stating that:

> . . . The individual continues breathing into the mouthpiece or facemask until the nebulization treatment is finished. This may take about 12, 11, 10, 9, 8, 7, 6, 5, 4 or 3 minutes. In an alternative embodiment, the nebulization treatment is finished when at least substantially all the mist is removed from the nebulizer chamber. This may take about 12, 11, 10, 9, 8, 7, 6, 5, 4, or 3 minutes. . .

28. The Office appears to interpret the "or less" in Chaudry's paragraph [0063] as a continuation of "3 minutes", *i.e.*, referring to "less than 3 minutes" of nebulizing treatment time. Under this interpretation, however, the "12, 10, 9, 8, 6, 5, 4, 3 minutes, or less" would then refer not to the inhalation time itself, but to a comparative value reflecting the difference between Chaudry's inhalation time and the conventional inhalation time. In other words, the second sentence of paragraph [0063] would be interpreted as describing the alternative embodiment in which the fill volumes of the

present invention may reduce each nebulization treatment to about 'x' minutes **over** conventional nebulizer treatments. Without knowing the value of the duration of conventional inhalation time, one of ordinary skill in the art would not be able to assess what the reduced inhalation time is under the Office's interpretation of "or less" in Chaudry's paragraph [0063].

29. In addition, paragraph [0063] of Chaudry at best provides: (1) a description of reduced inhalation time that is general in nature (further generic/non-helpful prophetic teachings), and (2) the purported benefit for the reduced inhalation time is to improve patient compliance as a general result of requiring less time for each inhalation event.

30. Of course, a clinician in practice would only consider adopting a reduced single event inhalation time if the reduced inhalation time does not lead to significant side effects. In other words, a clinician in practice would not adopt the reduced inhalation time taught in Chaudry to improve patient compliance if the reduced inhalation time of a specific active agent would likely lead to adverse side effects.

31. This desire to avoid adverse events is important in the context of Chaudry. As stated on page 17 of the Gessler reference (Exhibit 5):

> "the inhalation time for delivery of an equivalent iloprost dose at the mouthpiece (2.8 μg) was reduced from 12 min with the jet nebulizer system to 2 min with the ultrasonic nebulizer, when retaining the same concentration of the iloprost solution (10 $\mu g \cdot mL^{-1}$). In preliminary catherer investigations, however, some increase in systemic side effects was observed when administering the total iloprost dose of 2.8 μg via the inhalation route for such a short time period."

32. Likewise, page 54 of the Voswinckel reference (Exhibit 6) also states that:

"A dose of more than 5 µg iloprost per inhalation or a reduction of inhalation time to less than 3 min induces in most patients considerable systemic prostanoid side effects like hypotension, dizziness, headache, jaw pain, nausea or [diarrhea]."

33. Thus, in my opinion, a clinician in practice would be aware of the "considerable" systemic side effects of at least one of the specifically disclosed vasodilators (iloprost) if inhaled too quickly, *e.g.* "2 min" described in Gessler or "less than 3 min" described in Voswinckel. Moreover, "iloprost" is listed side-by-side with "treprostinil" under the specifically recognized class of "prostacyclin analogs." *See* Chaudry's paragraph [0026], stating that:

. . .Vasodilators for use herein also include prostaglandins (Eicosanoids), including prostacyclin (Epoprostenol) and prostacyclin analogs, including Iloprost and Treprostinil, and prodrugs, salts and isomers thereof. . .

34. As such, a clinician in practice would not consider Chaudry's description of its single event inhalation time in paragraph [0063] as teaching toward "less than 3 minutes," at least not when the inhalable formulation contains iloprost or treprostinil. The specific teachings of Gessler and Voswinckel would cause a clinician in practice to avoid the shorter inhalation times allegedly disclosed by Chaudry assuming the correctness of the Office's interpretation of Chaudry.

35. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that making of willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title

18 of the United States Code and that such willful statements may jeopardize the validity of the applications or any patent issuing thereon.

Signed this 29th day of January, 2016.

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EDUCATION:

Medical University of South Carolina, Charleston, SC
Ph. D., Pharmaceutical Sciences; November 1989
Dissertation: Development of a Dry Coating Method for Formulating Sustained-Release Products
B.S., Pharmacy; May 1985

Clemson University, Clemson, SC
Pre-Professional Studies, Pre-Pharmacy; 1980-1982

EMPLOYMENT:

University of Wisconsin-Madison
School of Pharmacy
Director, Zeeh Pharmaceutical Experiment Station, July 2007 – present
Affiliate, Division of Pharmaceutical Sciences, February 2014 – present
Associate Director, Zeeh Pharmaceutical Experiment Station, April 2006 – June 2007
School of Medicine and Public Health
Senior Lecturer, Master of Science in Biotechnology Program, September 2013 – present

Current Responsibilities
- Key leadership position for providing laboratory services to UW and non-UW clients, including analytical, physical/chemical characterization (pre-formulation), and early-stage formulation services
- Provide pharmaceutics expertise and chemistry, manufacturing and controls (CMC) knowledge to support pharmaceutical and biopharmaceutical development collaborations on and off campus
- Advise and mentor Station staff
- Apply project management and business development experience to enhance Station operational effectiveness
- Share knowledge and expertise through Station participation in and sponsorship of educational programs addressing the process and science of drug development in collaboration with UW-Madison, School of Pharmacy, Extension Services in Pharmacy (continuing education division)
- Graduate Course Lectures
  - Introduction to Pharmaceutical Sciences – course introduction & formulation lectures
  - Biotechnology Operations – course co-coordinator, lectures on various aspects of biotech R&D

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Global Pharmaceutical Development Director / Applications Development Leader, April 2004 – April 2006
Pharmaceutical Technologies Group
Pharmaceutics Director / Technical Leader, August 2000 – April 2004

Prior Responsibilities
- Co-leader (with commercial leader), new business development: BioAqueous℠ Solubilization Services
- Oversight of multi-departmental technical activities for development of a drug delivery service offering including interfacial sciences, engineering, analytical, toxicology, intellectual capital management, licensing, manufacturing, project management, technical service and QA/regulatory
- Lead external technology development collaborations and alliances including a multi-year university research program
- Represent technical program during client interactions for commercial development activities
- Provide pharmaceutics expertise for various emerging corporate growth opportunities
- Serve as a mentor for potential future leadership staff through formal corporate program

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Pharmaceutical Sciences
Sr. Group Leader, Formulation and Process Development, November 1997 – August 2000
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Process Science and Technology
Research Leader, Liquids Process Development, September 1995 – February 1997
Research Leader, Pharmaceutical Technology Development, July 1994 – August 1995
Research Investigator, May 1992 – June 1994
Senior Scientist, September 1989 – April 1992

Previous Experience

- Management: Group of ten formulation and process development scientists, covering all dosage forms, mentoring of new CMC team leaders, department management team and division leadership committees
- Project Management: Chemistry manufacturing & controls (CMC) matrix team leader
  - Responsible for oversight of all cross-functional CMC activities for multiple development programs
  - Represented CMC interests on international product development teams
  - Lead technology transfer and manufacturing site new product implementation teams.
  - Key R&D contact for FDA pre-approval inspections of domestic and foreign contract manufacturing sites.
- Formulation and process development, optimization and scale-up using statistical experimental design
- Primary interface with external development and manufacturing sites for new dosage form technologies including: soft gelatin capsules, effervescent products, and sterile products blow-fill-seal technology

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Pharmaceutical Research and Development Laboratory
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Family Pharmaceuticals of America, Inc., Mt. Pleasant, SC
Mail-service and retail pharmacy, acquired by Medi-Mail, Inc. in 1994, subsequently acquired by Bergen Brunswig Corporation, now AmerisourceBergen Corporation
Minor Partner, subchapter-S corporation, January 1987 – June 1994
Part-time Pharmacist, June 1985 – August 1989
Pharmacy Intern, May 1983 – June 1985

PROFESSIONAL ACHIEVEMENTS:

68 Scientific Presentations (17 invited)

8 Publications and 3 book chapters

182 Short Course presentations (all invited), additional 17 presented at pharmaceutical companies

The Visiting Scientist Program for Schools of Pharmacy and Pharmaceutical Scientists
- Presented lectures/seminars at 14 schools/colleges of Pharmacy, 1993 – 2005

Guest Lecturer
- University of Wisconsin–Madison, Department of Pharmaceutical Sciences, 2006 – 2013
- South Carolina College of Pharmacy, MUSC Campus, 2007
- Medical University of South Carolina, Department of Pharmaceutical Sciences, 1991 – 1999
- University of Texas at Austin, College of Pharmacy, 2001 – 2006
- Michigan State University, ISPE Student Chapter, 2004
- Virginia Commonwealth University/Medical College of Virginia, School of Pharmacy, 1997

Grant Review Panels
National Institutes of Health, National Institute on Drug Abuse, Special Emphasis Review Panel for Abuse-Resistant and Abuse-Deterrent Drug and Devices, 2014
University of Minnesota, Center for Nanostructure Applications, 2007, 2008
National Science Foundation, Office of Industrial Innovation, Small Business Innovation Research/Technology Transfer, SBIR/STTR Phase I, Food Safety, Drug, and Nutraceutical Manufacturing Panel, 2006

UNITED THERAPEUTICS, EX. 2006
WATSON LABORATORIES V. UNITED THERAPEUTICS, IPR2017-01621
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LICENSURE:

South Carolina Pharmacist License, 1985 – present
Wisconsin Pharmacist License, 2010 – present

PROFESSIONAL MEMBERSHIP/ACTIVITIES/AWARDS

United States Pharmacopeia (USP)
2015-2020 and 2010-2015 Compounding Expert Committee
Award for Outstanding Contribution to the USP Standards-setting Process (committee), 2013
American Association of Pharmaceutical Scientists (AAPS), 1990–present (student member 1987–1989)
Annual Meeting paper screener 1994 – 2000, 2006 – 2009, 2011, 2013, 2015
Co-Chair 2004 Annual Meeting Short Course, Particle Engineering Technologies: Theory and Practice
Moderator (PT Podium Session: *Pharmaceutical Processing and Scale-up*), Tenth Annual Meeting and Exposition, Miami Beach, FL, 1995
Planning Committee and Moderator (PT Section), 1995 Southeast Regional Meeting, RTP, NC
AAPS **Appreciation Award** – Co-Chair, 1994 Southeast Regional Meeting, Durham, NC
European Federation for Pharmaceutical Sciences (EUFEPS), member 2003 – present
Sigma Xi, The Scientific Research Society, member 1988 – present
Editorial Advisory Board
Drug Development and Industrial Pharmacy, 2006 – present
Journal Article Reviewer
AAPS PharmSciTech, 2015
Biopharmaceutics & Drug Disposition, 2012
Drug Development and Industrial Pharmacy, 2000 – present
Drugs in R&D, 2012, 2013
European Journal of Pharmaceutics and Biopharmaceutics, 2007, 2010, 2011
International Journal of Pharmaceutics, 2007, 2009 – present
Journal of Biomedical Nanotechnology, 2006 (Special Issue: Nanotechnology in Advanced Drug Delivery)
Journal of Drug Delivery Science & Technology, 2008
Journal of Pharmacy & Pharmacology, 2009, 2011
Pharmaceutical Research, 2008
University of Wisconsin–Madison, Pharmacy Professional Development, Industry Courses
Applied Drug Development I (CMC introduction) Short Course, 2008-2010, On-line Short Course, 2015
Applied Drug Development II (pre-formulation) Short Course, 2007-present
Applied Drug Development III (formulation) Short Course, 2008-present
CMC Project Team Leader Short Course, 2010-present
Land O'Lakes June R&D Conference, planning committee 2008-present, chair 2013
Extension Services in Pharmacy **Appreciation Award** – Chair, 2013 June Land O'Lakes
Nanoparticles Short Course, 2007-2008
Medical University of South Carolina (MUSC)
Life Member, MUSC Alumni Association
The Rho Chi Society (Pharmacy Honorary), College of Pharmacy, 1987
Roche Pharmacy Communications Award, College of Pharmacy, 1985
McKesson Presidential Award, College of Pharmacy, 1985
ISPE **Award for Outstanding Service** to the Technology Transfer Task Team, November 2003 (book contributions)
The Dow Chemical Company, **Special Recognition Award**, December 2002 (creation and launch of BioAqueous℠ Solubilization Services)
Boy Scouts of America
Troop 628 Madison, WI
Advancement Coordinator, 2012 – Present
Troop Committee Secretary, 2010 – 2012
Cubmaster, Pack 628 Madison, WI, 2008 – 2010
Eagle Scout, Troop 1429 Charleroi, PA, July 26, 1976
Life Member, National Eagle Scout Association
Glacier's Edge Council, Madison/Janesville, WI
Mohawk District Committee
Advancement Chair, 2014 - Present

PUBLICATIONS

W Schwan, J Kolesar, MS Kabir, **E Elder**, J Williams, R Minerath, J Cook, C Witzigmann, A Monte, T Flaherty, (2015) Pharmacokinetic/Toxicity Properties of the New Anti-Staphylococcal Lead Compound SK-03-92, *Antibiotics*, 4: 617-626.

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ME Matteucci, BK Brettmann, TL Rogers, **EJ Elder**, RO Williams III, and KP Johnston, (**2007**) Design of Potent Amorphous Drug Nanoparticles for Rapid Generation of Highly Supersaturated Media, *Molecular Pharmaceutics*, 4(5): 782-793.

EJ Elder, JC Evans, BD Scherzer, JE Hitt, GB Kupperblatt, SA Saghir, and DA Markham, (**2007**) Preparation, Characterization, and Scale-up of Ketoconazole with Enhanced Dissolution and Bioavailability, *Drug Development and Industrial Pharmacy*, 33:7, 755 - 765.

TL Rogers, IB Gillespie, JE Hitt, KL Fransen, CA Crowl, CJ Tucker, GB Kupperblatt, JN Becker, DL Wilson, C Todd, CF Broomall, JC Evans, and **EJ Elder**, (**2004**) Development and Characterization of a Scalable Controlled Precipitation Process to Enhance the Dissolution of Poorly Water-Soluble Drugs, *Pharmaceutical Research*, 21(11), 2048-2057.

RD Connors and **EJ Elder**, (**2004**) Using a Portfolio of Particle Growth Technologies to Enable Delivery of Drugs With Poor Water Solubility, *Drug Delivery Technology*, 4(8), 78-83.

EJ Elder, JE Hitt, TL Rogers, CJ Tucker, SA Saghir, S Svenson, and JC Evans, (**2003**) Particle Engineering of Poorly Water Soluble Drugs by Controlled Precipitation, *Polymeric Materials Science and Engineering*, 89:741.

JC Evans, BD Scherzer, CD Tocco, GB Kupperblatt, JN Becker, DL Wilson, SA Saghir, and **EJ Elder**, (**2003**) Preparation of nanostructured particles of poorly water soluble drugs via a novel ultra-rapid freezing technology, *Polymeric Materials Science and Engineering*, 89:742.

BOOK CONTRIBUTIONS

EJ Elder, JE Hitt, TL Rogers, CJ Tucker, SA Saghir, S Svenson, and JC Evans, Particle Engineering of Poorly Water Soluble Drugs by Controlled Precipitation, Ch. 19 in Polymeric Drug Delivery Volume II - Polymeric Matrices and Drug Particle Engineering, Svenson, S., (Ed.), ACS Symposium Series, Vol. 924, pp. 292-304, American Chemical Society, Washington, DC, **2006**.

JC Evans, BD Scherzer, CD Tocco, GB Kupperblatt, JN Becker, DL Wilson, SA Saghir, and **EJ Elder**, Preparation of Nanostructured Particles of Poorly Water Soluble Drugs via a Novel Ultra-Rapid Freezing Technology, Ch. 21 in Polymeric Drug Delivery Volume II - Polymeric Matrices and Drug Particle Engineering, Svenson, S., (Ed.), ACS Symposium Series, Vol. 924, pp. 320-328, American Chemical Society, Washington, DC, **2006**.

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ERS TASK FORCE

European Respiratory Society Guidelines on the use of nebulizers

Guidelines prepared by a European Respiratory Society Task Force on the use of nebulizers

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The European Respiratory Society (ERS) recognizes that there are an increasing number of national and international guidelines for the management of asthma, chronic obstructive pulmonary disease (COPD) and other chest diseases. Some of these guidelines recommend nebulizer use in specific circumstances, using either a jet nebulizer or an ultrasonic nebulizer to administer a drug to the airways or lungs in the form of an aerosolized mist of fine droplets. Although many patients with severe chest disease are given nebulized treatment both in hospitals and in their own homes, it is recognized that much of this practice may not be evidence-based. Some present practice may be ineffective or even harmful. The manufacturers of hand-held inhalers are obliged to meet exacting standards such as dose-to-dose reproducibility. However, nebulizer devices are sold separately from nebulized drugs and the dose delivered to the lung can be increased 10-fold or more by changing from an inefficient nebulizer system to a highly efficient one. For these reasons, the ERS commissioned a Task Force to review the scientific and clinical principles of nebulized therapy and to produce a set of guidelines (evidence-based whenever possible) for users of nebulized treatment in Europe.

Aims of the European Respiratory Society Nebulizer Guidelines and target audience

It is hoped that the guidelines will improve clinical practice in the use of nebulized therapy throughout Europe. The most important considerations should be efficacy and patient safety. The guidelines will also serve as an educational and scientific resource for clinicians and scientists with an interest in inhaled therapy. These guidelines are aimed at a wide group of healthcare professionals practising in very different healthcare systems throughout Europe. The immediate target audience for the guidelines will be pulmonary physicians, but it is hoped that the messages will be communicated to all healthcare workers who are involved in treating patients with nebulized medication (doctors, nurses, pharmacists, paramedics, physiotherapists *etc.*). The ERS Guidelines will provide recommendations based on scientific and clinical evidence, as described in the next section, and they will provide practical advice for the majority of nebulizer users. The guidelines will also identify areas of ignorance where present practise is based on tradition or opinion rather than scientific evidence. It is also hoped that by identifying these gaps in present knowledge, the guidelines will spur on clinical scientists to undertake new trials to guide future practice.

The aims are summarized as: 1) to improve clinical practice; 2) to enhance the safety and efficacy of nebulizer use; 3) to serve as an educational and scientific resource for healthcare professionals; and 4) to stimulate future research by identifying areas of ignorance and uncertainty.

Format and development of European Respiratory Society Nebulizer Guidelines

The ERS commissioned a Task Force to oversee the production of these guidelines. The membership of the Task Force is indicated above. The methodology of producing the guidelines is described in a series of detailed papers in the *European Respiratory Review* [1, 2]. These papers will serve as the scientific and clinical background for the ERS Nebulizer Guidelines. They also describe the levels of evidence on which the guidelines are based.

Evidence and recommendations have been graded in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) and the Agency for Health Care Policy and Research (AHCPR) scoring system

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[3, 4]. The background papers in the *European Respiratory Review* have reviewed each topic in detail and the evidence for each statement or recommendation is graded from I-IV as described in the AHCPR publications. The Task Force has used this evidence and the AHCPR scoring system to grade the recommendations contained in these guidelines as follows. 1) Grade A requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency, addressing the specific recommendation (AHCPR levels Ia and Ib). 2) Grade B requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (levels IIa, IIb and III). 3) Grade C requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities (including opinions of the ERS Nebulizer Task Force). It indicates absence of directly applicable studies of good quality (level IV).

Problems with the scientific background of clinical nebulizer use

Shortage of clinical trials

Trials of nebulized treatment may be especially difficult to initiate because of funding difficulties. Most nebulizer trials involve existing licensed medicines (frequently off patent) and existing devices so they are unlikely to attract funding from the pharmaceutical industry or from large medical charities. Furthermore, large-scale randomized clinical trials of long-term nebulized therapy are extremely costly. This may explain why so many nebulizer trials involve single doses or short treatment periods. It is hoped that the guidelines will stimulate research (and funding for research) into this important area.

Quality of reporting of published trials which involved nebulizer use

The Task Force had difficulty in finding good quality randomized clinical trial evidence to support large areas of present clinical practice. Furthermore, in many cases, authors of published papers have provided little detail about the nebulizer systems which were used in their studies. Important details such as the nebulizer fill volume, nebulization time or the flow rate of the driving gas were frequently omitted. This makes it difficult to reproduce clinical trials or to extrapolate clinical practice from one study to another. One aim of the present guidelines is to alert clinical scientists and journal editors to this issue.

It is recommended that journal editors and reviewers of research protocols should encourage authors to use a single standardized nebulizer system within each research study, and the authors should be obliged to describe this "nebulizer protocol" or "standardized operating procedure" fully in any publication. In some international studies, it may be necessary to use different nebulizer systems in each country but this should be stated clearly in the paper.

It is recommended that the minimum information required to describe a nebulized treatment in a scientific publication should be: drug preparation and dispensed dose; nebulizer device (including details of accessories such as mouthpiece or mask); Comité European de Normalisation (CEN) specification for the device (if available); driving gas source or compressor type and flow rate; fill volume; nebulization time or other end-point (*e.g.* nebulization to dryness); special characteristics of the system or its use, *e.g.* continuously nebulizing, venturi effect only during inspiration, manually operated, breath activated, *etc.*; patients instructed in proper use of nebulizer device.

Responsibilities of manufacturers

In most countries, the purchase of medical equipment such as nebulizers is not regulated as tightly as the purchase of pharmaceuticals and patients may purchase nebulizer equipment without medical advice. Furthermore, many nebulizer chambers are presently sold with little or no printed information regarding their use. It is hoped that the new European Standard will resolve this problem.

It is recommended that all nebulizer chambers or nebulizer systems should be sold with full instructions regarding their use, maintenance and cleaning.

Responsibilities of prescribers

It is recognized that many different types of doctor may initiate nebulized therapy or be asked by a patient to supply medication for use in a nebulizer system which has been purchased by the patient or by a patient's relative without medical advice.

It is recommended that the person who prescribes a nebulized medication should accept responsibility for ensuring that the use of nebulized drugs is appropriate and that the patient is given appropriate advice.

This may, in many cases, include referral to the local nebulizer assessment service or advice to undertake a formal assessment of nebulized therapy as described in these guidelines.

Technical aspects of nebulizer use

What is a nebulizer?

Within these guidelines, a nebulizer is a device that can convert a liquid into aerosol droplets suitable for patient inhalation. To avoid confusion between nebulizers and an expanding range of hand-held metered-dose inhalers, these guidelines will discuss only nebulizer devices in which the end-user must load the medication into the device prior to each treatment. Air-jet nebulizers are the most widely used, although ultrasonic nebulizers are becoming more common. Because air-jet nebulizers are more commonly used throughout Europe, they will form the basis of the technical aspects of nebulizer operation, although it should not be forgotten that new nebulizer designs are becoming available and ultrasonic nebulizers may become increasingly popular for home use.

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What is a nebulizer system?

These guidelines recognize the influence of all components attached to the nebulizer which affect performance, including not just characteristics of the nebulizer itself, but also: flow/pressure characteristics of the compressed air (or other power source), connection tubing, patient interface including mouthpiece or face mask, *etc.* If one component of the "nebulizer system" is changed, the performance and overall efficiency of the drug delivery also changes and it is then necessary to redefine the nebulizer system.

Drug solutions versus *suspensions*

Most nebulized drugs fall into two physicochemical categories. Drug solutions contain a drug that is dissolved in saline or occasionally in other liquids (cyclosporine, for example, is dissolved in alcohol). Drug suspensions contain a drug that is not soluble in water or other respirable liquids, they exist as a mixture of small drug particles suspended in liquid. Drug suspensions are inherently more complicated to describe as they are a mass of suspended particles which may or may not be present within the droplets which is clinically important, whereas with solutions, it is assumed that all the drug is homogeneously dispersed throughout all droplets. For example, conventional ultrasonic nebulizers cannot be used to administer suspensions such as nebulized budesonide.

Respiratory tract deposition of nebulized drugs

The three main factors which determine where in the respiratory tract a nebulized drug droplet will deposit are: droplet size, pattern of breath inhalation and age/condition of the lung. Amongst these, the easiest to control is the size of the droplets. On entering the lung, nebulized droplets may deposit by three main mechanisms. Larger droplets can deposit by impaction on airway bifurcations, while smaller aerosols deposit more by sedimentation and diffusion in the smaller airways and alveoli. Figure 1 presents the general relationship between droplet size and deposition in the respiratory tract for tidal-breath inhalation within a healthy adult lung. It is clear from this figure that there is no single area in the respiratory tract where a droplet of a given size (*e.g.* 1 μm) will definitely deposit, although the figure does demonstrate that it is more likely that a 1 μm droplet will deposit in the peripheral lung than in the upper respiratory tract.

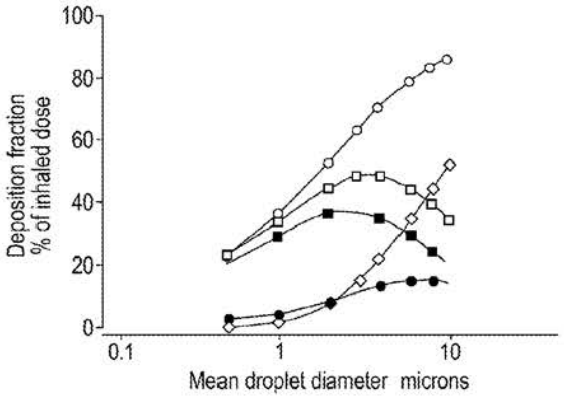

Fig. 1.–Relationship between aerosol aerodynamic diameter and deposition in the healthy adult lung (based on *in vitro* models). ○: total body; □: total lung; ◇: oropharyngeal; ●: central airways; ■: peripheral airways. Reproduced with permission [5].

Nebulizers, like hand-held inhalers, do not emit droplets of only one size (*i.e.* monodisperse). Rather, droplet size present a distribution usually encompassing a 10-fold range from which various descriptors may be derived. Perhaps the most simple, widespread and useful single measure of droplet size is the mass median aerodynamic diameter (MMAD) which is independent of the distribution (lognormal or skewed). Half of the "mass" of nebulized aerosol is contained in droplets which are larger than the MMAD and half smaller. Comparing a nebulizer's MMAD to the deposition curves in figure 1 will generally indicate where in the respiratory tract the droplets will deposit. It may also be valuable to measure the standard deviation (geometric) of the MMAD because this is a useful measure of the spread of droplet size within the distribution. The speed of inhalation is also an important factor in determining where a droplet of a specific size impacts, the faster the inhalation speed, the more likely the droplet is to impact in the upper airways. The age of the patient as well as the condition of the respiratory tract further influence the site of deposition. Despite these complications, the measure of aerosol size, often expressed as MMAD, is the single most useful parameter in predicting the site of deposition.

To complicate the area further, there exist many different methods of measuring nebulized aerosol size and each produces different results which makes it difficult for both the lay person and expert to interpret them. To simplify interpretation of nebulized droplet size, these guidelines have adopted the measure of aerosol size defined by a European Standard (prEN13544-1) and recommend that this methodology be used as the primary means of establishing nebulized droplet size. This will facilitate a more meaningful comparison of droplet size data between different nebulizer systems. Figure 2 presents a schematic of how droplet size is measured using the European Standard. Table 1 provides a summary of the nebulized aerosol droplet size that may be best suited for common clinical applications.

Ten-fold differences in nebulizer system performance!

The inherent differences in delivered aerosol between nebulizer systems currently available throughout Europe are significant. These differences can be ⩾10-fold. Important factors influencing the total dose delivered to a patient's airways include the initial volume fill, the efficiency by which nebulized aerosol is made available for patient inhalation, and

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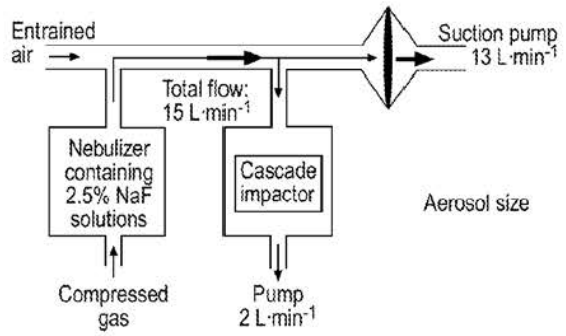

Fig. 2.–Schematic of Comité European de Normalisation methodology to measure nebulized aerosol droplet size. A constant inhalation of 15 L·min^{-1} is drawn over (or through) the nebulizer. Nebulized aerosol containing a NaF solute tracer mixes with the entrained air. A low flow cascade impactor (Marple Series 2968X) samples aerosol at 2 L·min^{-1} from this flow, and impacted aerosol can be subsequently desorbed and analysed from each size fraction from which the droplet size distribution can be determined (not to scale).

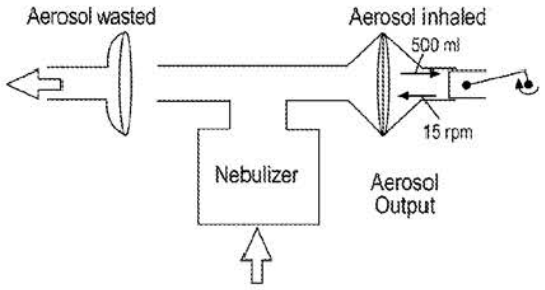

Fig. 3.–Schematic of Comité European de Normalisation methodology to measure nebulized aerosol output. "Inhaled" aerosol output is subject to sinus flow breath simulation and aerosol is collected onto low resistance electrostatic filters. Aerosol contains trace concentrations of sodium fluoride which can be subsequently desorbed and quantified electrochemically (not to scale). rpm: revolutions per minute.

the amount of residual or "dead" volume left in the nebulizer on cessation of operation. Aerosol dose is a vague concept in nebulized drug therapy. It is not common practice to prescribe a "dose delivered to lung", but prescribers usually specify the amount of drug to be dispensed in a particular volume of nebulizer solution. Prescriptions do not usually specify the nebulizer system. The choice of nebulizer varies and is often selected by a person other than the prescriber (*e.g.* hospital supplies dept). Nebulization therapy usually continues until the volume left in the nebulizer is so low that the nebulizer ceases to function continuously and begins to "sputter". This volume is typically ~1 mL, but may be as low as 0.5 mL or as high as 1.5 mL. The amount left is very high compared to a typical volume fill (*e.g.* 2.5 mL). Thus, treatment time becomes critically dependent not only on the rate of aerosol output and volume fill, but also on the minimum volume a nebulizer system requires to operate. Lung delivery of nebulized drugs will also be increased greatly when breath-activated nebulizers are used (at present, half of the nebulizer output is wasted during expiration).

As with droplet size, these guidelines recommend that methods embodied in the European Standard are used to determine the: 1) rate of aerosol output; 2) total emitted aerosol dose from a particular nebulizer system; and 3) minimum volume required for effective nebulization. The latter is particularly important as it is mainly this that defines "treatment time" and nebulizer efficiency defined by the proportion of initial volume fill that is eventually delivered to the patient. Figure 3 illustrates how such measurements are performed using European Standard methods incorporating a simulated breathing pattern.

Type testing using the European Standard

In the near future, nebulizer manufacturers will be required to test each of their nebulizer systems with a

Table 1.–Site of action of commonly nebulized drug aerosol therapies and the droplet size thought ideal for maximum clinical benefit

Drug	Target airway site	Special considerations
β_2-agonists acute Adults and children	Central-peripheral	Use O_2 as driving gas unless there are concerns about CO_2 retention
β_2-agonists chronic Adults and children	Central-peripheral	Reduce nebulization time for treatment compliance
Anti-cholinergic Adults and children	Central	Mouthpiece (preferable) or tight sealing face mask (Mouthpiece for glaucoma patients)
Corticosteroid Children and adults	Central-peripheral	Minimize skin and eye exposure Mouthpiece (preferably) (or tightly sealed face mask)
Amino-glycosides or Colomycin Adults	Central-peripheral	Mouthpiece Filter or exhaust exhaled gases Pretreat with β-agonist when necessary
Pentamidine Adults	Peripheral	Mouthpiece Pretreat with nebulized β-agonist Filter or exhaust exhaled gases
Amphotericin Adults	Central	Dilute with water not saline Filter or exhaust exhaled gases
rhDNase	Central	Mouthpiece

O_2: oxygen; CO_2: carbon dioxide; rhDNase: recombinant human deoxyribonuclease.

reference solution according to the European Standard (prEN13544-1). This will result in standardized information being supplied with every nebulizer. This information will include the following. 1) Description of the nebulizer system which includes the flow rates and volume fills at which tests were made. 2) Rate of aerosol output and total aerosol output. 3) The droplet size distribution curve from which the median size (MMAD) and spread (goblet size deposition (GSD)), and per cent aerosol mass within any given range can be obtained (*i.e.* >5 μm, 2–5 μm, ≤2 μm).

The methods on which the European Standard is based are designed to reflect clinical conditions as closely as possible. The consistency of methods to obtain this *in vitro* information through the European Standard will essentially provide a type test of each nebulizer system. This will allow for a meaningful comparison of relative performances of different nebulizer systems, and this in turn can be used to guide the optimal use of nebulizers in clinical practice.

There are some important limitations in interpreting test data supplied by manufacturers complying with the European Standard. The first is that data supplied by manufacturers relate only to drug solutions that have properties similar to saline. Test data cannot be readily extended to suspensions (*e.g.* budesonide) or to solutions that have a significantly greater viscosity than saline (*e.g.* some antibiotics). The second is that the rates and amounts of aerosol delivery have been obtained using a simulated adult healthy breathing pattern and these cannot be readily transferred to paediatric applications or to diseased adults. The test methods adopted within the European Standard are sufficiently flexible to accommodate additional test configurations.

It is recommended that where applicable, suppliers should be asked for additional data on specific drug solutions and suspensions, and alternative breathing patterns.

Characteristics of good and bad nebulizer systems

Nebulizer systems offer a great range of performance and how good or bad an individual system is depends on what it is intended to do. For example, if a system was required to deliver the maximum amount of "useful" aerosol (droplets 0.5–5 μm) in the minimum amount of time, with a minimum of inconvenience, then the characteristics of a "good" system would include the following. 1) Fast rate of nebulization, implying that the maximum amount of nebulized aerosol is potentially available to the patient over any given time. 2) Minimum waste of drug aerosol, implying that the maximum amount of aerosol released is delivered to the patient and not emitted into the environment. 3) Low residual volume, implying that more of the volume fill will be delivered to the patient as aerosol. 4) Well-defined droplet size distribution. If, however, the same system was required to deliver only a modest volume of drug aerosol, then the system described earlier becomes "bad" because such an efficient system of delivery will deliver an unnecessarily large aerosol dose with possible increased local and systemic side-effects.

These guidelines recognize that consideration must be given to matching nebulized drug delivery to the performance of nebulizer systems. This requirement will vary according to the needs of different patient groups or stages of the disease. The two main factors to take into account are: 1) how much nebulized drug is ideally required for delivery to the patient; and 2) the aerosol size required to deliver nebulized droplets to the site of action. Small aerosols (<5 μm) will deposit peripherally, whereas droplets ~5 μm will mainly deposit in airways that are more central.

The guidelines recognize that little clinical evidence exists to answer these questions and it is therefore difficult to choose the ideal nebulizer system for a given application. This being the case, these guidelines recommend that a scheme is developed to define the best available nebulizer system for various therapies, in order to reduce variability in nebulized dose delivery and thereby improve clinical practice.

Choice of nebulizer system

For bronchodilator drugs, any nebulizer system that complies with the CEN standards could be used in accordance with the manufacturers instructions. However, end-users and purchasers should avoid using inefficient systems that may waste most of the drug dose. It is suggested that a system with a good CEN performance (output and droplet size) should be chosen. Such a system would require lower doses of medication, or shorter treatment times, that may be more convenient for patients and also yield savings in overall treatment costs.

Although a face mask may theoretically deliver less medication to the lungs, two clinical studies have shown equivalence between face masks and mouthpieces for bronchodilator effects, possibly due to the tendency of breathless patients to mouth-breathe (Grade B). A face mask should ideally be avoided if a nebulized steroid is administered (to avoid steroid administration to the facial skin and eyes) (Grade C). It should also be avoided or sealed very tightly if anticholinergic agents are to be administered to patients with glaucoma (Grade C).

How to select the optimal system for a given patient or usage

All healthcare systems throughout Europe currently have some system by which nebulized drugs are prescribed for each clinical application. In addition, all prescribers and users of nebulized therapy will commonly have experience using one (or more) nebulizer system for each clinical application. Local practices may differ greatly, possibly within institutions. It is recommended that a standard operating practice (SOP) be adopted for each nebulizer system in use (Grade C). This will provide a baseline in determining the clinical effectiveness of that nebulizer system for each given application. This can then be

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Table 2. – Parameters to be standardized in the use of nebulizer systems

Nebulizer type
Choice of driving gas
Driving gas pressure
Driving gas flow rate
Drug and formulation
Nebulizer fill volume (as recommended by manufacturer)
Time of nebulization
Accessories (Mouthpiece/face mask *etc.*)
Residual solute volume (amount of drug left in chamber)

used to assess potential improvements to the nebulizer system, as outlined in the three steps discussed later.

Implementation and use of standard operating practices as a means of improving the efficacy of nebulized drug therapy

Step 0: standardize the way current nebulizer systems are used. If health practitioners can agree an SOP for the way in which nebulizer systems are used locally, they can be sure that future clinical outcomes are patient specific, rather than due to a significant change in drug output from the nebulizer. Parameters to consider are listed in table 2. Nebulizer manufacturers can provide advice on the optimum operating parameters for a particular nebulizer.

Step 1: assess drug output from the current nebulizer system. The scarcity of useful *in vitro* data describing nebulizer system performance has perhaps contributed to an arbitrary choice of nebulizer system. However, the standardization of nebulizer aerosol output and size made possible through the European Standard allows any given SOP to be re-assessed. For a specific clinical application, the SOP can be used in conjunction with data from the manufacturer to allow the dose delivered using this SOP to be derived. This dose can be the total output or can be modified by the fraction of the aerosol in the optimal size range (table 1), to give a "useful" dose. If appropriate, the potential systemic exposure arising from drug not in the "useful" range, either: 1) by being too large, being swallowed and subsequently orally available; or 2) by depositing in an inappropriate region of the lung, and being directly absorbed into the systemic circulation with minimal local efficacy should also be considered. Based on this approach, potential modifications to the existing SOP can be assessed to see whether drug delivery can be further optimized by a change in one of the operating parameters, *e.g.* gas-flow rate.

Step 2: evaluate alternative nebulizer systems. This information can be re-evaluated over time, as more efficient or cheaper nebulizers emerge. Consideration can then be given to altering prescription convention and/or adopting alternative nebulizer systems whose nominal delivered dose and droplet size (available from the manufacturer using the same standard *in vitro* data) may be better suited to that given clinical application. However, as in step 1, any changes to SOP should be supported by appropriate follow-up of outcomes such as clinical benefits or side-effects.

It is recommended that the effect of significant changes to nebulizer usage be monitored by the appropriate follow-up of clinical outcomes (Grade C).

Future developments in nebulized drug delivery

The Task Force drafting these guidelines anticipates that technical advances in microtechnology and other areas will drive improvements in nebulizer design. At the very least, these improvements will offer a significant increase in efficiency in nebulized drug delivery. While these systems offer the potential to improve the quality of nebulized drug therapy, there are risks if they are adopted with insufficient consideration of the consequences of improvements in efficiency. However, if local practices adopted the recommendations of instituting and reviewing SOPs, new and improved nebulized therapies could be safely integrated with net benefits to patients requiring nebulized drug therapy. It is likely that newer, more efficient systems will deliver inhaled drugs more effectively and thus reduce the wastage and cost associated with inefficient systems.

Clinical uses of nebulizers

Nebulized treatment may be considered for three main reasons. 1) Where a patient is perceived to require very high doses of inhaled bronchodilator medication. 2) If a patient needs an inhaled drug such as recombinant human deoxyribonuclease (rhDNase) or an antibiotic which cannot be given by any other means. 3) It is sometimes considered for patients who are unable to use other devices or in situations such as acute severe asthma where patient cooperation with other devices may be problematic.

It is clear from the technical discussion that nebulized drugs can be divided into water-soluble drugs which behave like saline (*e.g.* bronchodilators) and drugs with individual physicochemical properties which may require unique nebulizer equipment (*e.g.* rhDNase). Therefore, the ERS Guidelines will discuss these applications (bronchodilator and nonbronchodilator) separately. The commonest application of nebulized therapy is to deliver bronchodilator drugs to patients with asthma or COPD.

Use of nebulized bronchodilator drugs in acute exacerbations of adult asthma and chronic obstructive pulmonary disease

Readers are referred to national and international guidelines for the overall management of patients with acute exacerbations of asthma and COPD. These guidelines will discuss only those aspects of care which are directly related to nebulizer use. There is strong evidence that for both adults and children with acute asthma, and for adults with COPD, equivalent bronchodilator effects can be obtained using multiple

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doses from hand-held inhalers as can be obtained with presently available nebulized delivery systems (these studies have usually involved the use of large volume spacers by patients who have achieved a satisfactory inhaler technique with the spacer device). However, nebulizers continue to be used in most European hospitals because they may be regarded as more convenient for healthcare staff to administer and because less patient education or cooperation is required. This usage does not imply that nebulized therapy is superior and this should be made clear to patients and their relatives.

Hand-held inhalers (when used with spacer devices and a good inhaler technique) and nebulizers are equally effective in achieving bronchodilation in acute asthma or COPD exacerbations (Grade A). Nebulizers are widely used for the convenience of hospital staff and to overcome problems with inhaler techniques, especially with very breathless patients (Grade C).

Delivery system in acute asthma or chronic obstructive pulmonary disease. Where their use is indicated, nebulizer systems should be chosen and configured as described in the technical section of these guidelines. In hospital settings for asthma patients, the driving gas should be oxygen (O_2) (for acutely ill patients) or air (for stable patients). COPD patients should ideally receive monitored oxygen therapy while using an air-driven nebulizer system (to avoid increasing carbon dioxide (CO_2) retention), however, shorter nebulization periods (<10 min) may make this less of an issue with future nebulizer systems. Theoretically a mouthpiece may be better as it avoids nasal deposition of drugs, although no advantage has been found in two small clinical studies in stable asthma and COPD. Patients may prefer a face mask, especially when acutely breathless, a situation where patients are likely to mouth-breathe and thus diminish the theoretical disadvantages of the face mask. A mouthpiece may avoid the risk of ocular complication with anticholinergic agents.

A nebulizer system which is known to be efficient should be used (use CEN data). Face masks or mouthpieces are probably equally effective (Grade B) but breathless patients may prefer face masks (Grade B).

Selection and dosage of nebulized bronchodilator drugs. Acute asthma. Adult patients should be given a β-agonist equivalent to 2.5–5 mg of salbutamol or 5–10 mg of terbutaline (Grade B). There is evidence that additional benefit can be obtained by adding anticholinergic treatment such as 500 μg ipratropium bromide (Grade A).

Acute exacerbations of chronic obstructive pulmonary disease. COPD patients who require nebulized therapy should be given a β-agonist equivalent to 2.5–5 mg of salbutamol or 5–10 mg of terbutaline (Grade B).

In contrast to stable COPD and acute asthma, no additional benefit has been demonstrated when anticholinergic therapy has been added to β-agonist therapy for acute exacerbations of COPD (Grade A).

Frequency and duration of nebulized treatment in acute adult asthma and exacerbations of chronic obstructive pulmonary disease. Treatment may be repeated within a few minutes if the patient has a suboptimal response to the first dose of nebulized treatment or continuous nebulized therapy may be administered until the patient is stable (Grade B).

A lack of response to repeated nebulized therapy indicates the need for review by senior clinicians and the possible need for additional treatment such as noninvasive ventilation or intensive care therapy (Grade C). In cases with a good response, the treatment should be repeated at 4–6-h intervals until recovery occurs (Grade C).

Patients should be changed to hand-held inhalers as soon as their condition has stabilized because this may permit earlier discharge from hospital (Grade B).

Use of nebulized bronchodilator drugs in chronic severe asthma and chronic obstructive pulmonary disease

The ideal prescription for inhaled therapy would use the simplest and most convenient device to deliver the lowest effective dose for each patient. For most patients using bronchodilator drugs, this will mean hand-held metered-dose inhalers (MDI) with or without a spacer or an alternative hand-held device such as a breath-activated inhaler or a dry powder inhaler. However, some patients benefit from higher doses of bronchodilator drugs which may be given more conveniently from a nebulizer. There is no clearly identified threshold dose where nebulized bronchodilator therapy becomes more effective or more convenient than hand-held inhalers. This "crossover point" is individual to each patient and will vary depending on which nebulizer system and inhaler are compared. The CEN data described will provide guidance in comparing the efficacy of different systems but the exact relationship between *in vitro* performance and *in vivo* clinical effect has not yet been well studied for most nebulizer systems.

It is recommended that hand-held inhalers should be used in increasing doses up to 1 mg salbutamol or equivalent. Doses >1 mg of salbutamol (2.5 mg of terbutaline) or 160 μg of ipratropium bromide or combinations of such therapy may be given more conveniently by using an efficient nebulizer system (see technical section). The exact cut-off point will depend on these technical factors and on patient related factors such as breathing patterns or different side-effect profiles. The availability and price of different hand-held inhalers in different countries may also influence the choice of device. Finally, for patients who require combined β-agonist and anticholinergic therapy, a combined nebulized solution (or combination MDI device) may be more convenient than multiple actuations from two separate hand-held inhalers. Clinical experience suggests that doses which require >10 puffs from hand-held inhaler systems tend to be unpopular with patients.

Most indications for bronchodilator therapy are best managed by the use of a hand-held inhaler device

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(including a spacer device if appropriate) (Grade A). Doses of salbutamol >1 mg or ipratropium bromide >160–240 μg may be given more conveniently using a jet nebulizer device (Grade C). High-dose therapy should only be considered for patients with severe airflow obstruction as defined in asthma and COPD Guidelines (Grade C). Nebulized therapy may also be required for some adult patients who, after assessment, cannot use a hand-held inhaler device, even with appropriate spacer attachments (Grade C). If nebulized therapy is thought to be inappropriate for individual patients with asthma or COPD, it is recommended that the patient should be referred for "inhaled therapy optimization" as described below (Grade C).

Inhaled therapy optimization protocol for patients with chronic obstructive pulmonary disease or severe asthma. It is recommended that patients should be referred for "inhaled therapy optimization" rather than a "trial of home nebulizer". The latter terminology implies that the "trial" will have an outcome which will be judged as a "success" or "failure". Experience has shown that patients who have completed a protocol similar to that described in this section of the guidelines have almost always finished the protocol by using inhaled treatments or devices that were different to their previous treatments. About 50% of such patients have expressed a preference for nebulized therapy and 50% expressed a preference for a hand-held inhaler, usually at a higher dose than they had previously taken. Whatever the outcome of this process, most such patients have reported improved symptom control on their chosen therapy following the optimization protocol.

For most patients with severe symptomatic COPD or chronic asthma, the outcome of such a protocol may be judged as "successful" whether or not nebulized therapy is chosen (Grade B).

Step 1. Check diagnosis and confirm severity (exclude other treatable conditions such as heart failure). Assess patient's baseline level of symptoms and lung function and ensure that the patient can use their existing inhaler device effectively.

It is proposed that each of the assessments listed later should take place over 2 weeks. Shorter periods may be inadequate to assess response and longer periods would probably reduce patient compliance (Grade C).

At each stage of the process, the patient's subjective and objective response should be recorded using the scoring system given in Appendix 1 (or a similar locally devised scoring system for symptoms and lung function) (Grade C).

Step 2. Ensure that patients have tried other appropriate therapy (*e.g.* trial of steroid or theophylline or long acting β-agonist and, for COPD patients, consideration of long-term oxygen therapy, pulmonary rehabilitation *etc.* if appropriate). A number of patients may benefit from nebulized therapy in addition to the above strategies.

Nebulizer therapy has not been shown to prolong life but long-term oxygen therapy will prolong life for eligible hypoxic COPD patients (Grade A). Quality of life studies have shown little benefit with nebulized treatment but worthwhile benefits were obtained when patients with advanced COPD were entered into pulmonary rehabilitation programmes. Pulmonary rehabilitation should, therefore, be considered instead of or in addition to nebulized therapy for patients with advanced COPD (Grade A).

Step 3. Optimize existing asthma or COPD therapy using a hand-held inhaler which the patient is able to use (*e.g.* salbutamol 200–400 μg *q.i.d.* (terbutaline 500–1,000 μg *q.i.d.*) or equivalent or ipratropium bromide 40–80 μg *q.i.d.* or a combination of these agents).

Step 4. If these measures are not beneficial, try increasing further the dose of inhaled therapy *via* hand-held inhaler. (*e.g.* up to 1,000 μg salbutamol *q.i.d.* and/or up to 160–240 μg ipratropium bromide *q.i.d.*).

Patients may find it inconvenient to take a total of >10 sequential inhalations from ≥1 hand-held inhalers devices (Grade C).

Step 5. If the patient responds poorly to the measures described earlier, consider a period of home nebulizer therapy with careful evaluation of the patient's response (ideally using loaned equipment).

Laboratory tests cannot predict who will benefit from nebulized therapy or which medication or dosage will be optimal for each patient (Grade A). Home assessment protocols such as those described in Appendix 3 are more valuable than laboratory-based studies (Grade B).

Step 6. Assess the patient's response to 2 weeks of therapy with nebulized β-agonist (salbutamol 2.5 mg *q.i.d.* or terbutaline 5 mg *q.i.d.* or equivalent).

Assess response as shown in Appendix 2 (Grade C).

Step 7. If the response to monotherapy is poor, consider one or more of the following: nebulized salbutamol 5 mg *q.i.d.* (terbutaline 10 mg *q.i.d.*) (Grade B); nebulized ipratropium bromide 250–500 μg *q.i.d.* (Grade B); mixture of salbutamol (2.5 or 5 mg) or terbutaline (5–10 mg) with ipratropium 500 μg *q.i.d.* (Grade B).

Step 8. Decide with the patient which of these therapeutic interventions was most beneficial, use the evaluation system given in Appendix 2. The programme may be terminated at any step if the patient reports a good response at that treatment step.

Assessment of response to nebulized therapy or altered hand-held inhaler therapy. There is no universally agreed system to assess each patient's response to inhaled bronchodilator treatment. It is suggested that the patient should keep a record of peak expiratory flow rate (PEFR) and symptoms twice daily but it is not known which symptom score (or quality of life

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score) should be used. It may also be helpful to measure spirometry at each visit (at completion of 2 weeks therapy with each type of treatment). However, these single measurements may be difficult to interpret. Exercise tests and placebo-controlled evaluations have also been suggested but improvements in exercise tests tend to be small or nonreproducible and these assessments can prove difficult in clinical practice outside of clinical trials. Future trials will evaluate more subtle and patient-centred quality of life issues.

Deciding on outcome of nebulizer assessment/optimization of inhaled therapy. There is little agreement about what constitutes a "positive" response to inhaled bronchodilator treatment. Approximately 20–30% of patients report definite subjective benefit associated with clear-cut objective benefit during periods of home nebulizer therapy. These patients are likely to benefit from long-term nebulizer therapy. Approximately 30% of patients report varying degrees of subjective benefit but little objective benefit during periods of home nebulizer therapy. Planning long-term therapy for these patients remains a difficult clinical problem. The choice of therapy is usually negotiated between the patient and their doctor on the basis of magnitude of symptomatic benefit and whether side-effects are acceptable. A longer period of assessment may be appropriate in these circumstances. Other patients (~35–50% of those assessed) report a preference for hand-held inhalers either because of lack of benefit from nebulized therapy or because of increased side-effects. These patients should not be commenced on home nebulizer treatment.

It is recommended that the protocol described in Appendix 1 and 2 should be used to assess a patient's response to each new inhaled therapy (Grade C).

Choice of device for home nebulizer therapy. For bronchodilator drugs, any efficient nebulizer system which meets CEN standards could be used in accordance with the manufacturers instructions.

Patients should be allowed to choose whether they prefer a face mask or a mouthpiece to administer their nebulized treatment, unless their therapy specifically requires a mouthpiece (*e.g.* nebulized pentamidine) (Grade C).

Occasional use of nebulized therapy for severe attacks. Many patients request a nebulizer for occasional use during sudden exacerbations. The Task Force felt that most such patients should be treated with high doses from hand-held inhalers or spacer devices but there are some situations (*e.g.* panicking patient) where a nebulizer may be easier to use than a hand-held inhaler. The theoretical risks (*e.g.* failing to take corticosteroids or failing to call for medical help) and the theoretical benefits (*e.g.* improved patient confidence or reduced hospital admissions) have not been confirmed in randomized clinical studies. The consensus view of the Task Force was that there was no good evidence of benefit or harm but some patients felt safer with this "back-up therapy" and even a small reduction in hospital admissions would make such therapy cost-effective. However, there is strong published evidence that patient education involving self-management and the issuing of written action plans can reduce morbidity and the use of health-service resources by asthmatic patients. For this reason, the Task Force felt that the self-management of acute exacerbations should be guided by an agreed self-management plan.

"Emergency nebulizers" should only be used in accordance with a self-management plan agreed with an appropriate specialist (Grade C).

Use of nebulizers by ambulance staff and paramedics. The Task Force felt that it was appropriate for ambulance staff and paramedics to institute bronchodilator treatment as early as possible in acute asthma, using nebulized bronchodilator therapy driven by O_2. For short urban ambulance journeys, COPD patients could be treated in a similar manner, but for journeys >15 min or for patients who are known to be vulnerable to CO_2 retention, a controlled O_2 system may be required (it is acknowledged that it may be difficult for ambulance staff to identify individual patients for whom the risk of hypercarbia and acidosis may be greater than the risk of hypoxia). Ambulance staff should be instructed to stop nebulized therapy and administer controlled low-dose O_2 if a patient with COPD should become drowsy during nebulized treatment using O_2 as a driving gas.

Ambulance staff should commence nebulized bronchodilator therapy (*e.g.* salbutamol 2.5–5 mg or Terbutaline 5–10 mg) as early as possible for patients with acute asthma or acute exacerbations of COPD (Grade B).

Ambulance staff should make peak flow measurements whenever possible before administering nebulized drugs (Grade C).

Use of nebulizers in paediatric asthma

Children differ from adults in more than just size, they have, for example, different breathing patterns, tidal volumes and airway geometry. Most paediatric use of nebulized therapy occurs in the management of acute asthma. Because of the earlier considerations, careful attention to detail is important if nebulized therapy is given to children and infants. The findings of the Task Force were as follows. 1) As with adults, most patients can be treated just as well with hand-held inhalers and spacers (Grade A). 2) Nebulizers are frequently used for convenience or to overcome problems with inhaler technique (Grade C). 3) Adding anticholinergic therapy in severe asthma is beneficial (Grade A). 4) For long-term treatment of asthma, hand-held inhalers are as effective as nebulizers so it is very unusual for a child to require long-term, high-dose nebulized therapy for asthma (Grade B). 5) In the past, nebulizers were widely used to treat young children who were unable to use hand-held inhalers. The development of spacers with face masks has reduced this indication for nebulizer use in childhood (Grade B).

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Use of nebulizers in other paediatric conditions

In bronchiolitis, nebulized β_2-agonists or ribavarin have not consistently been shown to be beneficial and nebulized corticosteroids are ineffective in this condition. It is recommended that these treatments should not be used pending further trial data (Grade B).

In the management of croup, oral dexamethasone and nebulized corticosteroids are equally effective; corticosteroids from a hand-held inhaler with spacer device have not been shown to be effective in this condition (Grade A).

In surfactant deficient respiratory distress (hyaline membrane disease), nebulized surfactant is still the subject of investigation. Intratracheal instillation is the recommended route of administration (Grade C). There is conflicting evidence concerning the possible benefit of nebulized surfactant in older children with respiratory distress syndrome (Grade C).

Nebulized DNAse and N-acetyl cysteine have been used in paediatric intensive care units for sputum retention. There is no evidence of benefit from either agent but N-acetyl cysteine may cause bronchoconstriction. It is recommended that these treatments should not be used pending further trial data (Grade C).

There is conflicting evidence of possible benefits of nebulized prostacyclin (iloprost) in pulmonary hypertension in childhood (Grade B).

Use of nebulizers in cystic fibrosis

Nebulizers may be used to administer bronchodilator therapy, mucolytic therapy or antibiotics to patients with cystic fibrosis. However, nebulized therapy is time consuming and should be reserved for situations where it has been shown to be the best or only way to administer a given drug. The use of nebulized therapy should be evaluated and re-assessed regularly. A change in the treatment programme does not always show improvements of pulmonary function parameters but a successful regimen may prevent a fall in lung function over a long period of time. Other outcomes should also be considered, for example; weight gain/maintained weight, reduced exacerbation frequency, improved physical function, reduced tiredness, reduced breathlessness, shortened time spent on daily airway clearance therapy or improved quality of life. Long-term studies are required to show these effects.

There is evidence that selected patients with cystic fibrosis benefit from nebulized antibiotics (Grade A). There have been few controlled trials to determine the optimal dose and delivery system for such a treatment. Nebulized rhDNase has shown benefit in selected patients during medium-term treatment (Grade A). Long-term benefits of nebulized rhDNase are controversial (Grade B).

Some controlled trials of nebulized mucolytics of other kinds have shown little or no benefit. Objective effects on pulmonary secretion viscosity have so far been difficult to measure, subjective effects are difficult to interpret. However, these different kinds of nebulized mucolyties or saline are frequently used in some cystic fibrosis centres and not at all in others. There is a great need for long-term controlled trials with expanded parameters on the effects of nebulized mucolytics (Grade C). Careful attention to technical detail is required for special applications such as nebulized rhDNase and antibiotics (Grade C).

Choice of an appropriate nebulizer system is essential for the quality of the aerosol produced and the drug output. Other factors of importance are treatment strategy and inhalation technique. Theoretically, these patients may require more than two nebulizer systems to administer, for example, rhDNase, antibiotics or bronchodilator drugs. But a situation like this might have negative effects on adherence with the treatment and/or cleaning of the nebulizer systems.

A high capacity nebulizer system including a high output should be considered to keep down the time spent on nebulizer therapy. However, the drugs should be administered separately as it may be hazardous (and ineffective) to mix these agents except when safety and efficacy data are available concerning the particular mixture (Grade C).

Nebulized antibiotics and nebulizer use in bronchiectasis

Most nebulized antibiotic use occurs in patients with cystic fibrosis or bronchiectasis. As discussed earlier, much of this treatment is not evidence-based (there are no randomized controlled trials comparing different antibiotic regimens showing clear superiority of any particular regimen). Furthermore, the CEN data cannot be applied directly to antibiotics and other viscous solutions but would require separate assessment. When such treatment is considered desirable, the clinician should use a drug-nebulizer combination that has been reported to be efficacious in at least one published study (even if nonrandomized). The end-points of "success" are difficult to define in a relapsing condition such as bronchiectasis, perhaps exacerbation rate should be a key measurement. The use of nebulized bronchodilators and nebulized mucolytic agents in bronchiectasis have not been the subject of any large randomized trials and the advice given in the COPD and cystic fibrosis sections of the guidelines should be applied to bronchiectasis also. A nonrandomized trial has shown enhanced mucus clearance when nebulized saline or terbutaline was given as an adjunct to chest physiotherapy to patients with bronchiectasis.

The recommendations for cystic fibrosis also apply to patients with bronchiectasis where there is less experimental evidence of benefit from nebulized therapy (Grade C). It is recommended that individual patients should have a "n of one" trial (*i.e.* a trial including only one person) to determine if nebulized antibiotic therapy or other nebulized treatments are beneficial in their case (Grade C).

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Use of nebulizers in acquired immune deficiency syndrome, including Pneumocystis carinii *pneumonia*

In summary, the Task Force found that nebulized therapy in human immunodeficiency syndrome-infected patients can place patients and staff at risk of nosocomial infections including multi-drug resistant tuberculosis. For this reason, elaborate precautions are necessary if nebulized agents are used for diagnostic or therapeutic purposes in this patient group (Grade B).

Nebulizers are widely used to deliver hypertonic saline for sputum induction. This has a lower yield than bronchoscopy with bronchoalveolar lavage but, if positive, it may avoid the need for bronchoscopy. It is recommended that bronchoscopy is used in preference to sputum induction for safety reasons and because of the superior yield (Grade B).

Nebulized pentamidine is more effective than placebo but less effective than oral co-trimoxazole in the prophylaxis and treatment of *Pneumocystis carinii* pneumonia (Grade A). The effectiveness of nebulized pentamidine is highly dependent on the equipment and dose used and on the dosing schedule. Some non-randomized studies with more intensive regimens have given results equivalent to those obtained with oral co-trimoxazole (Grade C).

Nebulized corticosteroids

Nebulized corticosteroids have been used as a substitute for oral corticosteroids in moderate exacerbations of adult and paediatric asthma and to reduce the dose of oral steroid therapy in chronic asthma. Nebulized steroids have also been given to lung transplant recipients (see later). However, in each of these situations, an equivalent dose of inhaled steroid could be given more easily by the use of a hand-held inhaler. There is no clinical data to suggest superior benefit from nebulized corticosteroids (compared with steroid from hand-held inhaler with spacer device) in acute or chronic asthma.

Inhaled steroids delivered by hand-held inhaler and by nebulizer have been shown to have an oral steroid-sparing effect (Grade A). There is evidence that some conventional jet nebulizers and most ultrasonic nebulizers may deliver a lower dose of inhaled steroid to the lung than the same nominal dose from a hand-held inhaler. However, advanced breath-activated nebulizer systems have been shown to deliver equivalent lung doses compared with an effectively used hand-held inhaler system with spacer device (Grade B).

It is recommended that inhaled steroids should preferably be given by hand-held inhaler devices (using a spacer device) because of lack of evidence for any advantage from the nebulized route which is more time consuming and more expensive (Grade C).

Nebulizer use in the intensive care unit

MDI and nebulizers are used in intensive care units to deliver bronchodilator medication to mechanically ventilated adults and children. It is not yet known which treatment modality is more effective because it is difficult to undertake studies which are sufficiently large to permit the measurement of meaningful outcomes such as morbidity, mortality and duration of mechanical ventilation.

Some trials have suggested that MDI in combination with an in-line spacer device may be more efficient in delivering aerosolized drugs to the lungs in ventilated patients, where practical (Grade B).

No randomized trials exist today to prove the efficacy of aerosolized antibiotics for the treatment of nosocomial pneumonia or long-term benefit for the prophylaxis of nosocomial pneumonia (Grade C).

Trials of nebulized surfactant in acute respiratory distress syndrome (ARDS) are at an early stage at present. The optimal dosage is unknown and there may be a problem in achieving adequate drug delivery to the alveoli because some current nebulizers may denature the drug. It has been demonstrated that nebulized or intratracheally instilled surfactant does improve gas exchange in ARDS patients (Grade B), but randomized trials failed to prove beneficial in outcome measures (Grade A).

Trials of nebulized Prostacyclin (iloprost) in ARDS are at an early stage at present but physiological benefits on pulmonary hypertension have been demonstrated in some studies on patients with this condition (Grade B).

Use of nebulizers in bronchoscopy units

Nebulized bronchodilators may be given before bronchoscopy in patients with airflow obstruction or afterwards if bronchospasm occurs. It is likely that high doses from a hand-held inhaler would be equally effective (Grade C).

Some operators give nebulized anticholinergic treatment before bronchoscopy but this has not been proven to be clinically beneficial (Grade C). Nebulized lignocaine may be administered before the procedure as an alternative to lignocaine administered *via* the bronchoscope. If this is done, the clinician should select a nebulizer which delivers most particles to central airways (Grade B).

Treatment of airflow obstruction in patients with tracheostomy

Many patients with laryngeal cancer requiring laryngectomy also have co-existing COPD which is difficult to treat using conventional MDI. Nebulizers are frequently used to treat these patients. However, recent case reports indicate that MDI-spacer devices can be used with appropriate adaptors. This permits quicker treatment with lower doses of bronchodilators. For patients with an open tracheostomy, a 750 mL spacer with a baby sized face mask can be placed over the tracheal stoma to deliver bronchodilator therapy (Grade C).

For intubated patients or patients with permanent tracheostomy tubes, the MDI-spacer can be connected

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to the patients tracheostomy tube by means of an appropriately sized adaptor (Grade C). No controlled trial has compared these treatments with nebulized therapy but case reports suggest that patients may find MDI-spacer therapy quicker to administer (Grade C).

Use of nebulizers in palliative care

Nebulized bronchodilators may be used for the treatment of severe co-existing COPD in lung cancer patients (as described in the COPD section of these guidelines) (Grade B). The use of nebulized saline or mucolytics to loosen airway secretions in patients with advanced cancer remains of unproven value (Grade C).

Nebulized opiates have been shown to be ineffective in the treatment of breathlessness and this therapy is not recommended (Grade B). The use of nebulized lignocaine in lung cancer has not been subjected to any controlled study (Grade C).

Use of nebulized mucolytic therapy in chronic obstructive pulmonary disease

Nebulized mucolytic agents are used to treat COPD patients in some countries but there is very limited clinical trial evidence to support such use. Further controlled trials are needed. In the meantime, it is recommended that such treatment should be restricted to cases where benefit has been shown in "n or one trials" (Grade C).

Use of nebulizers in lung transplantation

Nebulized steroids and nebulized cyclosporin have been used as preventive therapy in lung transplant patients who are at risk of developing obliterative bronchiolitis because of frequent episodes of rejection in the first 3 months post-transplantation. This use is presently the subject of further research studies (Grade B).

Use of nebulizers in fungal lung diseases

There is evidence of modest benefit from nebulized amphoteracin-B in the prophylaxis of fungal pulmonary infections in neutropenic leukaemic patients (Grade A). However, drug intolerance due to airway side-effects (cough and bronchospasm) was a major concern, causing discontinuation of therapy in ~20% of patients.

There is evidence from nonrandomized trials that nebulized amphoteracin, when given to lung transplant patients with positive cultures for aspergillus or candida, may prevent the development of invasive fungal pneumonia (Grade B). A randomized trial of nebulized bronchopulmonary aspergillosis failed to show any benefits. This treatment is not recommended (Grade A). However, clinicians should consider the use of oral itraconazole which has been shown to produce clinical benefits in two recent randomized studies (Grade A). There is limited evidence of lack of benefit for the use of nebulized amphoteracin in the treatment of tracheobronchial fungal infections (Grade C).

Use of nebulizers in the treatment of pulmonary hypertension

There is evidence of long-term clinical and physiological benefit from nebulized prostacyclin (iloprost) in pulmonary hypertension in adults (Grade A). The relative benefits of parenteral and inhaled prostacyclin are still the subject of ongoing research protocols, the inhaled preparation had given superior physiological outcomes in some trials (Grade B).

Upper airway uses of nebulizers

Nebulized treatment has been used for a variety of nasal, pharyngeal, laryngeal and sinus conditions but there are limited controlled trial data to support such use (Grade C). Warmed humidified air has been shown to produce symptomatic benefit in patients with chronic rhinitis (Grade B).

Diagnostic uses of nebulizers

Nebulizers are used for a number of diagnostic purposes, most of which are highly specific (allergen or occupational challenge in asthma, reversibility testing in COPD, hypertonic saline for sputum induction, radioisotopes in ventilation studies or clearance studies). The majority of such uses are highly dependent on the use of specific equipment which has been validated in previous studies.

It is recommended that investigators should use equipment and solutions which have been validated in at least one published study or validated in their own laboratory (Grade C).

Service issues

Selection and purchase of nebulizer systems

The choice of nebulizer system will depend on the drug prescribed, the patient and disease being treated and on availability and price in each country. The background papers in the *European Respiratory Review* include a table describing present usage in various European countries. It is recommended that the CEN data should be used to guide the choice of system (see technical section). The final choice of system may depend on local factors but should be guided by the principles described earlier.

Running a local nebulizer or inhaled therapy optimization service

There is increasing evidence that the understanding of the use of nebulizers by patients and health

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professionals is poor, leading to inappropriate and suboptimal use. It is recommended that an appropriately trained specialist such as a chest physician, paediatrician, physiotherapist or respiratory nurse specialist (or a primary care physician with a special interest in respiratory diseases) should assess whether nebulizer therapy is indicated. Assessments should be undertaken using standard protocols as described earlier (Grade C). If nebulizer therapy is prescribed, the patient should have access to an appropriately run nebulizer service providing equipment, advice and support for patients who require long-term nebulizer therapy (Grade C).

The "local nebulizer service" should include the following: assessment and advice for patients who might benefit from home nebulizer therapy; loan or hire of nebulizer equipment; advice for healthcare professionals; access to servicing of equipment; audit of all aspects of nebulizer use in the locality. Patients should be provided with training (including practical demonstration) and clear written instructions in how to use and maintain their equipment (Grade C). The different healthcare professionals who may care for an individual patient need to communicate effectively with each other and with the patient (Grade C).

Cleaning, maintenance, and replacement of equipment

Cleaning nebulizer equipment involves getting rid of drug residues as well as dirt and microbes. The ideal standards and methods for such cleaning (and the optimal intensity and frequency of cleaning) have not yet been well established. It is important that nebulizer chambers, tubing and masks should not be re-used for multiple patients unless they have been sterilized (and are capable of withstanding sterilization) (Grade C). All other usage should be for individual patients with careful cleaning and disinfection of the whole nebulizer system on a regular basis (Grade C). The driving source should be cleaned and checked for safety and efficiency in accordance with the manufacturer's recommendations or at least once per year and the whole nebulizer system should be brought for this check-up (Grade C). Filters should be changed at intervals specified by the manufacturer (Grade C). Nebulizer chambers, tubing and masks should be changed regularly (Grade C).

It is recommended that the person in charge of the local nebulizer service should provide patients with advice and support to ensure that all nebulizers are used safely and efficiently including details of disassembly and cleaning (Grade C). It is suggested that manufacturers should undertake appropriate tests and trials to permit the production of evidence-based instructions.

Education of clinical staff and patients

It is recommended that a local "inhaled therapy coordinator" (doctor, nurse or physiotherapist) should be made responsible for the production and implementation of local policies for the use of inhaled therapy, including nebulizer therapy (Grade C). This will improve efficacy and patient safety and it is likely to be cost-effective as the inappropriate use of expensive nebulized drugs should be minimized (Grade C). This person should provide education for other healthcare professionals and patients in addition to running an assessment and support service for patients. This should include support and advice for physicians who prescribe nebulized drugs, although the prescriber remains responsible for the patient's treatment and safety (Grade C).

Follow-up of patients

It is suggested that long-term nebulizer users should have the support of a local service, as described earlier. Patients should be re-assessed soon after treatment starts (at ~1 month) and then re-assessed regularly (at least annually) to determine whether their treatment is still necessary and effective and to ensure that the patient continues to use the nebulized treatment safely and effectively (Grade C). This evaluation should include lung function testing, assessment of symptom control and breathlessness and sense of well-being. The clinician should also ask about side-effects of treatment and check that the treatment is still judged by the patient to be working (Grade C).

It may also be helpful to ask the patient to demonstrate their technique by using their own nebulizer system. The local nebulizer support team should maintain good communication with the patient's primary care physician, especially with regard to dose and frequency of nebulized therapy.

Implementation and dissemination of the European Respiratory Society Nebulizer Guidelines

There is a great need to improve technical standards and present clinical practice. Because of the complex ways in which inhaled therapy is used in different countries, the Task Force has tried to provide information and recommendations rather than rigid prescriptions or instructions which might not be applicable to many users. The ERS would encourage national and local dissemination of these guidelines (translated into local languages where necessary).

It is especially important to target healthcare professionals such as doctors, nurses and physiotherapists who may be involved in administration of nebulized treatment and the local purchase of nebulizer devices.

It is hoped that specialists in each country or region will initiate local programmes to implement the ERS Guidelines. The ERS will not issue any formal guidance on local implementation, this will be the responsibility of national and local respiratory societies. In some cases it may be necessary to prepare short abstracts, tables and wall charts or to tailor the guidelines to meet the needs of users and healthcare staff in different parts of Europe. The ERS will

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encourage such use of the guidelines by healthcare professionals throughout Europe.

National and local respiratory societies, pharmaceutical companies and equipment manufacturers will be encouraged to promote and distribute these guidelines or selected abstracts from the guidelines for the use of local clinicians and patients. It is hoped that clinicians will initiate local audit of practice before and after the introduction of these guidelines. Feedback from these clinicians to the ERS will be much appreciated by the Society.

A complimentary copy of the *European Respiratory Journal* paper which contains the guidelines will be circulated by the ERS to the editors of all major respiratory journals, general medical journals and pharmacological journals with a recommendation that editors should insist on the description of a standard operating practice in all papers which involve the use of nebulized drugs (this information should be circulated to referees and associate editors). The guidelines will be made available on the World Wide Web in the future. The guidelines will be reviewed and updated as the need arises.

Areas of uncertainty and future research needs

There are many areas of uncertainty where future research is needed. 1) The relationship between *in vitro* studies and *in vivo* effects needs further investigation. This issue will be especially important as newer, more efficient nebulizer systems are introduced into clinical use. 2) Matching nebulizer systems to individual drugs and to individual patients (*e.g.* width of "therapeutic windows" (see technical section of this paper)). 3) For patients who could receive a similar dose of the same drug from a hand-held inhaler device or from a nebulizer, are there specific situations where one system or the other might have advantages? 4) Cost-effectiveness and health resource utilization studies comparing nebulizers and hand-held inhaler therapy. 5) Methods to identify which patients with asthma and chronic obstructive pulmonary disease might benefit (or not benefit) from nebulized therapy using clinically relevant assessment systems. 6) How to decide whether or not a patient with asthma or chronic obstructive pulmonary disease has derived definite benefit from home nebulizer therapy. 7) Value (and possible risks) of nebulized bronchodilator therapy in chronically hypoxaemic patients with severe but stable chronic obstructive pulmonary disease. 8) Physiological effects of nebulized saline and mucolytic agents in chronic obstructive pulmonary disease and bronchiectasis. 9) Controlled comparisons of different nebulized antibiotics given by specific nebulizer systems and evaluation of the indications for the use of nebulized antibiotics and the effectiveness of this treatment. 10) Relative value of nebulized therapy and metered-dose inhaler therapy in mechanically ventilated patients using clinically meaningful end-points. 11) Role of mucolytic agents other than recombinant human deoxyribonuclease in cystic fibrosis. 12) Long-term benefits of nebulized antibiotics and recombinant human deoxyribonuclease in cystic fibrosis. 13) Clinical comparisons of nebulized corticosteroids with the equivalent dose of inhaled corticosteroid given by hand-held inhaler. 14) Best practice for cleaning and servicing of nebulizers. 15) Role of nebulized prostaglandin analogues in pulmonary vascular disease. 16) Role of nebulized therapy in palliative care. 17) Role of nebulized therapy in upper airway diseases.

Appendix 1: Assessment of subjective and objective response to therapy

Suggested tools to measure response to each treatment modality during "inhaled therapy optimization protocol" (to assess response to therapy with hand-held inhalers or nebulized therapy).

Objective response (compared with two weeks on usual treatment):

PEF worse	Score -1
PEF unchanged or rise of 0–10%	Score 0
PEF rise of 11–20%	Score 1
PEF rise >20%	Score 2 (but reconsider diagnosis of COPD)

Subjective response: ask the patient to respond to the following question: "compared with your previous therapy, how was your condition overall during this period of therapy?" (and record what symptoms have improved).

Worse	Score -1
Same or no definite change	Score 0
Definitely better	Score 1
Definitely much better	Score 2 (and ask the patient to state which symptoms have improved)

Appendix 2: Evaluation of outcome following each period of treatment during "inhaled therapy optimization protocol"

Possible outcomes for each period	Suggested action
Subjective Response +1 or +2 Objective Response +1 or +2	Consider continuing this treatment long-term (depending on side-effects and patient preference *etc.*)
Subjective Response +1 or +2 Objective Response 0	Consider longer reial of this treatment modality

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Subjective Response -1 or 0 Objective Response -1 or 0	Stop this treatment (and proceed to next step of assessment if appropriate)
Subjective Response -1 or 0 Objective Response +1 or +2	Reconsider diagnosis and consider longer trial

If objective response is +2, reconsider diagnosis of COPD.

Appendix 3: Summary of recommendations for optimization of inhaled therapy in severe chronic obstructive pulmonary disease and severe chronic asthma

1. Check diagnosis and confirm severity and baseline disability and ensure that the patient can use their existing inhaler device effectively. Assess response to each treatment as shown in Appendix 1.
2. Ensure that patients have tried other appropriate therapy including consideration of nondrug therapy such as a pulmonary rehabilitation programme.
3. Optimize existing asthma or COPD therapy using a hand-held inhaler which the patient is able to use (*e.g.* salbutamol 200–400 μg *q.i.d.* (terbutaline 500–1,000 μg) or equivalent or ipratropium bromide 40–80 μg *q.i.d.* or a combination of these agents).
4. If these measures do not achieve benefit, try further increasing the dose of inhaled therapy *via* hand-held inhaler (*e.g.* up to 1,000 μg salbutamol *q.i.d.* and/or up to 160–240 μg ipratropium bromide *q.i.d.*).
5. If the patient responds poorly to the above measures, consider a period of home nebulizer therapy (ideally using loaned equipment).
6. Assess the patient's response to 2 weeks of therapy with nebulized β-agonist (salbutamol 2.5 mg *q.i.d.* or terbutaline 5 mg *q.i.d.* or equivalent).
7. Consider ≥1 of the following: nebulized salbutamol 5 mg *q.i.d.* (terbutaline 10 mg *q.i.d.*); nebulized ipratropium bromide 250–500 μg *q.i.d.*; mixture of salbutamol (2.5 or 5 mg) or terbutaline (5–10 mg) with ipratropium 500 μg *q.i.d.*
8. Decide with the patient which of these therapeutic interventions was most beneficial: use the evaluation system given in Appendix 2.

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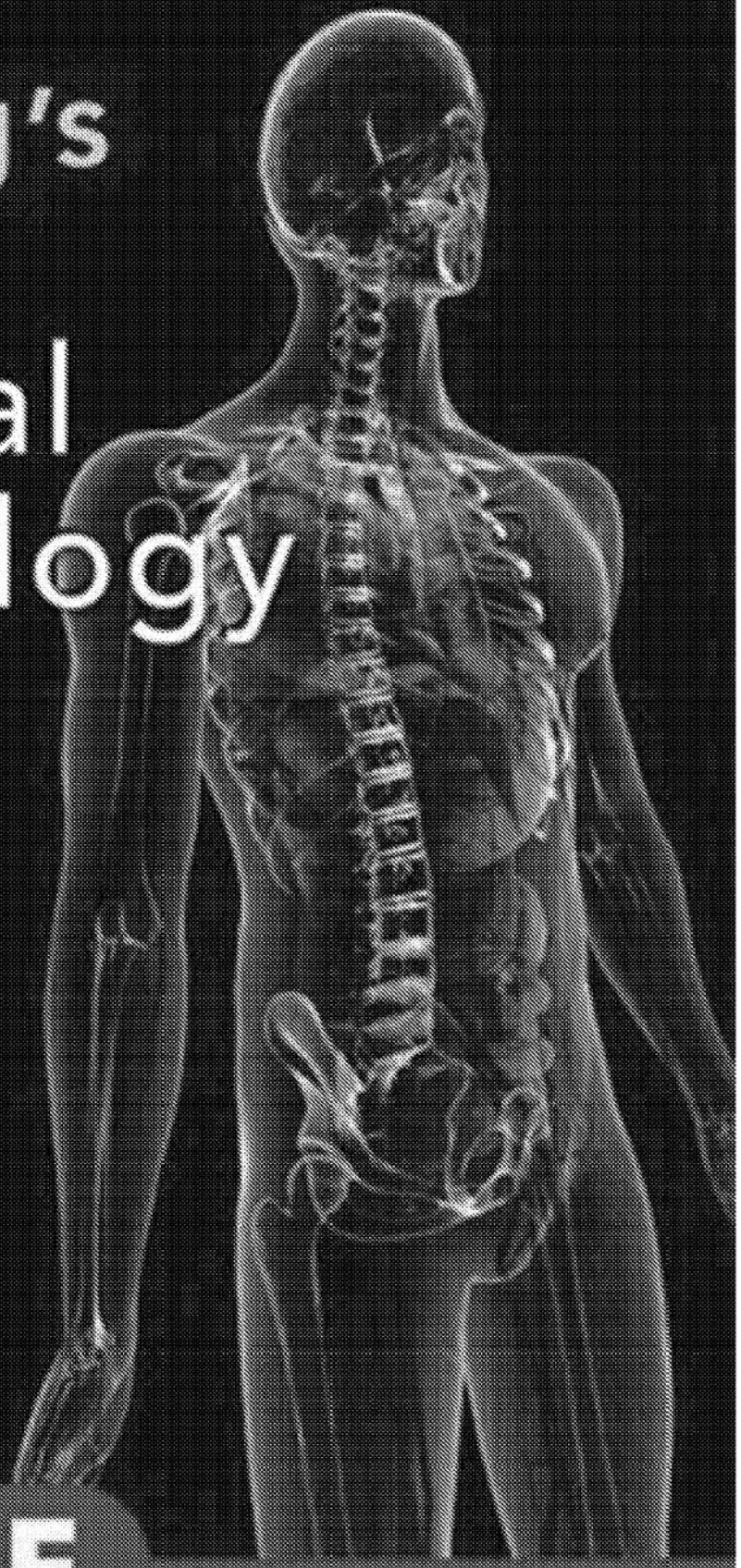

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TABLE 35–3 Effect of variations in respiratory rate and depth on alveolar ventilation.

Respiratory rate	30/min	10/min
Tidal volume	200 mL	600 mL
Minute volume	6 L	6 L
Alveolar ventilation	(200 − 150) × 30 = 1500 mL	(600 − 150) × 10 = 4500 mL

that is, the amount of air reaching the alveoli per minute, is less than the respiratory minute volume. Note in addition that because of the dead space, rapid shallow breathing produces much less alveolar ventilation than slow deep breathing at the same respiratory minute volume (Table 35–3).

It is important to distinguish between the **anatomic dead space** (respiratory system volume exclusive of alveoli) and the **total (physiologic) dead space** (volume of gas not equilibrating with blood; ie, wasted ventilation). In healthy individuals, the two dead spaces are identical and can be estimated by body weight. However, in disease states, no exchange may take place between the gas in some of the alveoli and the blood, and some of the alveoli may be overventilated. The volume of gas in nonperfused alveoli and any volume of air in the alveoli in excess of that necessary to arterialize the blood in the alveolar capillaries is part of the dead space (nonequilibrating) gas volume. The anatomic dead space can be measured by analysis of the single-breath N_2 curves (Figure 35–17). From mid-inspiration, the subject takes as deep a breath as possible of pure O_2, then exhales steadily while the N_2 content of the expired gas is continuously measured. The initial gas exhaled (phase I) is the gas that filled the dead space and that consequently contains no N_2. This is followed by a mixture of dead space and alveolar gas (phase II) and then by alveolar gas (phase III). The volume of the dead space is the volume of the gas expired from peak inspiration to the midportion of phase II.

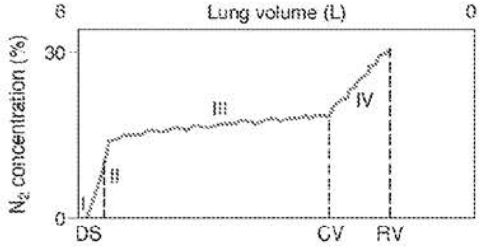

FIGURE 35–17 Single-breath N_2 curve. From mid-inspiration, the subject takes a deep breath of pure O_2 then exhales steadily. The changes in the N_2 concentration of expired gas during expiration are shown, with the various phases of the curve indicated by roman numerals. Notably, region I is representative of the dead space (DS); from I–II is a mixture of DS and alveolar gas; the transition form III–IV is the closing volume (CV), and the end of IV is the residual volume (RV).

Phase III of the single-breath N_2 curve terminates at the **closing volume (CV)** and is followed by phase IV, during which the N_2 content of the expired gas is increased. The CV is the lung volume above residual volume at which airways in the lower, dependent parts of the lungs begin to close off because of the lesser transmural pressure in these areas. The gas in the upper portions of the lungs is richer in N_2 than the gas in the lower, dependent portions because the alveoli in the upper portions are more distended at the start of the inspiration of O_2 and, consequently, the N_2 in them is less diluted with O_2. It is also worth noting that in most normal individuals, phase III has a slight positive slope even before phase IV is reached. This indicates that even during phase III there is a gradual increase in the proportion of the expired gas coming from the relatively N_2-rich upper portions of the lungs.

The total dead space can be calculated from the P_{CO_2} of expired air, the P_{CO_2} of arterial blood, and the tidal volume. The tidal volume (V_T) times the P_{CO_2} of the expired gas (P_{ECO_2}) equals the arterial P_{CO_2} (Pa_{CO_2}) times the difference between the tidal volume and the dead space (V_D) plus the P_{CO_2} of inspired air (P_{ICO_2}) times V_D **(Bohr's equation):**

$$P_{ECO_2} \times V_T = Pa_{CO_2} \times (V_T - V_D) + P_{ICO_2} \times V_D$$

The term $P_{ICO_2} \times V_D$ is so small that it can be ignored and the equation solved for V_D. If, for example,

$P_{ECO_2} = 28$ mm Hg

$Pa_{CO_2} = 40$ mm Hg

$V_T = 500$ mL

then,

$V_d = 150$ mL

The equation can also be used to measure the anatomic dead space if one replaces Pa_{CO_2} with alveolar P_{CO_2} (PA_{CO_2}), which is the P_{CO_2} of the last 10 mL of expired gas. P_{CO_2} is an average of gas from different alveoli in proportion to their ventilation regardless of whether they are perfused. This is in contrast to Pa_{CO_2}, which is gas equilibrated only with perfused alveoli, and consequently, in individuals with unperfused alveoli, is greater than P_{CO_2}.

GAS EXCHANGE IN THE LUNGS

SAMPLING ALVEOLAR AIR

Theoretically, all but the first 150 mL expired from a healthy 150-lb man (ie, the dead space) with each expiration is the gas that was in the alveoli **(alveolar air)**, but some mixing always occurs at the interface between the dead-space gas and the alveolar air (Figure 35–17). A later portion of expired air is therefore the portion taken for analysis. Using modern apparatus with a suitable automatic valve, it is possible to collect the last 10 mL expired during quiet breathing. The composition of alveolar gas is compared with that of inspired and expired air in Figure 35–18.

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Ultrasonic *versus* jet nebulization of iloprost in severe pulmonary hypertension

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Ultrasonic versus *jet nebulization of iloprost in severe pulmonary hypertension. T. Gessler, T. Schmehl, M.M. Hoeper, F. Rose, H.A. Ghofrani, H. Olschewski, F. Grimminger, W. Seeger.* ©*ERS Journals Ltd 2001.*

ABSTRACT: Inhalation of iloprost, a stable prostacyclin analogue, is a promising perspective in the treatment of pulmonary hypertension. In initial clinical studies, a conventional jet nebulizer system was successfully used to decrease pulmonary vascular resistance and pressure, requiring however, up to twelve inhalations of 12–15 min per day. The aim of this study was to investigate if the application of an equal dose of iloprost at a drastically reduced duration of inhalation with the use of a more efficient ultrasonic nebulizer, leads to comparable haemodynamic effects, without escalation of side effects.

The physical features of the jet nebulizer system (Ilo-Neb™) and the ultrasonic nebulizer (Multisonic Compact™) were characterized by laser diffractometry and a Tc^{99m}-tracer technique. Mass median aerodynamic diameters were 3.2 µm for the jet and 3.9 µm for the ultrasonic nebulizer. Total output (mean±SD) was 60±7 µL·min^{-1} (jet) and 163±15 µL·min^{-1} (ultrasonic), and efficiency of the devices was 39±3% (jet) and 86±5% (ultrasonic). Based on these data, a total inhalative dose of 2.8 µg iloprost was delivered by jet nebulization within 12 min and by ultrasonic nebulization within 4 min, in 18 patients with severe primary and secondary pulmonary hypertension (New York Heart Association class III and IV), in a randomized crossover design. Haemodynamics were assessed by right heart catheterization.

Inhalation with the ultrasonic device and jet nebulizer, reduced mean±SEM pulmonary artery pressure from 54.3±2.1 to 47.1±2.0 and from 53.5±2.2 to 47.0±2.2 mmHg, respectively, and mean±SEM pulmonary vascular resistance from 1073±109 to 804±87 and from 1069±125 to 810±83 dyn·s·cm^{-5}, respectively. Both modes of aerosolization were well tolerated.

In conclusion, due to the markedly higher efficiency and output of the ultrasonic device, wastage of drug is largely avoided and the duration of inhalation can be shortened to one-third, with comparable haemodynamic effects and without enforcing side effects.

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Severe pulmonary hypertension is a life threatening disease, characterized by an increase in arterial pressure and vascular resistance in the pulmonary circulation [1]. Dyspnoea and reduced exercise capacity are the prominent clinical symptoms; death is most closely associated with an increase in right atrial pressure and a decrease in cardiac output due to right-sided heart failure [2]. Several investigations with intravenous administration of prostacyclin have demonstrated the vasodilatory capacity of this prostanoid in primary pulmonary hypertension (PPH) [3–5] as well as in forms of secondary pulmonary hypertension (SPH) [6, 7]. Moreover, in a controlled study continuous prostacyclin infusion was shown to improve exercise capacity and survival in patients suffering from severe PPH [8]. Disadvantages of this intravenous approach are the lack of pulmonary selectivity, giving way to systemic side effects, as well as infectious complications related to the long-term use of an intravenous catheter.

In a recent approach to overcome these shortcomings, aerosolization of the stable prostacyclin analogue iloprost was employed for pulmonary vasodilation in both PPH and severe SPH [9–13]. Preferential vasorelaxation in the pulmonary circulation was demonstrated with this approach, the maximum pulmonary vasodilatory potency corresponding to that of intravenous prostacyclin. At present, limited data on long-term clinical use of iloprost inhalation are available, indicating an improvement in exercise capacity and pulmonary haemodynamics after 12 months of iloprost aerosol therapy in 24 patients with PPH [14]. Phase II (randomized, parallel-group comparative clinical) as well as phase III (double-blind, randomized, placebo-controlled clinical) studies addressing the impact of iloprost nebulization on exercise capacity and mortality in PPH and severe secondary pulmonary hypertension are currently under way.

In all previous studies investigating short-term or long-term iloprost nebulization [9–14], a continuous output jet nebulizer with a reservoir and filter system was used. However, the limited output of this device requires long inhalation periods of 12–15 min for

delivery of an adequate iloprost dose for pulmonary vasodilation. Moreover, the therapeutic use of iloprost aerosolization in pulmonary hypertension demands multiple daily inhalation manoeuvres, since the pulmonary vasodilatory effect of each single inhalation levels off within ~1 h, thus resulting in a total duration of inhalation of up to 3 h per day. In addition, limited efficiency of the jet nebulizer system causes a notable waste of the drug. Therefore, a reduction of inhalation time with the use of a more efficient nebulizer system will markedly improve iloprost aerosol therapy. A recently developed ultrasonic nebulizer device might offer the possibility to overcome these limitations. However, no data on aerosol delivery of prostanoids with this different technical approach are presently available. The present study characterized the physical features of the ultrasonic nebulizer. Based on these data, a comparison of the haemodynamic effects of an equivalent dose of iloprost delivered in a crossover design by the jet nebulizer within 12 min and the ultrasonic device within 4 min during right heart catheter tests, was performed. Patients with severe primary and secondary pulmonary hypertension were used. It was investigated whether the iloprost application at a notably shorter duration of inhalation would result in comparable pulmonary vasodilatory effects without enforcing side effects.

Methods

Physical characterization of the devices

The following parameters of the devices were analysed: particle size distribution, total output of the nebulizer, effective output at the mouthpiece and aerosol loss in the different components of the device. Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the aerosol were determined using a laser diffractometer (Helos™; Sympatec, Clausthal, Germany) at room temperature and with a distance of 1 cm between mouthpiece and laser beam. The jet nebulizer system investigated in this study (Ilo-Neb™; Nebu-Tec company, Elsenfeld, Germany) consisted of a Bennett-Raindrop™ jet nebulizer, a reservoir, filters, valves and tubes and was driven by a Pari Boy™ compressor (Pari, Starnberg, Germany) at 80 kPa (fig. 1). For the ultrasonic nebulizer system (Multisonic Compact™; Schill company, Probstzella, Germany) with an operating ultrasound frequency of 1.7 MHz (fig. 2), an airflow of 40 L·min^{-1} was applied for particle size measurements. The filled-in volume was 4 mL iloprost diluted in physiological saline for both devices.

The total output of the nebulizers and the output at the mouthpiece were quantified by a Tc^{99m}-tracer-technique with an additional filter at the mouthpiece of the system for aerosol trapping. To mimic aerosol inhalation in patients, a volunteer performed the inhalation manoeuvres through the filter at the mouthpiece (tidal volume ~1.5 L, breathing frequency ~11·min^{-1}, inspiration:expiration ratio ~1:1.8). After each inhalation period (12 min for the jet nebulizer, 4 min for the ultrasonic nebulizer), the systems were disassembled

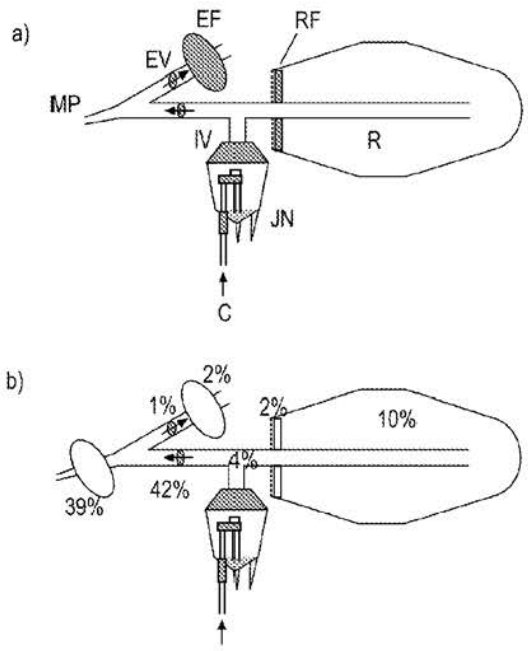

Fig. 1. – Schematic depiction of a) the jet nebulizer device, with b) deposition fractions of a Tc^{99m}-labelled test aerosol in the different parts of the device being given as per cent of total output. In these experiments, the output at mouthpiece was captured in an additional filter mounted at this site. EF: expiration filter; EV: expiration valve; MP: mouthpiece; IV: inspiration valve; RF: reservoir filter; R: reservoir; JN: Bennett-Raindrop™ jet nebulizer; C: Pariboy™ Compressor.

and the activity deposited in the various parts of the nebulizer was determined using a gamma-counter. The efficiency, defined as the ratio of the output at the mouthpiece to total output of the nebulizer, was calculated from the activities in the components.

Patients

A total of 18 patients with severe pulmonary hypertension was included in the investigation, all of whom were classified as New York Heart Association class III or IV. Seven patients suffered from primary pulmonary hypertension and 11 patients showed pulmonary hypertension related to thromboembolism (six patients), connective tissue disease (three patients), lung fibrosis (one patient) and portal hypertension (one patient) (diagnosis according to World Health Organization conference [1]). Diagnostic procedures included transthoracic or transoesophageal echocardiography, chest radiography, high resolution and spiral computer tomography of the lung, ventilation-perfusion scans, lung function testing including carbon monoxide-diffusion capacity, pulmonary angiograms and pulmonary artery catheter. Baseline values for mean±SEM pulmonary artery pressure at rest, and pulmonary vascular resistance were 54.1±2.2 mmHg and 1076±121 dyn·s·cm^{-5}, respectively.

All patients gave written informed consent to the test trial, which was approved by the local institutional ethics committees of the participating centres.

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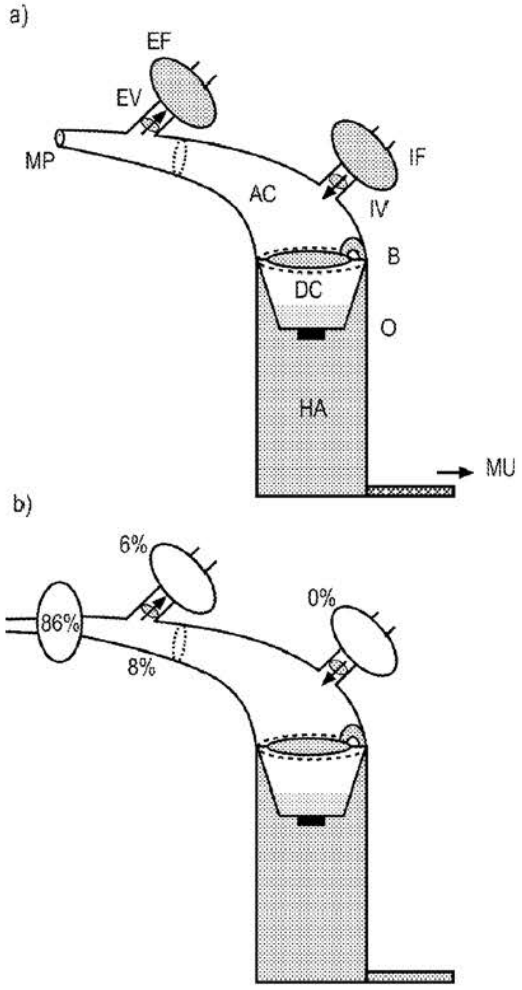

Fig. 2. – Schematic depiction of a) the ultrasonic nebulizer device, with b) deposition fractions of a Tc^{99m}-labelled test aerosol in the different parts of the device being given as per cent of total output. In these experiments, the output at mouthpiece was captured in an additional filter mounted at this site. EF: expiration filter; EV: expiration valve; MP: mouthpiece; AC: aerosol chamber; DC: drug chamber; HA: hand apparatus; IV: inspiration valve; IF: inspiration filter; B: baffle; O: oscillator; MU: main unit.

Catheter and inhalation protocol

Before starting the device comparison with inhaled iloprost, a fibreoptic thermodilution pulmonary artery catheter was employed for measurement of pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), central venous pressure (CVP) and cardiac output (CO). A femoral artery catheter was used to assess systemic arterial pressure (SAP). Based on these data, cardiac index (CI), pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated.

Each patient inhaled with both devices in a randomized order. The first inhalation was performed after achieving a stable baseline of haemodynamic variables; the second inhalation started 2 h after the end of the first inhalation. PAP, PAWP, CVP, CO and SAP were recorded before (baseline) and 0, 5, 15, 30 and 60 min after the end of each inhalation.

For inhalation manoeuvres with the jet nebulizer, iloprost was diluted in saline to a final concentration of 10 $\mu g \cdot mL^{-1}$, and 4 mL of the solution were placed in the nebulizer. The nebulizer was then driven with room air at a pressure of 80 kPa for an inhalation period of 12 min. For inhalation manoeuvres with the ultrasonic nebulizer system, iloprost was diluted in saline to a final concentration of 5 $\mu g \cdot mL^{-1}$ and 4 mL of the solution were introduced into the nebulizer. Patients then inhaled the nebulized drug for a period of 4 min. This procedure was based on the physical characterizations of the nebulizers, targeting to achieve an equivalent dose (2.8 µg) of the vasodilatory prostanoid at the mouthpiece with both systems.

Statistics

All values are presented as means±SEM unless otherwise noted. Statistical comparisons of haemodynamic parameters at 0, 5, 15, 30 min after inhalation *versus* baseline (pre inhalation) were performed for each device using paired t-tests. The exact Wilcoxon matched pair signed-rank test was used if data did not show normal distribution in Kolmogorov-Smirnov tests. For multiple testing, the Holm correction was applied [15].

To compare the influence of the different devices on haemodynamic parameters, the differences of post *versus* pre inhalation values for both devices were calculated. These differences were analysed with the same statistical procedures as described above.

Results

The physical parameters of both nebulizers are shown in table 1. In figure 1 and 2, the aerosol deposition in the different parts of the devices is depicted: 61% of the generated aerosol was lost within the jet nebulizer device, compared to only 14% in the ultrasonic device. Based on these data, the "standard" iloprost aerosol application, as investigated in previous clinical studies with employment of the currently tested jet nebulizer device, was calculated to result in a total iloprost dose at the mouthpiece of 2.8 µg (12 min inhalation period, iloprost concentration 10 $\mu g \cdot mL^{-1}$). To achieve an equivalent dose when using the ultrasonic nebulizer device, the iloprost concentration was reduced to 5 $\mu g \cdot mL^{-1}$ and the inhalation time to 4 min to match the higher output at the mouthpiece of the ultrasonic nebulizer.

The kinetics of haemodynamic parameters pre-, and up to one hour postiloprost inhalation, for both devices are shown in figures 3 and 4. The iloprost inhalations with both devices were well tolerated. Side effects, such as cough or flush occurred in only few patients to very moderate degrees and never led to discontinuation of inhalation. The iloprost delivery *via* both devices resulted in a significant reduction of PAP, PVR and the PVR/SVR ratio, as well as in an increase of CI (figs 3 and 4; table 2). In addition, some minor and

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Table 1. – Comparison of physical parameters of the nebulizer devices

	Jet nebulizer system	Ultrasonic nebulizer system
MMAD μm	3.2±0.1	3.9±0.2
GSD	1.8±0.0	1.6±0.1
Total output of nebulizer $\mu L \cdot min^{-1}$	60±7	163±15
Output at mouthpiece $\mu L \cdot min^{-1}$	23±3	140±13
Efficiency %	39±3	86±5

Data are presented as mean±SD; n=6. MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation.

rapidly transient decrease in systemic arterial pressure was noted. All changes in haemodynamic variables largely levelled off within ~1 h. There was no statistically significant difference between responses to the jet and ultrasonic nebulization techniques, except for the CI, which increased more rapidly and more prominently when applying the iloprost dose in the ultrasonic nebulization manoeuvre, as compared to the standard jet nebulization protocol (increase in CI 0.44 $L \cdot min^{-1} \cdot m^{-2}$ *versus* 0.19 $L \cdot min^{-1} \cdot m^{-2}$ assessed 5 min after termination of inhalation manoeuvre; $p<0.05$).

Discussion

The physical characterization of both the jet and ultrasonic nebulizers, demonstrated that particle sizes of both systems are within a range suitable for alveolar deposition [16–18]. Particle sizes of the presently investigated ultrasonic nebulizer (Multisonic Compact™) are dependent on the gas flow through the system; the applied flow of 40 $L \cdot min^{-1}$ matches realistic mean inspiratory flow conditions, resulting in a MMAD of 3.9 μm.

The total output of the ultrasonic nebulizer (163 $\mu L \cdot min^{-1}$) is 2.7 times higher than that of the jet nebulizer. The difference between the two systems is even more pronounced with regard to the output at mouthpiece: this parameter, describing the amount of aerosol delivered *de facto* to the inhaling patient, is more than six times higher in the ultrasonic nebulizer system as compared to the jet nebulizer. This is mainly due to a notable aerosol loss at the inspiration valve of the jet nebulizer device (fig. 1), with preferential deposition of large particles. The design of the ultrasonic nebulizer does not require any valve in the inspiratory aerosol flow, leading to a high efficiency of the device: 86% of the total aerosol output is available at the mouthpiece for inhalation. Moreover, the ultrasonic device offers, due to its compact construction, the advantage of an easy handling and maintenance, as compared to the jet nebulizer.

Both systems avoid drug contamination of the environment by the use of filters, thereby minimizing the risk of drug exposure to the medical staff. This is of particular importance when aerosolizing highly efficacious drugs, such as vasoactive agents or antibiotics, as demonstrated for pentamidine in recent studies [19, 20].

Based on the data of the physical characterization, the inhalation time for delivery of an equivalent iloprost dose at the mouthpiece (2.8 μg) was reduced from 12 min with the jet nebulizer system to 2 min with the ultrasonic nebulizer, when retaining the same concentration of the iloprost solution (10 $\mu g \cdot mL^{-1}$). In preliminary catheter investigations, however, some increase in systemic side effects was observed when administering the total iloprost dose of 2.8 μg *via* the inhalation route for such a short time period. Therefore, we reduced the iloprost concentration from 10 $\mu g \cdot mL^{-1}$ to 5 $\mu g \cdot mL^{-1}$ when employing the ultrasonic nebulizer, and consequently doubled the inhalation time to 4 min with this device. This inhalation protocol was generally well tolerated. Furthermore, by diluting the prostanoid solution, drug waste in the dead space of the nebulizer was reduced.

When directly comparing the haemodynamic effects of equivalent iloprost doses delivered either by jet or ultrasonic nebulization in a crossover design, a marked pulmonary vasodilation with a decrease in pulmonary artery pressure and pulmonary vascular resistance, and increase in CI was noted in response to both modes of aerosol administration. Strength and time course of the iloprost effect were comparable for both devices. Thus, the total amount of inhaled iloprost and not the duration of the inhalation manoeuvre (4 *versus* 12 min) is obviously the main determinant for both the strength and the duration of the pulmonary vasodilation effect. This is also true for the systemic effects, as both modes of aerosol administration caused preferential pulmonary vasodilation (reflected by a decrease

Table 2. – Haemodynamic parameters pre- and postinhalation (greatest effects)

	Jet nebulizer system		Ultrasonic nebulizer system	
	Pre	Post	Pre	Post
mPAP mmHg	53.5±2.2	47.0±2.2	54.3±2.1	47.1±2.0
PVR $dyn \cdot s \cdot cm^{-5}$	1069±125	810±83	1073±109	804±87
CI $L \cdot min^{-1} \cdot m^{-2}$	2.24±0.17	2.48±0.15*	2.22±0.17	2.66±0.19*
PVR/SVR	0.56±0.04	0.49±0.04	0.56±0.03	0.50±0.03
mSAP mmHg	91.8±3.8	86.3±2.7	90.6±2.5	82.5±2.4
SVR $dyn \cdot s \cdot cm^{-5}$	1877±135	1612±100	1874±124	1462±113

mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CI: cardiac index; SVR: systemic vascular resistance; PVR/SVR: ratio of PVR tp SVR; mSAP: mean systemic artery pressure; Pre: pre-inhalation value; Post: extreme value up to 60 min postinhalation (all extreme values are minimums except those marked with * which are maximum). Values are given as mean±SEM for n=18 patients.

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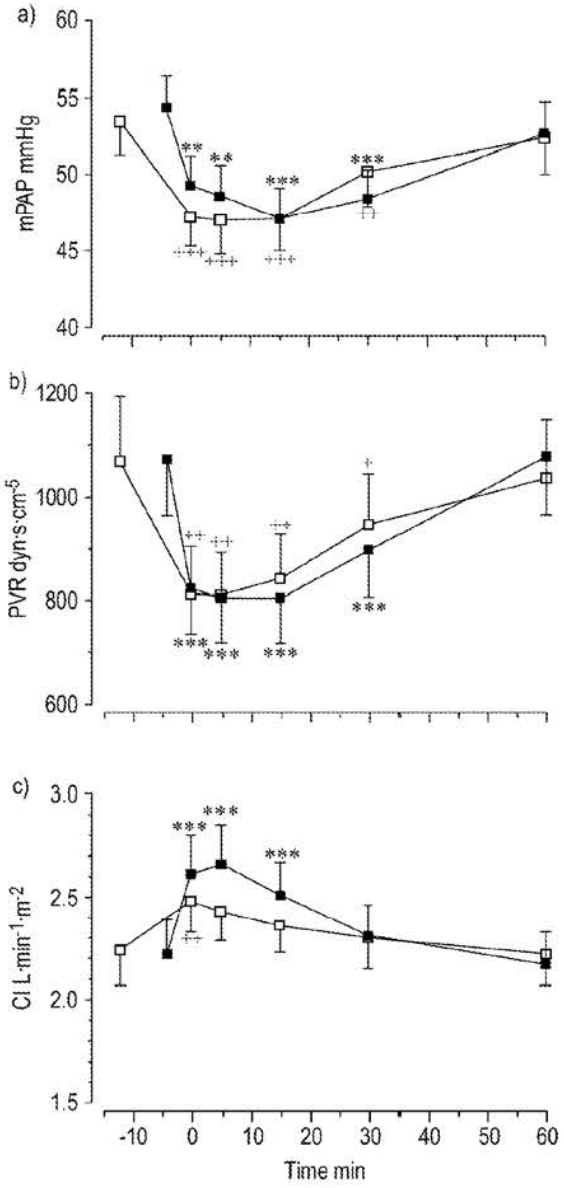

Fig. 3. – Responses of mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR) and cardiac index (CI) to iloprost inhalation (2.8 μg) *via* jet nebulizer (12 min; □) and ultrasonic nebulizer (4 min; ■). To normalize for the different length of the inhalation period, time was set at zero at the end of the aerosolization manoeuvre for both techniques. Statistical differences between pre- and postaerosolization data are indicated for both approaches (*: p<0.05; **: p<0.01; ***: p<0.001 for ultrasonic nebulization; $^{+}$: p<0.05; $^{++}$: p<0.01; $^{+++}$: p<0.001 for jet nebulization).

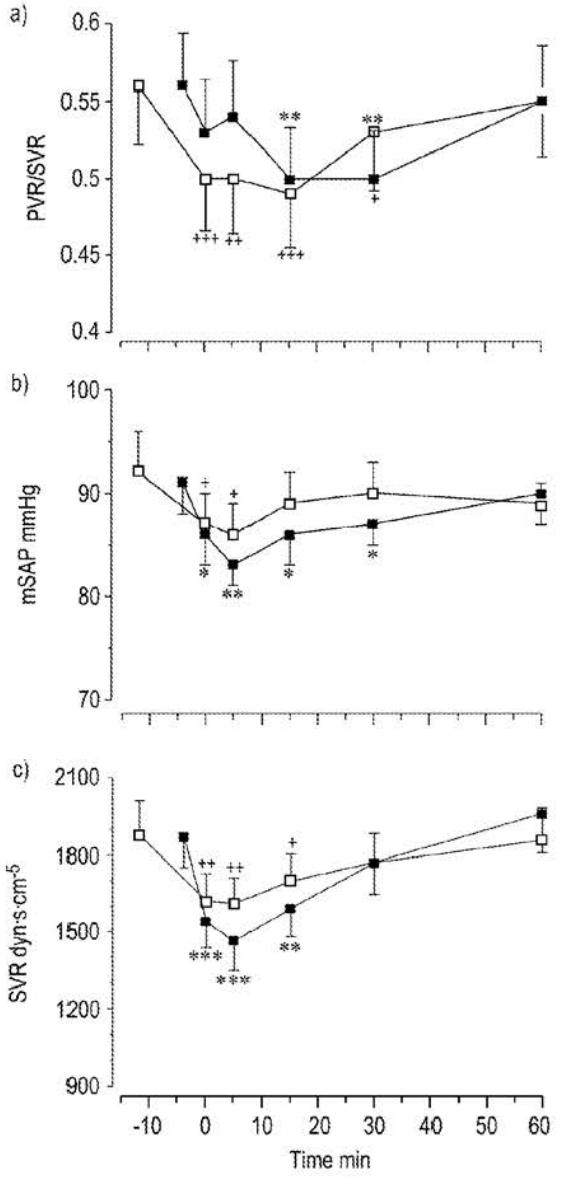

Fig. 4. – Responses of the ratio of pulmonary vascular resistance to systemic vascular resistance (PVR/SVR), mean systemic artery pressure (mSAP) and systemic vascular resistance (SVR) to iloprost inhalation (2.8 μg) *via* jet nebulizer (12 min; □) and ultrasonic nebulizer (4 min ■). To normalize for the different length of the inhalation period, time was set at zero at the end of the aerosolization manoeuvre for both techniques. Statistical differences between pre- and postaerosolization data are indicated for both approaches (*: p<0.05; **: p<0.01; ***: p<0.001 for ultrasonic nebulization; $^{+}$: p<0.05; $^{++}$: p<0.01; $^{+++}$: p<0.001 for jet nebulization).

in the PVR/SVR ratio), with a very minor drop in systemic arterial pressure. Although not significantly different by statistical analysis (excepting CI increase), there was a tendency for a more prominent pulmonary and systemic vasodilatation potency (with corresponding cardiac output response) in the early postaerosolization period upon employment of the ultrasonic nebulization manoeuvre. These observations might support the hypothesis of a spill-over to the systemic circulation and hence systemic vasodilatation acting as a driving force of increased cardiac output.

The pulmonary vasodilator effect levelled off within ~1 h, independent of the device used. Therefore, the inhalation frequency remains unchanged with up to 12

inhalations per day; the notably shorter duration of inhalation with the new device, however, may improve compliance and quality of life of the patients. Nevertheless, the long-term impact of iloprost aerosol therapy in pulmonary hypertension patients has still to be confirmed by the ongoing double-blind randomized studies.

The maximum decrease in pulmonary artery pressure and resistance in response to 2.8 μg iloprost delivered by jet or ultrasonic nebulization in the present study ranged somewhat lower than the maximum pulmonary vasodilator effect previously described for this approach in severe pulmonary hypertension [9–13]. However, these previous studies included mostly patients suffering from PPH or pulmonary hypertension associated to connective tissue disease. In contrast, the present investigation included more SPH than PPH patients, including six patients with severe pulmonary hypertension related to thromboembolism (classed as SPH patients). This fact may well explain the somewhat lower pulmonary vasodilator response in the present study as compared to the previous investigations with iloprost aerosol delivery.

In conclusion, ultrasonic nebulization is suitable for inhalation of iloprost in severe pulmonary hypertension, inducing preferential pulmonary vasodilation. Markedly higher efficiency and output of the currently investigated ultrasonic device, in comparison to a standard jet aerosolization technique, avoids wastage of drug and allows shortening of the inhalation time to ~30%, with comparable haemodynamic effects. The delivery of a standard iloprost dose of 2.8 μg in the notably reduced inhalation time did not induce side effects and was well tolerated by all patients. Long-term use of the ultrasonic nebulization device, performed in selected patients beyond the scope of the present study, as yet has shown no technical drawbacks. Thus employment of ultrasonic aerosol generation offers more effective alveolar deposition of vasoactive drugs in severe pulmonary hypertension, as compared to conventional jet nebulization.

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Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension

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ABSTRACT

Background: The stable prostanoid analogue treprostinil is approved as continuous infusion for treatment of pulmonary arterial hypertension. Unique drug characteristics may render this prostanoid feasible for inhalation therapy with a metered dose inhaler.

Methods and results: Randomised open label investigation of acute haemodynamic effects, safety and tolerability of inhaled treprostinil delivered in seconds by a metered dose inhaler (MDI-TRE). Inhaled nitric oxide (NO) and MDI-TRE were applied once during right heart catheter investigation to 39 consecutive patients with pre-capillary pulmonary hypertension. Doses of 30 μg, 45 μg and 60 μg MDI-TRE were investigated in separate groups of patients. Haemodynamics and blood gases were measured for 2 h following treprostinil application. Acute haemodynamic responses to NO and MDI-TRE were comparable. MDI-TRE significantly improved haemodynamics compared to placebo inhalation. MDI-TRE induced effects were comparable to a historical control group that inhaled treprostinil from an ultrasonic nebuliser. The 120 min area under the curve for PVR changes due to placebo, 30 μg, 45 μg or 60 μg MDI-TRE was 1114 ± 998, −870 ± 940, −2450 ± 2070 and −2000 ± 900 min*%. Reduction of systemic vascular resistance and pressure were not clinically relevant. No significant side effects were observed. No impact on ventilation/perfusion matching by treprostinil was demonstrated in 5 patients with pre-existing gas exchange limitations by use of the multiple inert gas elimination technique.

Conclusions: The application of inhaled treprostinil with a metered dose inhaler is feasible and well tolerated. It induced a sustained pulmonary selective vasodilatation.

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1. Introduction

Pulmonary arterial hypertension may be treated with prostacyclin or its stable analogues iloprost and treprostinil [1–4]. Prostacyclin, due to its short half life, may only be administered as continuous intravenous infusion. Iloprost treatment provided clinical efficacy by intravenous [3] and inhaled application [5]. Treprostinil has a significantly extended half life [6]. It is approved for i.v. as well as s.c. infusion, the latter avoiding septic events associated with indwelling intravenous catheters. The subcutaneous application however often leads to infusion site pain. We therefore sought for an alternative application route for treprostinil and already demonstrated that the inhalation of treprostinil is safe, well tolerated and evokes acute pulmonary selective vasodilatation without relevant systemic side effects [7]. Continuous treatment with inhaled treprostinil administered four times daily was noted to be effective and without relevant side effects in small open label non-randomized trials [8,9]. A clinical phase IIb trial investigating inhaled treprostinil adjunct to sildenafil or bosentan treatment in PAH has just been completed.

In preceding studies we found that quite high doses of inhaled treprostinil could be safely deposited in the lung in as little as a single breath [8]. This suggested for the first time the possibility to deliver a potent vasodilator for pulmonary hypertension treatment with a metered dose inhaler.

In this open label study of acute vasodilator challenge during right heart catheter investigation we addressed the safety, tolerability and pulmonary vasodilator potency of inhaled treprostinil

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applied in seconds by a metered dose inhaler (MDI-TRE) and compared it to inhaled nitric oxide, which is the standard medication to test pulmonary vasoreaction. We provide evidence for a long lasting acute effect of MDI-TRE on pulmonary haemodynamics in the absence of systemic side effects and gas exchange deteriorations.

2. Methods and patients

The protocol was approved by the institutional review board of the University of Giessen. Written informed consent was obtained before enrolment.

A total number of 39 consecutive patients with moderate to severe pre-capillary pulmonary hypertension were enrolled in an open label, placebo controlled trial. Randomisation to the treatment groups that received either 30 μg, 45 μg or 60 μg treprostinil, which were completed one after the other, relied on the random schedule of patients for routine diagnostic right heart catheter procedures. Patient characteristics were: f/m = 25/14, age 59 ± 2.3 years, mean pulmonary artery pressure (PAP) 45 ± 1.8 mmHg, pulmonary vascular resistance (PVR) 734 ± 52 dynes*s*cm^{-5}, pulmonary capillary wedge pressure (PCWP) 8.6 ± 0.5 mmHg, central venous pressure (CVP) 6.4 ± 0.7 mmHg, cardiac output (CO) 4.5 ± 0.2 l/min, central venous oxygen saturation (SvO_2) 62.3 ± 1.2 mmHg (mean ± SEM). Disease aetiologies were idiopathic pulmonary arterial hypertension (iPAH; $n = 13$), PAH of other causes ($n = 10$) and non-operable chronic thromboembolic pulmonary hypertension (CTEPH; $n = 16$). The patient characteristics of the separate groups are shown in Table 1.

Baseline values were determined 20 min after placement of the catheter (7F Swan Ganz Catheter, Edwards Life Sciences, Irwin, CA, USA). Heart rate, pulmonary and systemic blood pressures and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Cardiac output (CO) was measured with the thermodilution method by bolus-injection of 10 ml cooled sterile saline solution. At least three CO measurements were done at each time point and averaged. Following initial baseline recordings, we applied 20 ppm inhaled nitric oxide (NO) for a duration of 5 min to every patient previous to the treprostinil inhalation as a comparative agent. After NO was stopped and PAP and CI had returned back to baseline, patients of the three separate dose groups received a single dose of either 30 μg ($n = 12$), 45 μg ($n = 9$) or 60 μg ($n = 20$) metered dose inhaler-treprostinil sodium (MDI-TRE). Dose escalations in single patients were not performed, each patient received only a single dose and the effect was recorded for 120 min. Treprostinil was applied with the Respimat® metered dose inhaler (Boehringer, Ingelheim, Germany). Physical aerosol characteristics of the MDI devices were controlled by laser diffractometry as previously reported [10]. The mass median aerodynamic diameter (MMAD) of treprostinil-aerosol was 4–5 μm, which was suitable for alveolar deposition. Treprostinil-aerosol volume delivered by one puff from the MDI was 15 μl. The MDI was either filled with a concentration of 1000 μg/ml treprostinil sodium (15 μg TRE per puff) or with 2000 μg/ml (30 μg TRE per puff). The different doses in this study were applied as 2 puffs of 1000 μg/ml (30 μg), 3 puffs of 1000 μg/ml (45 μg) or 2 puffs of 2000 μg/ml (60 μg). Haemodynamics and gas exchange parameters were recorded for 120 min after MDI-TRE inhalation. The Respimat® device was chosen for this study because the implemented "soft mist" technology seemed to be well suited for the peripheral lung deposition of highly active drugs like prostanoids as it generates a rather slow stream of aerosol instead of a sharp pulse that may result in higher oral and pharyngeal deposition.

The impact of MDI-TRE on ventilation–perfusion matching was measured in five patients (30 μg TRE, $n = 2$; 45 μg TRE, $n = 1$; 60 μg TRE, $n = 2$) with pre-existing gas exchange limitations by use of the multiple inert gas elimination technique (MIGET) as it was previously described [11,12].

3. Statistical analysis

Mean values, standard deviation, standard error of the mean or 95% confidence intervals were calculated. Statistical analysis of areas under the curve was done by use of a paired t test. For analysis of repeated measurements over time comparing placebo and MDI-TRE or MDI-TRE and ultrasonic nebulisation one way ANOVA for repeated measurements with Bonferroni post test was performed. Statistical analysis was done with the Graph Pad Prism 5 software.

4. Results

4.1. Safety and tolerability

The inhalation of treprostinil sodium from a metered dose inhaler was well tolerated, only mild and transient cough for a maximum of 1 min was reported by some patients. No systemic side effects like headache, flush, nausea or dizziness were observed.

4.2. Acute haemodynamic changes due to MDI-TRE

Doses of 30 μg, 45 μg and 60 μg MDI-TRE reduced PVR from 575 ± 104 dynes to 494 ± 109 dynes, from 964 ± 184 dynes to 720 ± 229 dynes and from 667 ± 149 dynes to 530 ± 132 dynes, respectively (mean ± 95% confidence interval). Mean pulmonary artery pressure was reduced by 30 μg, 45 μg or 60 μg MDI-TRE from 40.1 ± 4.9 mmHg to 33.3 ± 4.4 mmHg, from 50.4 ± 6.2 mmHg to 38.1 ± 8.4 mmHg and from 39 ± 4.8 mmHg to 32.2 ± 4.9 mmHg, respectively. Pulmonary vasodilatation surpassed the observation time of 120 min in the 45 μg and 60 μg groups. The lower dose of 30 μg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal drop in PVR was comparable, arguing for a prolonged effect of higher dose depositions. In contrast, placebo inhalation did not induce pulmonary vasodilatation but lead to a slight increase in PVR over the time of the right heart catheter investigation (Fig. 1). Because the

Table 1
Patient characteristics of the investigated groups. Treprostinil was administered by a metered dose inhaler device (MDI-TRE) or in a historical group by an ultrasonic device (US-TRE). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO_2 = arterial oxygen saturation; SvO_2 = central venous oxygen saturation. Data are mean ± standard error of the mean.

	Placebo ($n = 4$)	MDI-TRE 30 μg ($n = 11$)	MDI-TRE 45 μg ($n = 8$)	MDI-TRE 60 μg ($n = 20$)	US-TRE 32 μg ($n = 6$)	US-TRE 48 μg ($n = 6$)	US-TRE 64 μg ($n = 3$)
Age [years]	61 ± 8	54 ± 4.2	54 ± 6.5	65.5 ± 3.1	56.8 ± 3.7	51.2 ± 2.4	57.3 ± 9.1
PAP [mmHg]	49.5 ± 10.1	46.5 ± 3.0	53 ± 3.0	39.7 ± 2.0	44.2 ± 2.2	55.5 ± 3.1	45.3 ± 5.2
PVR [dynes]	896 ± 163	608 ± 57.7	1029 ± 119	663 ± 81	856 ± 78	939 ± 69	769 ± 267
CO [l/min]	4.46 ± 0.9	5.3 ± 0.5	4.0 ± 0.4	4.4 ± 0.3	3.8 ± 0.2	3.9 ± 0.2	4.5 ± 1.1
SAP [mmHg]	98 ± 8.1	88.5 ± 3.1	80.5 ± 3.6	86.1 ± 2.0	96.3 ± 2.5	91.2 ± 5.1	99 ± 3.2
SaO_2 [%]	85.3 ± 4.5	90.0 ± 1.2	89.5 ± 1.2	90.6 ± 0.5	92.8 ± 1	92 ± 1.2	94.2 ± 1.3
SvO_2 [%]	57.5 ± 3.9	65.5 ± 1.7	59.0 ± 3.8	62.5 ± 1.6	63.6 ± 1.1	62 ± 3.6	66.3 ± 1.5

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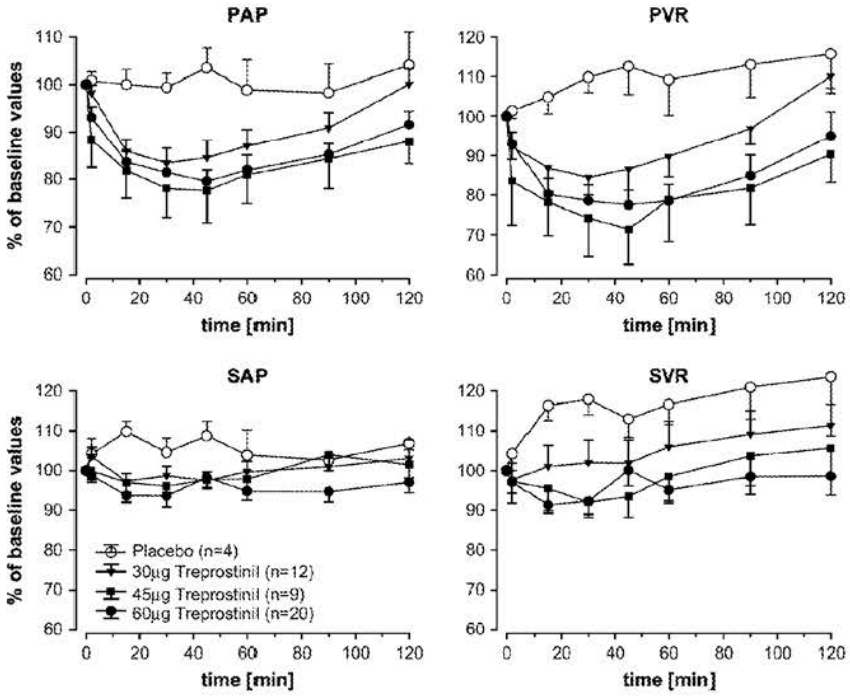

Fig. 1. Pulmonary and systemic changes in haemodynamics following the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg treprostinil (black circles) applied by a metered dose inhaler. Metered dose inhaler application of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 min at doses of 45 and 60 µg. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 min. Baseline was set as 100%. PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SAP = systemic arterial pressure; SVR = systemic vascular resistance. Data are given as mean ± SEM. One way ANOVA for repeated measurements was performed compared placebo and treprostinil: $p < 0.01$ for PVR, PAP, and SVR (all doses). SAP was not changed with 30 or 45 µg, but significant with 60 µg treprostinil ($p < 0.01$).

"negative" effect of placebo inhalation had proven to be very reproducible no new placebo data were derived but taken from a previous study in order not to expose additional patients to prolonged catheter time. The effect of MDI-TRE on systemic vascular resistance and pressure was not clinically significant. Cardiac output was increased over the whole observation period, whereas heart rate was rather unchanged. Arterial oxygen saturation was not influenced by MDI-TRE (Fig. 2). The maximal changes in haemodynamic and gas exchange parameters compared to baseline values are depicted in Table 2. Statistical analysis of PVR, PAP and cardiac output (one way ANOVA for repeated measurements) showed significant changes for all treprostinil doses compared to placebo. Systemic pressure was significantly affected in the highest dose group of 60 µg MDI-TRE (Figs. 1 and 2). In addition, areas under the curve for PVR were calculated for placebo and MDI-TRE doses for the 120 min observation period (Fig. 3). Significant effects of 45 and 60 µg MDI-TRE compared to placebo were observed.

4.3. Comparison of nitric oxide and MDI-TRE effects

We compared the acute effects of NO inhalation and treprostinil inhalation intra-individually. Mean PAP, PVR and CO changes due to nitric oxide inhalation were not significantly different from MDI-TRE induced changes (Fig. 4). The values for mPAP at NO baseline vs. MDI-TRE baseline in the three dose groups (30, 45, 60 µg) were 43.4 ± 2.9 vs. 41.0 ± 2.5 mmHg, 53.0 ± 2.7 vs. 49.1 ± 3.2 mmHg, and 40.1 ± 2.3 vs. 39.0 ± 2.5 mmHg, respectively. The baseline values for PVR in the groups receiving 30, 45 or 60 µg MDI-TRE were 603 ± 76 vs. 585 ± 58 dynes*s*cm^{-5}, 1070 ± 100 vs. 939 ± 102 dynes*s*cm^{-5}, and 660 ± 72 vs. 667 ± 67 dynes*s*cm^{-5}. Nitric oxide reduced mPAP to 36.2 ± 2.7 (30 µg MDI-TRE group), 43.8 ± 3.4 (45 µg MDI-TRE group) and 35.4 ± 2.8 (60 µg MDI-TRE group). Nitric oxide reduced PVR to 497 ± 63 dynes*s*cm^{-5} (30 µg MDI-TRE group), 802 ± 100 dynes*s*cm^{-5} (45 µg MDI-TRE group) and 616 ± 81 dynes*s*cm^{-5} (60 µg MDI-TRE group).

4.4. Comparison of treprostinil application by MDI or ultrasonic nebuliser

For better judgement, the MDI findings were compared with a historical cohort from our center that was investigated with very similar treprostinil doses (32 µg, 48 µg, 64 µg) inhaled by the ultrasonic nebuliser Optineb (Nebutec, Elsenfeld, Germany) which is also used in the current phase IIb trial. Data from this cohort have been published before [8] but we felt it would be meaningful to present a direct comparison (Fig. 5). The comparison (which is not an intra-individual comparison) showed quite similar responses in terms of PVR reduction for all respective dose groups. Fig. 5 shows only the 45 µg/48 µg comparison, the two other dose pairs (30 µg/32 µg and 60 µg/64 µg) were comparable.

4.5. Ventilation/perfusion distributions

To assess the impact of MDI-TRE on gas exchange and intrapulmonary ventilation–perfusion matching in detail, multiple inert gas elimination technique was used in 5 patients that displayed gas exchange problems already at baseline. These patients were chosen because they are believed to be more prone to gas exchange deterioration induced by pulmonary vasodilators. Characteristics of these patients were PAP 54.6 ± 3.2 mmHg, PVR 892 ± 88 dynes, SaO_2 91.7 ± 0.5%, SvO_2 65.2 ± 1.8%. Aetiologies were iPAH ($n = 2$),

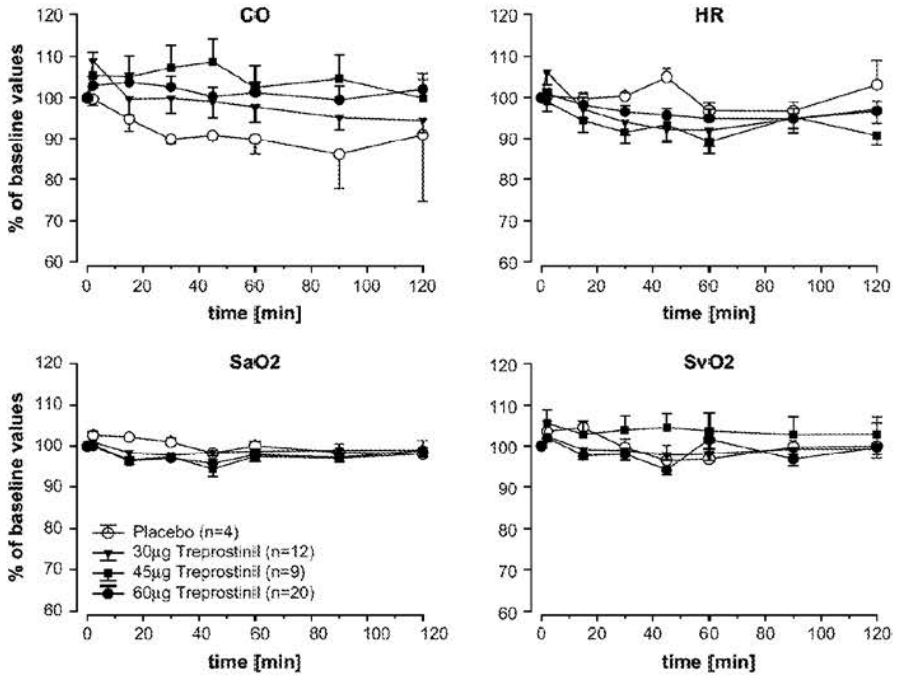

Fig. 2. Haemodynamic changes induced by the inhalation of placebo (open circles), 30 µg treprostinil (triangles), 45 µg treprostinil (squares) or 60 µg treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 min. Baseline was set as 100%. CO = cardiac output; HR = heart rate; SaO_2 = arterial oxygen saturation; SvO_2 = central venous oxygen saturation. Data are given as mean ± SEM. One way ANOVA for repeated measurements was performed compared placebo and treprostinil: CO ($p < 0.01$ for all doses), HR and SaO_2 were not significant. SvO_2 was significantly changed only by 45 µg treprostinil ($p < 0.01$).

CTEPH ($n = 3$). The maximal relative reduction of SaO_2 after inhalation of MDI-TRE in these patients was −3.8 ± 1.5% compared to baseline values. Shunt flow at baseline, during nitric oxide inhalation and 60 min after MDI-TRE inhalation was 6.4 ± 4.3%, 5.4 ± 3.0% and 8.3 ± 3.4% (n.s.), respectively (mean ± 95% confidence interval; Fig. 6).

5. Discussion

Inhaled treprostinil is the most recent development of non-parenteral prostanoid application. It necessitates only four inhalations per day for clinical efficacy and may be applied in approximately 1 min by use of an ultrasonic nebuliser [7,8]. The current ultrasonic nebulisers at hand for PAH therapy are highly developed instruments but still are quite cumbersome to handle, to clean and to sterilise and also comprise a substantial size and weight to carry. The Inhalation from a metered dose inhaler

Table 2
Maximal changes of haemodynamic parameters in percent from baseline values following metered dose inhaler delivery of placebo ($n = 4$), 30 µg treprostinil ($n = 12$), 45 µg treprostinil ($n = 9$) or 60 µg treprostinil ($n = 20$). Highest (max) or lowest (min) values observed during the observation period are shown. Data are given mean ± SEM. PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate.

	Placebo	30 µg TRE	45 µg TRE	60 µg TRE
PAP (min)	−0.6 ± 3.0	−16.6 ± 3.2	−22.4 ± 6.8	−20.5 ± 2.4
PVR (min)	+1.4 ± 1.9	−15.6 ± 4.4	−28.6 ± 8.9	−22.5 ± 3.7
CO (max)	−0.3 ± 1.1	+8.8 ± 3.8	+8.6 ± 5.6	+3.8 ± 2.0
SVR (min)	+4.3 ± 4.3	−2.3 ± 4.2	−8.0 ± 3.9	−8.7 ± 2.1
SAP (min)	+2.7 ± 1.7	−2.7 ± 1.9	−3.9 ± 1.5	−6.4 ± 2.9
HR (max)	+5.0 ± 2.1	−6.1 ± 2.9	−0.9 ± 2.4	+1.1 ± 0.9

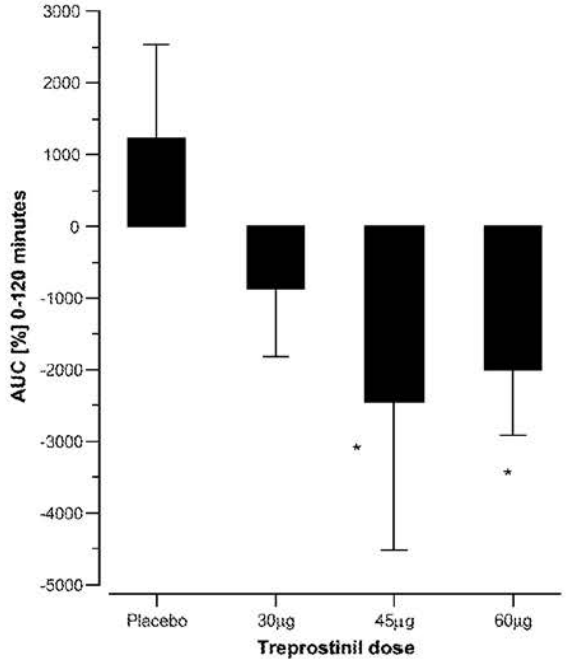

Fig. 3. Areas under the curve for changes in pulmonary vascular resistance (PVR) were calculated for an observation period of 120 min after inhalation metered dose inhaler application of treprostinil. PVR was markedly lowered, the increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean ± 95% confidence intervals. Asterisks mark significant differences compared to placebo ($p < 0.05$).

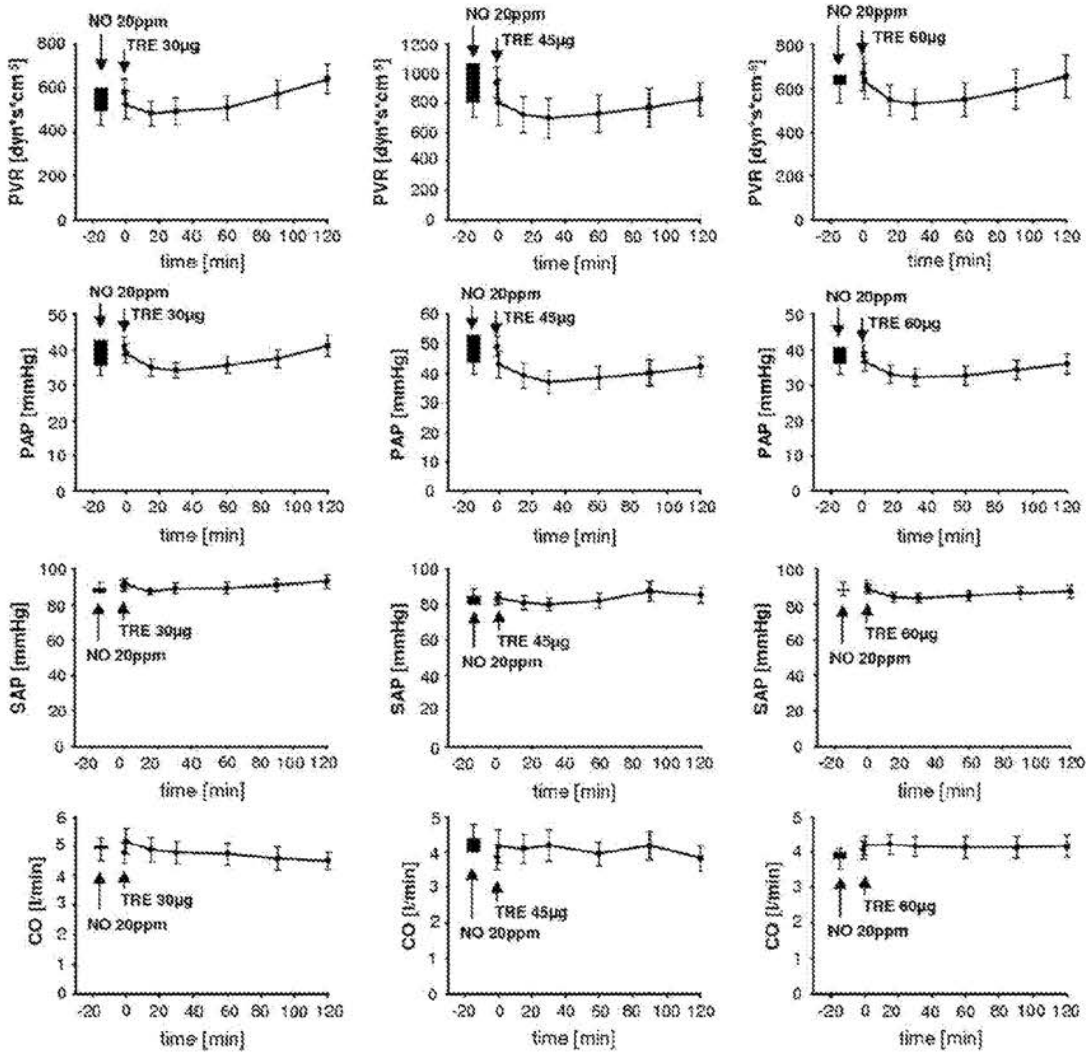

Fig. 4. Comparisons of the haemodynamic effects elicited by nitric oxide (bars) and treprostinil (lines). The data on pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (PAP), mean systemic pressure (SAP) and cardiac output (CO) are presented for the three groups receiving either 30 µg, 45 µg or 60 µg treprostinil from the metered dose inhaler. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 min. Baseline was set as 100%. Data are shown as mean ± 95% confidence intervals in absolute values.

would provide several advantages with respect to instrument size, ease of use and minimal exposure of patients who need to take their therapy in public. We provide data on inhaled treprostinil applied by a metered dose inhaler with focus on the safety, feasibility and acute haemodynamic effects. The inhalation of 2–3 puffs treprostinil from the MDI induced pulmonary selective vasodilatation with a peak effect after 30–45 min and a sustained haemodynamic effect at the end of the observation period of 2 h.

Prostacyclin is not feasible for inhalation due to its very short half life of only a few minutes. Iloprost leads to potent and selective pulmonary vasodilatation after a single inhalation of the approved doses of 2.5–5 µg. The acute effect of inhaled iloprost may last up to 90 min [13]. Long term treatment with repetitive inhalations of iloprost was shown also to reduce pulmonary vascular resistance at trough levels and to improve patient exercise capacity and survival [5]. A dose of more than 5 µg iloprost per inhalation or a reduction of inhalation time to less than 3 min induces in most patients considerable systemic prostanoid side effects like hypotension, dizziness, headache, jaw pain, nausea or diarrhoea. It was an unanticipated finding that treprostinil, besides the positive consequences of a longer half life for inhalation therapy, was tolerated at single doses up to 60 µg without relevant side effects. The inhalation of an effective treprostinil dose in one single breath was achieved with highly concentrated treprostinil sodium solution of 2000 µg/ml without side effects [8]. We believe that the absence of systemic side effects despite rapid application of treprostinil in high doses is provided by an outstanding pulmonary selectivity of inhaled treprostinil. The reasons for this can be speculated on as being due to storage and slow release of treprostinil in the lung tissue or alveolar lining layer. This phenomenon should be addressed in further studies on pharmacokinetics, tissue distribution and receptor binding and activation. In addition, differential prostanoid-receptor expression in pulmonary and systemic vascular beds could cause preferential pulmonary vasodilatation and less systemic effects [14]. In this respect it has been shown

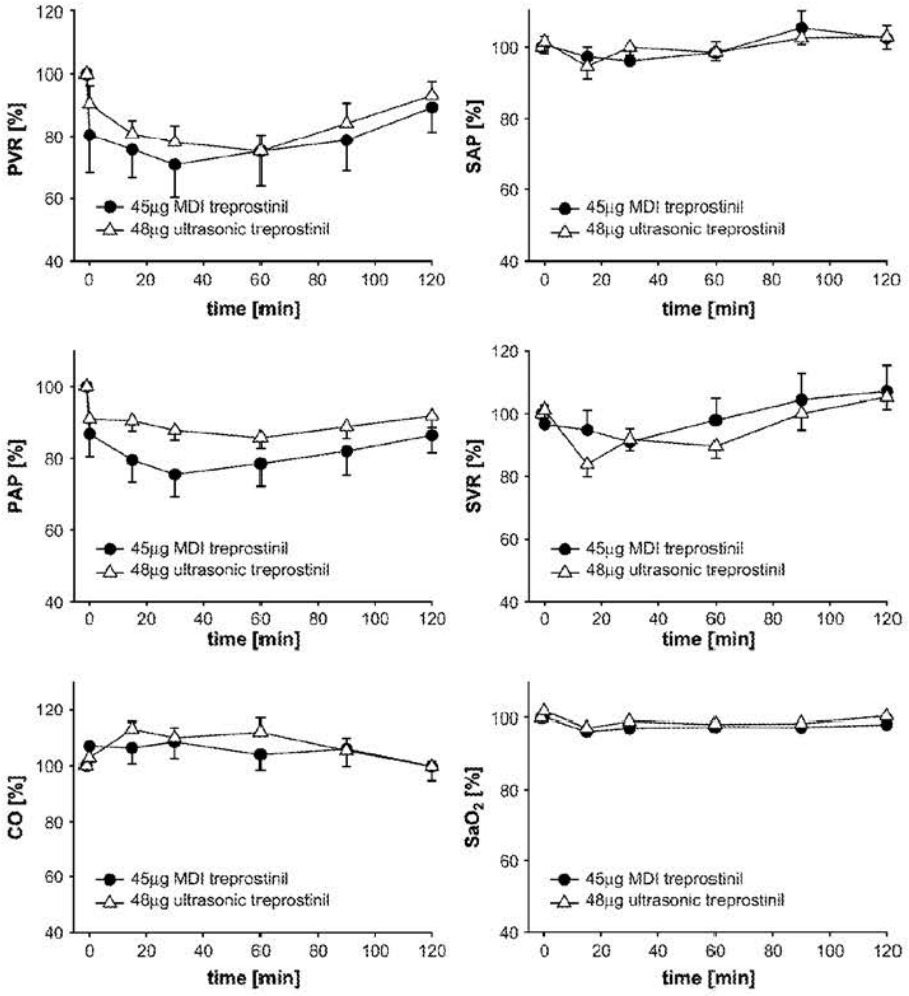

Fig. 5. Comparison of treprostinil inhalation with a metered dose inhaler (closed circles) and ultrasonic nebulisation (open triangles). MDI-treprostinil was applied in seconds as a 45 µg dose at the mouthpiece and compared to 48 µg ($n = 6$) treprostinil delivered by an ultrasonic nebuliser over 6 min of continuous inhalation time, respectively. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 min. Baseline was set as 100%. Data are shown as mean ± 95% confidence intervals as percent of baseline (baseline set to 100%). One way ANOVA for repeated measurements was performed compared MDI-TRE and ultrasonic nebulisation. No significant differences between devices were observed ($p > 0.05$ for all parameters).

recently in macrophages that treprostinil, in opposite to PGI2 and iloprost, does not only activate the IP receptor but also the EP2 receptor [15]. Another sign for partial pulmonary vascular selectivity of treprostinil is that about twofold dose of inhaled treprostinil achieves the same acute vasodilation as compared to inhaled iloprost [8]. If given intravenously up to 10-fold higher doses of treprostinil (20–60 ng/kg/min) are tolerated as compared to iloprost (2–5 ng/kg/min) [3,16].

We show that the effects of metered dose inhaler-treprostinil on pulmonary haemodynamics are similar or superior to the acute effects of inhaled nitric oxide. MDI-treprostinil compared to 6 min continuous inhalation ultrasonic nebuliser inhalation achieved similar results for 30/32 µg, 45/48 µg and 60/64 µg dose comparisons.

The aerodynamic aerosol diameter of MDI treprostinil of 4–5 µm is certainly at the upper limit for alveolar deposition, so reduction of aerodynamic aerosol diameter might improve MDI-TRE deposition.

The inhalation of a highly concentrated aerosol is theoretically prone to disturbances of gas exchange, because the deposition of even small amounts of aerosol may deposit significant drug doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This might lead to increase in shunt flow and low V/Q areas. We addressed this question in selected patients with MIGET, the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected based on pre-existing gas exchange limitations. We did not find a significant increase in low V/Q areas or shunt fraction after inhalation of MDI-TRE, in fact the distribution of perfusion was not different to that at baseline or nitric oxide inhalation. This proves an excellent matching of MDI-TRE induced vasodilatation to local ventilation which is also reflected by unchanged arterial oxygen saturations.

This study had certain limitations: a direct intra-individual comparison of ultrasonic and MDI drug application was not done due to the long lasting drug effect and limited catheter time. The groups that received different treprostinil doses are not very large and heterogeneous with respect to severity of disease and distribution of aetiologies. Therefore direct dose-effect correlations cannot be obtained. However, this study was designed to prove the

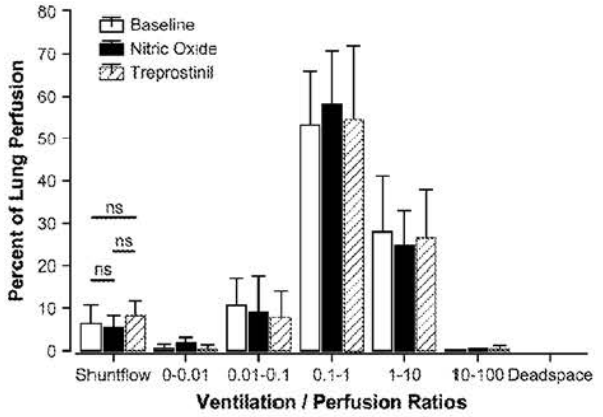

Fig. 6. Ventilation/perfusion matching assessed with the multiple inert gas elimination technique. Five patients (30 μg TRE, $n = 2$; 45 μg TRE, $n = 1$; 60 μg TRE, $n = 2$) with pre-existing gas exchange limitations were investigated for changes in ventilation–perfusion ratios. All patients presented with significant shunt flow at baseline. Shunt flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation from a metered dose inhaler (MDI-TRE; ns = not significant). MDI-TRE applied at high treprostinil concentrations did thus not negatively affect ventilation–perfusion matching and gas exchange. Data are given as mean ± 95% confidence intervals.

feasibility and safety of MDI treprostinil application and did not primarily address dose effects or clinical efficacy. Safety can only be reported for single drug inhalation in this report, no safety data for long term MDI-TRE application were determined.

6. Conclusion

Inhaled treprostinil is the first prostacyclin analogue which can be applied in effective doses by a metered dose inhaler in seconds. This may provide a breakthrough for inhaled pulmonary hypertension therapy in terms of device size, ease of handling, patient autonomy and compliance. The long term efficacy of this approach needs to be addressed in a controlled clinical trial.

Funding sources

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Conflict of interest

R. Voswinckel, B. Enke, F. Reichenberger, A. Kreckel, S. Krick, R.T. Schermuly, T. Schmehl, T. Gessler and H. Gall have nothing to disclose. H.A. Ghofrani receives grant and contract support by Pfizer Ltd., Altana Pharma AG, Schering AG; in addition, he serves on advisory board of Pfizer Ltd.. F. Grimminger receives grant and contract support by Pfizer Ltd. and Altana Pharma AG. W. Seeger receives grant and contract support by Schering, Altana Pharma, Myogen Inc. Westminster, LungRX and Aventis Pharma. H. Olschewski, is consultant and investigator for Schering AG, LungRX, CoTherix, Encysive and Myogen and received research grants from Schering AG. L.J. Rubin is investigator and consultant for Actelion, Pfizer, LungRx, Gilead, MondoBiotech, Encysive and Schering.

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Guidance for Industry

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2002

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Guidance for Industry

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GUIDANCE FOR INDUSTRY[1]

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This document provides guidance for industry on the chemistry, manufacturing, and controls (CMC) documentation that should be submitted in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for nasal spray and inhalation solution, suspension, and spray drug products intended for local and/or systemic effect. This guidance covers CMC information recommended for inclusion in the application regarding the drug product components, manufacturing process, and associated controls for each of these areas, but does not address the manufacture of drug substances. The guidance also provides recommendations on labeling. This guidance does not address propellant-based inhalation and nasal aerosols (also known as oral and nasal metered-dose inhalers, MDIs), inhalation powders (also known as dry powder inhalers, DPIs), and nasal powders.[2]

This guidance sets forth information that should be provided to ensure continuing quality and performance characteristics for these drug products. The guidance does not impose mandatory requirements but does suggest approaches that are appropriate for submitting CMC-related regulatory information. The guidance provides recommendations for drug

[1] This guidance has been prepared by the Inhalation Drug Products Working Group of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMCCC) in the Center for Drug Evaluation and Research (CDER) at the FDA.

[2] In November 1998 (63 FR 64270), the Agency made available a draft guidance document on *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*. When finalized, this guidance will provide CMC recommendations for MDIs and DPIs.

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products that are used to treat a variety of diseases and patient populations. Therefore, CMC recommendations may vary depending on the specific drug product and stage of development. For example, the recommendations in this guidance should be considered during the investigational stages and phased in by the initiation of critical clinical studies (phase 2 and phase 3 studies) to provide supporting documentation for an NDA. Applicants are encouraged to discuss significant departures from the approaches outlined in this guidance (including decisions to provide less CMC documentation than recommended) with the appropriate Agency review division before implementation to avoid expending resources on development avenues that may later be deemed inappropriate.

Reference to information in Drug Master Files (DMFs) for particular portions of the CMC section of the application is appropriate if the DMF holder provides written authorization that includes specific reference (e.g., submission date, page number, item name and unique identifier) to the pertinent and up-to-date information (21 CFR 314.420(d)). Refer to FDA's *Guideline for Drug Master Files* (September 1989) for more information about DMFs.

II. BACKGROUND

A. Nasal Sprays

Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in nonpressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump or could have been premetered during manufacture. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local and/or systemic effects.

Although similar in many features to other drug products, some aspects of nasal sprays may be unique (e.g., formulation, container closure system, manufacturing, stability, controls of critical steps, intermediates, and drug product). These aspects should be considered carefully during the development program because changes can affect the ability of the product to deliver reproducible doses to patients throughout the product's shelf life. Some of the unique features of nasal sprays are listed below:

- Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation, and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition.

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- Energy is required for dispersion of the formulation as a spray. This is typically accomplished by forcing the formulation through the nasal actuator and its orifice.

- The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product. The design of the container closure system affects the dosing performance of the drug product.

- The concept of classical bioequivalence and bioavailability may not be applicable for all nasal sprays, depending on the intended site of action. The doses administered are typically so small that blood or serum concentrations are generally undetectable by routine analytical procedures. Additional information will be provided in a future guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.*[3]

B. Inhalation Solutions and Suspensions

Inhalation solution and suspension drug products are typically aqueous-based formulations that contain therapeutically active ingredients and can also contain additional excipients. Aqueous-based oral inhalation solutions and suspension must be sterile (21 CFR 200.51). Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local and/or systemic effects and are to be used with a specified nebulizer. Unit-dose presentation is recommended for these drug products to prevent microbial contamination during use. The container closure system for these drug products consists of the container and closure, and can include protective packaging such as foil overwrap. Recommendations on overwrapping of inhalation drug products packaged in semipermeable container closure systems are provided in section III.G.5.

C. Inhalation Sprays

An inhalation spray drug product consists of the formulation and the container closure system. The formulations are typically aqueous based and, by definition, do not contain any propellant. Aqueous-based oral inhalation sprays must be sterile (21 CFR 200.51). Inhalation sprays are intended for delivery to the lungs by oral inhalation for local and/or systemic effects. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multidose presentations. The use of preservatives or stablilizing agents in inhalation spray formulations is

[3] A notice of availability for the June 1999 draft guidance Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action published in the Federal Register on June 24, 1999 (64 FR 33869).

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discouraged. If these excipients are included in a formulation, their use should be justified by assessment in a clinical setting to ensure the safety and tolerability of the drug product. The dose is delivered by the integral pump components of the container closure system to the lungs by oral inhalation for local and/or systemic effects. The container closure system of these drug products consists of the container, closure, and pump, and can also include protective packaging.

Current container closure system designs for inhalation spray drug products include both **premetered** and **device-metered** presentations using mechanical or power assistance and/or energy from patient inspiration for production of the spray plume. Premetered presentations contain previously measured doses or a dose fraction in some type of units (e.g., single or multiple blisters or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Typical device-metered units have a reservoir containing formulation sufficient for multiple doses that are delivered as metered sprays by the device itself when activated by the patient.

Inhalation spray and nasal spray drug products have many similarities. Therefore, many of the unique features listed in section II.A for nasal sprays are also characteristic of inhalation spray drug products. Moreover, the potential wide array of inhalation spray drug product designs with unique characteristics will present a variety of development challenges. Regardless of the design, the most crucial attributes are the reproducibility of the dose, the spray plume, and the particle/droplet[4] size distribution, since these parameters can affect the delivery of the drug substance to the intended biological target. Maintaining the reproducibility of these parameters through the expiration dating period and ensuring the sterility of the content and the functionality of the device (e.g., spray mechanism, electronic features, sensors) through its lifetime under patient-use conditions will probably present the most formidable challenges. Therefore, changes in components of the drug product or changes in the manufacturer or manufacturing process that can affect these parameters should be carefully evaluated for their effect on the safety, clinical effectiveness and stability of the product. If such changes are made subsequent to the preparation of the batches used in critical clinical, bioequivalence, or primary stability studies, adequate supportive comparative data should be provided to demonstrate equivalency in terms of safety, clinical effectiveness, and stability of the product.

The remaining portion of this guidance will focus on specific chemistry, manufacturing, and controls information recommended for inclusion in the drug product section of applications for nasal spray and inhalation solution, suspension, and spray drug products.

[4] The term *particle/droplet* refers to a combination of droplets and particles or droplets alone, depending on the formulation and conditions of measurement.

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III. DRUG PRODUCT

A. Formulation Components

A list of all components (i.e., ingredients) used in the manufacture of the drug product formulation, regardless of whether they undergo chemical change or are removed during manufacture, should be included in the application. Each component should be identified by its established name, if any, and by its complete chemical name, using structural formulas when warranted for specific identification. If any proprietary preparations or other mixtures are used as components, their identity should be fully described including a complete statement of their composition and other information that will properly identify the material.

B. Formulation Composition

The application should include a statement of the quantitative composition of the unit formula of the drug product, specifying the name and amount of each active ingredient and excipient contained in a stated quantity of the formulation. For components in the final formulation, the amounts should be expressed in concentration (i.e., amount per unit volume or weight), as well as amount per container and per spray, where applicable. The target container net content should also be indicated. Similarly, a production batch formula representative of the one to be employed in the manufacture of the drug product should be included. Any calculated overage for an ingredient should be designated as such and the percentage shown. The overage should be scientifically justified and documented in both the unit formula and batch formula. For these products, overages can be included only for justified reproducible manufacturing losses and/or for an ANDA product to match the overage present in the Reference Listed Drug. Any intended change in the formulation of the commercial product from that used in the submitted batches (e.g., critical clinical, biobatch, primary stability, production) should be clearly indicated by providing the composition of each formulation.

The composition of suspension formulations may be crucial in defining the physical stability and the performance characteristics of the drug product. The density and suspension properties of the solid materials of the formulation and the potential for agglomeration should be considered. Moreover, interaction of the suspended drug substance with the various internal container closure system components can also contribute to a nonhomogeneous distribution of drug substance. The above mentioned phenomena, which may be exacerbated with time, can contribute to inconsistent particle size distribution and medication dose delivery. See also the discussions in sections III.F.1.c and III.F.2.c.

C. Specifications for the Formulation Components

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1. Active Ingredients

Information regarding the comprehensive characterization of the physical and chemical properties of the drug substance should be included in the application. Important properties of the drug substance used in suspension formulations can include, but are not necessarily limited to, density, particle size distribution, particle morphology, solvates and hydrates, polymorphs, amorphous forms, solubility profile, moisture and/or residual solvent content, microbial quality, dissociation constants (pKa), and specific rotation.

Appropriate acceptance criteria and tests for routine control (i.e., release, stability, and retest) should be instituted for those drug substance parameters considered key to ensuring reproducibility of the physicochemical properties of the drug substance. Specification parameters can include, as applicable, color, appearance (visual and microscopic), specific identification, moisture, residue on ignition, specific rotation, assay, impurities, microbial limits (U.S. Pharmacopeia (USP) <61>)[5], melting range, particle size distribution, crystalline forms, amorphous content, residual solvents, and heavy metals. Some of these parameters may not be pertinent for drug substances used in solution formulations.

The purity of the drug substance and its impurity profile should be characterized and controlled with appropriate specifications. Important impurity-related parameters can include organic volatile impurities and/or residual solvents, organic impurities (synthesis-related and degradation products), and inorganic impurities (e.g., heavy metals, reagents, catalysts). Any impurity found in the drug substance at a concentration of 0.10 percent or 1.0 milligram (mg) per day intake (whichever is lower), relative to the parent drug substance, should be identified. Moreover, the drug substance impurities should be appropriately qualified. Justification of acceptance criteria for the drug substance impurities should be based on toxicological considerations and levels of impurities found in the submitted batches (e.g., critical clinical, biobatch, primary stability, production). For guidance on toxicological qualification, the applicant is encouraged to refer to the following guidance documents: (1) ICH *Q3A Impurities in New Drug Substances* (January 1996),[6] (2) *NDAs: Impurities in Drug Substances* (February 2000), and (3) *ANDAs: Impurities in Drug Substances* (November 1999). The applicant can also contact the responsible review division for guidance on toxicological qualification.

For suspension formulations, the specification for drug substance should include controls for particle size distribution and physical properties (e.g., shape, crystal

[5] Sample size for microbial limits testing should be 10 grams unless otherwise justified.

[6] The guidance, *Q3A Impurities in New Drug Substances*, will be superseded by FDA's guidance for industry, *Q3A(R) Impurities in New Drug Substances*, once it is issued in final form. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

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habit, morphology, surface texture) of the drug substance, parameters that are often critical for reproducible drug product performance. If laser diffraction methodology is used for testing the particle size distribution, it is crucial that test procedure instrumental parameters (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, beam width) be defined accurately and with sufficient detail for Agency laboratories to validate the adequacy of the methodology. In addition, the potential effect of micronization processes on the levels of amorphous content and foreign particulates in the drug substance should be considered.

In general, acceptance criteria for all parameters defining the physicochemical properties should be based on historical data, thereby providing continuity of quality and reproducible performance of future batches of the drug substance. For additional information on various aspects of drug substance chemistry, manufacturing, and controls documentation, see the FDA *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987).

2. Excipients

Because of the route of administration and the sensitive nature of various patient populations using oral inhalation (solution, suspension, spray) drug products, more thorough characterization with additional comprehensive controls (e.g., strength, quality, purity), as compared to drug products for other routes of administration, should be considered for excipients used in these drug products. Moreover, for nasal and inhalation suspension formulations, additional controls should be applied to critical excipients to ensure safety and effectiveness of the drug product. Critical excipients for suspension formulations (e.g., microcrystalline cellulose for nasal sprays) are those that can affect the suspension and/or particle characteristics and, therefore, the quality, stability, or performance of the drug product. The suitability of the physicochemical properties of these critical excipients should be thoroughly investigated and documented.

Unless otherwise indicated, the comments below regarding excipients pertain to nasal spray and inhalation solution, suspension, and spray drug products.

The source of each excipient should be assessed, and the material supplied should meet appropriate acceptance criteria that are based on test results from a minimum of one batch used to prepare the submitted batches of drug product (e.g., critical clinical, biobatch, primary stability, production). However, for critical excipients of suspension formulations, the sources should be identified and test results from multiple batches should be provided. Likewise, when the supplier of an excipient is changed prior to submission of the application, the new supplier's ability to

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provide material of comparative quality should be assessed and supporting data should be provided.

For noncompendial excipients, appropriate authorization to a DMF that provides information on the noncompendial excipient or an equivalent package of information prepared by the excipient manufacturer should be provided in the application. The information should include analytical procedures, acceptance criteria, and a brief description of the manufacture and controls.

When a USP or *National Formulary* (NF) monograph material is used, the associated specifications may not always provide adequate assurance with regard to the assay, quality, or purity of the material or its performance in the drug product. In these cases, monograph specifications should be supplemented with appropriate controls (e.g., particle size distribution, crystal forms, amorphous content, foreign particulates) to ensure batch-to-batch reproducibility of these components. This can be particularly relevant for compendial excipients that have an impact on the purity of inhalation drug products or performance properties (e.g., droplet and particle size distribution, spray content uniformity) of suspension drug products. The additional test procedures should be included, and the acceptance criteria should reflect the data for the excipients used in the submitted batches (e.g., critical clinical, biobatch, primary stability, production). Acceptance criteria for physicochemical parameters of a qualified polymeric excipient (e.g., molecular weight distribution, viscosity) that are wider than what is reflective of the data on the submitted batches can be justified by demonstrating that the proposed ranges of the excipient attributes do not adversely affect the quality of the drug product. Justification should be based on adequate release and stability data that is specific to the drug product prepared with the excipient attributes near the limits of the allowable range.

The suitability of the toxicological properties of the excipients for these drug products should be thoroughly investigated and documented. Toxicological qualification of these excipients may be appropriate under various circumstances, including (1) increased concentration of an excipient above that previously used in inhalation and nasal drug products, (2) excipients that have been used previously in humans but not by the inhalation or nasal route, and (3) novel excipients not previously used in humans in the United States. The extent of toxicological investigation to qualify the use of an excipient under such circumstances will vary, and the applicant is encouraged to contact the responsible review division to discuss an appropriate strategy for toxicological qualification.

If excipients are accepted based on certificates of analysis from the manufacturers with the applicant performing a specific identification test upon receipt, the applicant should also develop validated procedures, have access to all of the manufacturer's analytical and other test procedures, or use contract laboratories to allow them to establish the reliability of the test results at appropriate intervals, as required under 21 CFR 211.84. The applicant should confirm the supplier's

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results by (1) testing an adequate number of batches of each excipient used in preparing the submitted drug product batches (e.g., critical clinical, primary stability, biobatch, production batches) and (2) providing a commitment to test a predetermined number of batches of each excipient used in preparing postapproval drug product batches.

D. Manufacturers

The name, street address, and, if available, registration number[7] of each facility involved in the manufacture of the drug substance should be listed along with a statement of each manufacturer's specific operations and responsibilities. The same information should be provided for each facility involved in the manufacturing, processing, packaging, controls, stability testing, or labeling of the drug product, including all contractors (e.g., test laboratories, packagers, labelers). For sterile drug products, building numbers, filling rooms, and filling lines should also be identified. Manufacturers of critical and novel excipients should be identified by name and address.

E. Method of Manufacture and Packaging

A detailed description of the manufacturing, processing, and packaging procedures for the drug product should be included.

All aqueous-based oral inhalation drug products must be manufactured as sterile products (21 CFR 200.51), and their sterility should be ensured through the expiration dating period.

If micronization is used for the drug substance and/or excipients, the process should be fully validated and the equipment, operating conditions, and process controls should be described in detail. For example, the description of the controls for a milling operation could include the rate of feed, air pressure, air flow rate, particle size being fed, number of times a lot is micronized, re-use of carryovers from previous micronized lots. Potential contamination of the material during the micronization process should be controlled with appropriate tests and acceptance criteria. See the discussion of testing attributes specific for micronized material (e.g., particle size distribution, crystal forms, amorphous content, foreign particulates) discussed in section III.C.1.

A copy of the actual (executed) batch record, including process controls, and controls for critical steps and intermediates should be submitted, as appropriate, for representative batches (e.g., critical clinical, biobatch, primary stability). A schematic diagram of the proposed production process, a list of process controls, and a master batch production and controls record should be submitted. A brief

[7] Information on when registration is required and how to register is available in 21 CFR 207.

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description of the packaging operations and associated process controls for these operations should also be included.

The manufacturing directions should include control procedures and specific information on processing variables (such as times, mixing speeds, and temperatures) to decrease controllable process variability and increase consistency in the quality of the drug product. Any formulation overfill per container to achieve a labeled deliverable volume should be appropriately justified.

A description of the controls for critical steps and intermediates, a description of the associated analytical procedures, and appropriate data to support the acceptance criteria should be provided. These controls should be performed at specified production steps and can include, for example, assay, osmolality, pH, viscosity, consistency of filling, and quality of sealing.

If protective packaging (such as a foil overwrap) is used for the drug product, the application should include a brief description of the primary and protective packaging operations and relevant process controls. In these cases, proper sealing, in terms of adhesion (e.g., heat seal, adhesive) or mechanical seal of the protective packaging, should be ensured. Appropriate integrity testing and acceptance criteria for seal completeness and for seal strength should be established to ensure acceptable sealing properties within a batch and among batches.

See section III.G.5 for recommendations on the use of protective packaging and labeling by embossing or debossing for inhalation drug products packaged in semipermeable containers.

F. Specifications for the Drug Product

A complete description of the acceptance criteria and analytical procedures with analytical sampling plans (i.e., number of samples tested, individual or composite samples specified, number of replicate analyses per sample) should be provided to ensure the identity, strength, quality, purity, and performance of the drug product throughout its shelf life and during the period of patient use. The proposed validated test procedures should be documented in sufficient detail to permit validation by Agency laboratories.[8]

Comprehensive and well-defined in vitro performance characteristics should be established before initiating critical clinical or bioequivalence studies.

[8] Guidance relating to validation of analytical procedures is available in the ICH guidances (Q2A) *Text on Validation of Analytical Procedures* (March 1995) and *Q2B Validation of Analytical Procedures: Methodology* (November 1996) and CDER s guidance on *Submitting Samples and Analytical Data for Methods Validation* (February 1987). CDER s 1987 guidance will be superseded by the guidance on *Analytical Procedures and Methods Validation*, when finalized. A notice of availability for a draft version of this guidance published in the *Federal Register* on August 30, 2000 (65 FR 52776).

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Appropriate, validated test procedures and corresponding acceptance criteria that are reflective of the test results for submitted batches (e.g., critical clinical, biobatch, primary stability, production) are crucial to defining and controlling these characteristics.

1. Nasal Sprays

The following test parameters are recommended for nasal spray drug products. Appropriate acceptance criteria and validated test procedures should be established for each test parameter. In general, the acceptance criteria should be reflective of the data obtained from the submitted batches (e.g., critical clinical, biobatch, primary stability, production). Certain tests performed during the manufacturing process (e.g., pH, osmolality, viscosity, net content) can substitute for the release testing, if justified. However, the acceptance criteria should remain a part of the drug product specification.

a. Description

The appearance of the content of the container (i.e., formulation) and the container closure system (e.g., pump, container components) should conform to their respective descriptions (e.g., color and clarity of formulation, size and shape of pump components, texture of inside of the container) as an indication of the drug product integrity.

If any color is associated with the formulation (either present initially or from degradative processes occurring during shelf life), then a quantitative test with appropriate acceptance criteria should be established for the drug product.

b. Identification

A specific identification test or tests should be used to verify the identity of the drug substance in the drug product. Identification using a single chromatographic procedure is not considered to be specific. A second independent and complementary procedure (e.g., UV-spectroscopy, IR), two chromatographic procedures where the separation is based on different principles, or a combination of tests into a single procedure (e.g., HPLC/MS) should be used. If the drug substance is a salt, an identification test should be included for the counterion.

c. Assay

The assay of the drug substance in the container should be determined analytically with a stability indicating procedure unless the use of a nonstability indicating method is justified. Assay can be performed indirectly by determining concentration and actual net content, if justified. A suitable assay procedure should be designed to address potential

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stability issues such as degradation of the drug substance, adherence of the drug substance to the container and closure components, and the potential effect of solvent evaporation and/or leakage.

For a drug product that contains a chiral drug substance, an achiral assay can be used when studies have demonstrated that racemization is insignificant during manufacture of the drug product and on storage. Otherwise, a chiral assay or a combination of an achiral assay and a validated procedure to control the presence of the opposite enantiomer should be used.

d. Impurities and Degradation Products

The levels of impurities and degradation products should be determined by a validated analytical procedure or procedures. Acceptance criteria should be set for individual and total impurities and degradation products. All related impurities appearing at levels of 0.1 percent or greater should be specified. Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification. For identification and qualification thresholds and other relevant information, refer to ICH guidance *Q3B Impurities in New Drug Products* (November 1996) and, when finalized, the guidance for industry *ANDAs: Impurities in Drug Products* (December 1998).[9]

e. Preservatives and Stabilizing Excipients Assay

If preservatives, antioxidants, chelating agents, or other stabilizing excipients (e.g., benzalkonium chloride, phenylethyl alcohol, edetate) are used in the formulation, there should be a specific assay for these components with associated acceptance criteria. Acceptance criteria for the chemical content of preservatives at the time of product release and through the product shelf life should be included in the drug product specification. For information on preservative effectiveness testing, refer to section IV.L below.

f. Pump Delivery

A test to assess pump-to-pump reproducibility in terms of drug product performance and to evaluate the delivery from the pump should be performed. The proper performance of the pump should be ensured primarily by the pump manufacturer, who should assemble the pump with parts of precise dimensions. Pump spray weight delivery should be verified by the applicant for the drug product. In general, pump spray weight delivery acceptance criteria should control the weight of the

[9] A notice of availability for this draft guidance published in the *Federal Register* on January 5, 1999 (64 FR 516).

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individual sprays to within • 15 percent of the target weight and their mean weight to within • 10 percent of the target weight. However, for small dosage pumps (e.g., 20 µL) other acceptance criteria may be justified. Acceptance testing for pump delivery on incoming pump lots can substitute for the release testing of pump delivery for the drug product, if justified. However, the acceptance criteria for pump delivery should be included in the drug product specification.

g. Spray Content Uniformity (SCU)

The spray discharged from the nasal actuator should be thoroughly analyzed for the drug substance content of multiple sprays from beginning to the end of an individual container, among containers, and among batches of drug product. This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. At most, two sprays per determination should be used except in the case where the number of sprays per minimum dose specified in the product labeling is one. Then the number of sprays per determination should be one spray. To ensure reproducible in vitro dose collection, the procedure should have controls for actuation parameters (e.g., stroke length, actuation force). The test can be performed with units primed following the instructions in the labeling. The amount of drug substance delivered from the nasal actuator should be expressed both as the actual amount and as a percentage of label claim.

This test is designed to demonstrate the uniformity of medication per spray (or minimum dose), consistent with the label claim, discharged from the nasal actuator, of an appropriate number (n = 10 from beginning and n = 10 from end) of containers from a batch. The primary purpose is to ensure SCU within the same container and among multiple containers of a batch.

The following acceptance criteria are recommended. However, alternative approaches (e.g., statistical) can be proposed and used if they are demonstrated to provide equal or greater assurance of SCU.

• • For acceptance of a batch (1) the amount of active ingredient per determination is not outside of 80 to 120 percent of label claim for more than 2 of 20 determinations (10 from beginning and 10 from end) from 10 containers, (2) none of the determinations is outside of 75 to 125 percent of the label claim, and (3) the mean for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.

  If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim,

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but none are outside of 75 to 125 percent of label claim and the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim, an additional 20 containers should be sampled for second-tier testing.

- For the second tier of testing of a batch, the acceptance criteria are met if (1) the amount of active ingredient per determination is not outside of 80 to 120 percent of the label claim for more than 6 of all 60 determinations, (2) none of the 60 determinations is outside of 75 to 125 percent of label claim, and (3) the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.

h. Spray Pattern and Plume Geometry

Characterization of spray pattern and plume geometry are important for evaluating the performance of the pump. 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 typically should be established during the characterization of the product and is not necessarily tested routinely thereafter. (See discussion of plume geometry testing for inhalation spray drug products in section III.F.2.p and for nasal spray drug products in section IV.K.)

The proposed test procedure for spray pattern should be provided in detail to allow duplication by Agency laboratories. For example, in the evaluation of the spray pattern, the spray distance between the nozzle and the collection surface, number of sprays per spray pattern, position and orientation of the collection surface relative to the nozzle, and visualization procedure should be specified. The acceptance criteria for spray pattern should include the **shape** (e.g., ellipsoid of relative uniform density) as well as the **size** of the pattern (e.g., no axis is greater than x millimeters and the ratio of the longest to the shortest axes should lie in a specified range, for example, 1.00• 1.30). Data should be provided to demonstrate that the collection distance selected for the spray pattern test will provide the optimal discriminatory capability. Variability in the test can be reduced by the development of a sensitive detection procedure and by providing procedure-specific training to the analyst.

Acceptance testing for spray pattern on incoming pump lots can substitute for the release testing of spray pattern for the drug product, if justified (e.g., spray patterns from pumps with drug product formulation and with the proposed simulating media are the same). However, the acceptance

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criteria for spray pattern should be included in the drug product specification.

i. 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. If a laser diffraction method is used, droplet size distribution can be controlled in terms of ranges for the D_{10}, D_{50}, D_{90}, span $[(D_{90}-D_{10})/D_{50}]$, and percentage of droplets less than 10 μm. Appropriate and validated and/or calibrated droplet size analytical procedures should be described in sufficient detail to allow accurate assessment by Agency laboratories (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, beam width).

For solution nasal sprays, acceptance testing for droplet size distribution on incoming pump lots with placebo formulation can substitute for the release testing of droplet size distribution for the drug product, if justified (i.e., droplet size distributions from pumps with drug product formulation and with the placebo are the same). However, the acceptance criteria for droplet size distribution should be included in the drug product specification.

j. Particle Size Distribution (Suspensions)

For suspension nasal sprays, the specification should include tests and acceptance criteria for the particle size distribution of the drug substance particles in the formulation. The quantitative procedure should be appropriately validated, if feasible, in terms of its sensitivity and ability to detect shifts that may occur in the distribution.

When examining formulations containing suspending agents in the presence of suspended drug substance, and it is demonstrated that the currently available technology cannot be acceptably validated, a qualitative and semiquantitative method for examination of drug and aggregated drug particle size distribution can be used. Supportive data, along with available validation information, should be submitted. For example, microscopic evaluation can be used and such an examination can provide information and data on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, and crystal growth.

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k. Particulate Matter

For both solution and suspension nasal sprays, there should be validated tests and associated acceptance criteria for particulate matter. Particulate matter can originate during manufacturing, from formulation components, and from the container and closure components. Levels of particulate matter in the drug product can increase with time, temperature, and stress. If stability data generated in support of the application demonstrate that levels of particulate matter do not increase with time, this can be sufficient to justify testing of this attribute only on batch release.

l. Microbial Limits

The microbial quality should be controlled by appropriate tests and acceptance criteria for total aerobic count, total yeast and mold count, and freedom from designated indicator organisms. For a description of this test, refer to the procedure in USP <61>. Furthermore, appropriate testing should show that the drug product does not support the growth of microorganisms and that microbiological quality is maintained throughout the expiration dating period.

m. Net Content

Nasal spray drug products should include acceptance criteria for net content of the formulation in the container. The net content of each test container should be in accordance with the release specification. For a description of this type of testing, refer to the procedure in USP Chapter <755> Minimum Fill.

n. Weight Loss (Stability)

Nasal spray drug products should include acceptance criteria for weight loss on stability. Since storage orientation plays a role in assessment of the sealing characteristics of the container closure system, weight loss for the drug product stored in upright and inverted or upright and horizontal positions should be evaluated.

o. Leachables (Stability)

The drug product should be evaluated for compounds that leach from elastomeric or plastic components of the container closure system. Examples of leachables are nitrosamines, monomers, plasticizers, accelerators, antioxidants, and vulcanizing agents. Refer to Glossary for definition of leachables and extractables. The development of validated analytical procedures to identify, monitor, and quantify leached components in the drug product should be done during investigational

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and/or development studies. These procedures can, in turn, be used for testing of the drug product throughout the expiration dating period. Appropriate acceptance criteria for the levels of leached compounds in the formulation should be established. For additional discussion, see the container closure system section of this guidance (section III.G). As stated in section III.G, if a correlation is established between levels of leachables in the drug product (through the shelf life or until an equilibrium is demonstrated) and the extractables of a drug product container and closure components, evaluation of leachables in future routine stability studies may not be needed. In general, the levels of extractables should be greater than the levels of leachables for the correlation to be considered valid.

p. pH

For both solution and suspension nasal sprays, the pH or apparent pH, as appropriate, of the formulation should be tested and an appropriate acceptance criterion established.

q. Osmolality

For formulations containing an agent to control the tonicity or for products having a label claim regarding tonicity, the osmolality of the formulation should be tested and controlled at release with an appropriate procedure and acceptance criterion.

r. Viscosity

For formulations containing an agent contributing to the viscosity, this parameter should be tested and controlled at release and on stability with an appropriate procedure and acceptance criterion.

2. Inhalation Solutions, Suspensions, and Sprays

The following test parameters are recommended for inhalation solution, suspension, and spray drug products. Appropriate acceptance criteria and validated test procedures should be established for each test parameter. In general, the acceptance criteria should be reflective of the data obtained from the submitted batches (e.g., critical clinical, biobatch, primary stability, production). Certain tests performed during the manufacturing process (e.g., pH, osmolality, viscosity, net content) can substitute for the release testing if justified. However, the acceptance criteria should remain a part of the drug product specification.

a. Description

See nasal sprays, section III.F.1.a.

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b. Identification

See nasal sprays, section III.F.1.b.

c. Assay

See nasal sprays, section III.F.1.c. For a semipermeable container closure system, the potential for off-setting assay loss from degradation with apparent assay gain from evaporative effects should be considered. For unit dose inhalation solutions and suspensions, test results for content uniformity can be substituted for assay.

d. Impurities and Degradation Products

See nasal sprays, section III.F.1.d.

e. Preservatives and Stabilizing Excipients Assay

If the use of preservatives or stabilizing excipients is justified (refer to section II.C), see nasal sprays, section III.F.1.e and section IV.L.

f. Sterility

All aqueous-based oral inhalation solutions, suspensions, and spray drug products must be sterile (21 CFR 200.51), i.e., labeled as sterile and confirmed by testing. For test methodology, refer to USP <71> Sterility Tests.

g. Particulate Matter

See nasal sprays, section III.F.1.k. The acceptance criteria should include limits for foreign particulate matter less than 10 micrometers (μm), greater than 10 μm, and greater than 25 μm.

h. pH

See nasal sprays, section III.F.1.p.

i. Osmolality

See nasal sprays, section III.F.1.q.

j. Net Content

See nasal sprays, section III.F.1.m.

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k. Weight Loss (Stability)

Acceptance criteria for the weight loss of individual units on stability should be included for inhalation drug products packaged in semipermeable container closure systems. The test is used to assess the moisture transmission properties of the container closure system and protective properties of a secondary packaging, when used.

l. Leachables (Stability)

See nasal sprays, section III.F.1.o. Additionally, for inhalation solutions and suspensions packaged in semipermeable containers (e.g., low density polyethylene) with protective packaging or if the immediate containers are indirectly exposed to components of the packaging that include paper labels (for example, inks, paper, adhesives components), the levels of the leachables originating from the packaging, labels, or related materials should be determined. Refer to section III.G. Procedures used for these determinations should be validated and have suitable detection and quantitation limits for the potential leachables. The associated acceptance criteria for the leached compounds should be toxicologically qualified and documented. Refer to section III.G .

m. Particle Size Distribution (Suspensions)

See nasal sprays, section III.F.1.j.

n. Pump Delivery for Inhalation Sprays

See nasal sprays, section III.F.1.f.

o. Spray Content Uniformity (SCU) for Inhalation Sprays

The recommendations for acceptance criteria and tests for SCU from the actuator/mouthpiece of inhalation sprays under defined optimum test conditions are the same as for nasal sprays (refer to section III.F.1.g). Acceptance criteria and tests would apply to both device-metered (e.g., reservoir) and premetered (e.g., blisters) inhalation spray drug products. For device-metered inhalation spray drug products, the SCU should be established and monitored at the beginning and end of the labeled number of sprays.

In addition, the content uniformity of the premetered dose units should be controlled by separate test and acceptance criteria.

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p. Plume Geometry for Inhalation Sprays

Characterization of plume geometry is important for evaluating the performance of inhalation sprays. The design of the device and the nature of the formulation are two characteristics that can affect the plume geometry.

Plume geometry can be evaluated by a variety of procedures (e.g., the time sequence sound-triggered high speed flash photography method, videotape recording and taking pictures of different frames). Photographs should be of high quality. The approaches used should allow monitoring the plume development to define the shape (e.g., two side views, at 90° to each other and relative to the axis of the plume) of the individual spray plume over time.

The proposed test procedure for analysis of the geometry of a single spray plume should be provided in detail to allow its validation by Agency laboratories. For example, the procedure should indicate the visualization technique, the specified times (in microseconds) for visualization after spraying, and the examination orientations. The acceptance criteria for plume geometry should include limits that control the shape and size of the evolving spray plume (e.g., measurement after the specified elapsed times of the length, width, spray cone angle from two orientations). Variability in tests involving manual manipulations can be reduced by providing procedure-specific training to the analyst.

q. Particle/Droplet[10] Size Distribution for Inhalation Sprays

The particle/droplet size distribution is a critical parameter, and its control is crucial for maintaining the quality of both solution and suspension formulated inhalation spray drug products. This parameter is dependent on both the formulation and the container closure system. The optimum aerodynamic particle/droplet size distribution for most oral inhalation products has generally been recognized as being in the range of 1 to 5 μm.

From a pharmaceutical viewpoint, the aerodynamic particle/droplet size distribution of the outgoing spray is one of the most important parameters for an inhalation product. The measurement of the aerodynamic size distribution is influenced by the characteristics of the spray (e.g., shape, velocity) and is not solely determined by the size of the individual droplets/particles initially present in the spray plume.

[10] The term *particle/droplet* refers to a combination of droplets and particles or droplets alone, depending on the formulation and conditions of measurement.

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A multistage cascade impactor fractionates and collects droplets/particles of the formulation by aerodynamic diameter through serial multistage impactions. Such a device with all associated accessories should allow determination of a size distribution throughout the whole dose including, in particular, the small particle/droplet size fraction of the dose. It also provides information that allows the complete mass balance of the total labeled dose to be determined. However, to minimize distortions and to ensure reproducibility, it is important to specify certain conditions such as information on the calibration of the equipment, flow rate, duration, size and shape of the expansion chamber or inlet stem, and the procedure, accessories, and adapter that introduce the inhalation spray into a specified impactor. These important parameters should be selected to obtain a complete profile of the dose. The rationale and documentation for selection of the above parameters should be presented. When multiple cascade impactors of the same design are used, data should be provided to demonstrate comparability between impactor units.

The number of sprays used to determine particle/droplet size distribution by multistage cascade impactor should be kept to the minimum justified by the sensitivity of the analytical procedure used to quantitate the deposited drug substance. The amount of drug substance deposited on the critical stages of the cascade impactor should be sufficient for reliable assay, but not so excessive as to bias the results by masking individual spray variation.

The aerodynamic particle/droplet size distribution analysis and the mass balance obtained (drug substance deposited on surfaces from the mouthpiece to the cascade impactor filter) should be reported. The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per spray basis. If the procedure is based on a single actuation determination, then the range can be broadened to reflect the limits allowed for an individual actuation. At the time of application submission, data for the mass amount of drug substance found on each accessory and each of the various stages of the cascade impactor should be reported. In addition, data can also be presented in terms of the percentage of the mass found on the various stages and accessories relative to the label claim.

Acceptance criteria expressed in terms of mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) alone, as well as in terms of *respirable fraction* or *respirable dose* are not considered adequate to characterize the particle/droplet size distribution of the whole dose. Acceptance criteria can be proposed in terms of mass amount of drug substance found on appropriate groupings of stages and/or accessories. However, if this approach is used, at a minimum there should

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be three to four groupings to ensure future batch-to-batch consistency of the particle/droplet size distribution.

Inhalation spray drug products can vary widely in design and mode of operation. These differences can lead to particle/droplet size distribution properties that are unique for the drug product and that cannot be characterized by cascade impaction alone. Under such conditions, a complementary validated measurement procedure should be used (e.g., light scattering, time-of-flight) for a more definitive delineation of the critical particle/droplet size distribution parameter and assurance of batch-to-batch reproducibility for inhalation spray drug products. For these complementary procedures, it is crucial that instrumental and operational parameters (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, beam width) be defined accurately and with sufficient detail for Agency laboratories to assess the adequacy of the methodology. The associated specifications should control the particle/droplet size distribution (e.g., three to four size ranges[11]) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions.

G. Container Closure Systems

This subsection applies to container closure systems for nasal spray and inhalation solution, suspension, and spray drug products. For these drug products, the container closure system consists of the container, closure, pump, and any protective packaging, if applicable. Comments below apply to all product types unless otherwise specified. Comments pertaining to pumps apply to both nasal and inhalation spray drug products. In this guidance the word *pump* refers to all components that are responsible for metering, atomization, and delivery of the formulation to the patient. A properly performing pump should repeatedly spray discrete, accurate, small doses of the formulation in the desired physical form.

The administered dose of nasal and inhalation spray drug products is directly dependent on the design, reproducibility, and performance characteristics of the container closure system. The selection of a suitable pump for a given set of formulation characteristics (e.g., viscosity, density, surface tension, rheological properties) is of paramount importance for the correct performance of the pump and, ultimately, the drug product. Actuation parameters (e.g., force, speed, hold and return times) should also be considered when selecting the pump. Moreover, the design (e.g., number and dimensions of inlet channels, swirl chambers) and performance of the pump, as well as the compatibility of the pump, container, and closure with formulation components, should be thoroughly investigated and established before initiating critical clinical, bioequivalence, and primary stability

[11] Size ranges such as D_{10}, D_{50}, D_{90}, and span $((D_{90} - D_{10})/D_{50})$.

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studies. The device should be designed to prevent partial metering of the formulation when used according to the patient instructions for use. The use of some type of actuation counting mechanism for multidose drug products is encouraged to promote patient compliance. If the device includes electronic components that can affect the performance or reliability of the drug product, the applicant should refer to the applicable recommendations outlined in the appropriate guidances from the Center for Devices and Radiological Health (CDRH).[12]

For device-metered nasal or inhalation spray drug products designed for use with replaceable reservoirs, the device should be specific for the intended formulation reservoir only and should not allow use of an alternate reservoir that contains a different formulation. It is also recommended that a mechanism that would prevent unintentional multiple dosing be included, if applicable.

The composition and quality of the materials used in the manufacture of the container closure system components should be carefully selected. For safety considerations, materials should be chosen that minimize or eliminate leachables without compromising the integrity or the performance of the drug product.

The identity and concentration of recurring leachables in the drug product or placebo formulation (i.e., drug product formulation without drug substance) should be determined through the end of the drug product's shelf life. If possible, the results should be correlated with the extractables profiles of the container closure components determined under the various control extraction study conditions. Evaluation of leachables in the drug product formulation in future routine stability studies may not be needed when such a correlation exists. In general, the levels of extractables should be greater than the levels of leachables for the correlation to be considered valid. For ANDAs, the applicant can compare the extraction profiles of the container and closure components with the leachables profiles of the drug product (or placebo) after storage under accelerated stability conditions for 3 months. If equilibrium is not reached by 3 months, real-time long-term data should be used to establish an appropriate expiration dating period. A commitment should be provided to confirm the results for the drug product (or placebo) on initial production stability batches at or near expiry. If the compared results are within the applicant's acceptance criteria but there are qualitative differences, the results should be discussed with the responsible review division.

Relevant information (see below) should be provided on the characteristics of each of the critical components of the container closure system to ensure its

[12] Contact CDRH for additional guidance and copies of (1) *Reviewer Guidance for Premarket Notification Submissions* (November 1993), Anesthesiology and Respiratory Devices Branch, Division of Cardiovascular, Respiratory, and Neurological Devices and (2) *Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(K) Review* (August 1991).

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suitability for manufacturing the drug product. Information should also be provided on acceptance criteria, test procedures, and analytical sampling plans (i.e., number of samples tested, individual or composite samples specified, number of replicate analyses per sample) for the critical components. Critical components are defined as (1) those that contact the patient (mouth or nose) or the formulation, (2) those that affect the mechanics of the overall performance of the device, or (3) any protective packaging. For additional information on container closure systems, refer to FDA's guidance for industry on *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999).

The following information should be included in the application. Reference to information in Drug Master Files (DMFs) for container, closure, and pump information is acceptable if the DMF holder provides written authorization that includes specific reference (e.g., submission date, page number, item name and unique identifier) to the pertinent and up-to-date information (21 CFR 314.420(d)). However, CDER recommends that, at a minimum, the information identified below (with asterisks) be included in the application so that the applicant can ensure continued product quality with respect to the container closure system.

- Fabricators of the container, closure, and the assembled pump*
- Fabricators for each part of the pump
- Unique identifiers for different parts of the pump
- Unique identifiers of the container, closure, and the assembled pump*
- Engineering drawings of the container, closure, and pump components
- Precise dimensional measurements of the container, closure, pump, and pump components*
- Composition and quality of materials of the container, closure, and pump components*
- Control extraction methods and data for elastomeric and plastic components*
- Toxicological evaluation of extractables*
- Acceptance criteria, test procedures, and analytical sampling plans*
  - Physicochemical parameters and dimensional measurements of the container, closure, and pump components*
  - Qualitative and quantitative extractable profiles from the container, closure, and pump components*
  - Performance characteristics of the pump*

Additional information on select topics is provided below.

1. Fabricator, Chemical Composition, and Physical Dimensions

The fabricator, chemical composition (e.g., resins, additives, colorants, adhesives, inks), and physical dimensions of each component and the assembled pump should be specified. The composition of the container, closure, coating material

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(if applicable), and individual pump components should be provided. For the materials used in fabrication of the critical components of the container closure system, specific citations should be made, where applicable, to the indirect food additive regulations in Title 21 of the Code of Federal Regulations. The dimensional measurements of metering pump components should be held to very tight tolerances through precision measurements. The applicant can rely on the certificate of analysis for the dimensional controls for the individual pump components for each incoming shipment of assembled pumps. Devices with unique or new delivery mechanisms should be accompanied by a description and drawings that clarify the device operation. Moreover, it is recommended that assembled and disassembled components of the container closure system for all drug products be available, if requested by the Agency, to facilitate the review process.

2. Control Extraction Studies

The purpose of the control extraction study is to define quantitative extractable profiles for elastomeric or plastic packaging components under specified test conditions and to establish an acceptance criterion for each of the extractables from the container, closure, and critical components of the pump used for the submitted batches (e.g., critical clinical, preclinical, biobatch, primary stability, production). For critical components that affect the mechanics of the overall performance of the device but do not contact either the patient (mouth or nose) or the formulation, a qualitative approach for control of the extractable profile may suffice. The extractable profiles of the specified container, closure, and pump components should be established and documented under defined experimental conditions. The documentation should include the sample size, type and amount of solvents, temperature, duration, extraction procedures, analysis procedures, and data. Solvents of various polarities should be used for initial determination of the profiles (e.g., water and appropriate organic solvents).

Extraction studies should be performed, and the profile of each extract should be evaluated both analytically and toxicologically. The application should provide adequate analytical information, obtained using a variety or combination of procedures (e.g., chromatography with mass spectroscopy), to identify and quantify each extractable and establish appropriate acceptance criteria. A toxicological evaluation should be made of the extractables from the container, closure, and critical pump components, and the results submitted in the application. For critical components that only affect the mechanics of the overall performance of the pump, a toxicological evaluation of extractables is not necessary. The appraisal should include appropriate in vitro and in vivo tests and can also be supported by applicable citations and additional safety data. The results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted. A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profiles. Special attention should be paid to elastomeric components because of

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the potential for release of additional leachables (e.g., PNAs (polynuclear aromatics), nitrosamines, vulcanization accelerators) into the formulation, which can alter the toxicological profile of the drug product. Since some extractables may be carcinogenic, appropriate risk assessment models may be warranted to establish acceptance criteria. Applicants are encouraged to contact the responsible review division for further guidance.

3. Routine Extraction

Based on the analytical and toxicological evaluation of the extractables from the control extraction studies, the applicant should establish discriminatory test procedures and set appropriate acceptance criteria for the extractable profiles for routine testing for each critical component of the container closure system. This testing will provide continued assurance of the batch-to-batch consistency of the composition and purity of the container and closure components. An extraction test should be performed on every incoming component batch using water and other suitable solvents selected from the control extraction studies, to determine the individual and total extractables. For nasal spray drug products, if the level of extractables for each component is relatively low, it may be appropriate to establish a limit only for the total weight of extractables from each individual critical component.

If a correlation is established between the extractables from the raw materials used for fabrication of the container and closure components and those emanating from the molded components, and assurance is provided that no additional additives are introduced during the fabrication process, then routine extraction studies can be performed on each raw material batch, with a reduced testing schedule of individual component batches.

Test procedures and analytical sampling plans (i.e., number of samples tested, individual or composite samples specified, number of replicate analyses per sample) should be provided. The specificity, linearity, range, accuracy, precision, detection limit, quantitation limit, and robustness of the proposed validated test procedures, including system suitability testing, should be documented with proper standards during validation in the control extraction studies.[13]

4. Acceptance Criteria

The application should include specifications for the container, closure, each component of the pump, the assembled pump, labels, adhesives, ink, and

[13] Guidance relating to validation of analytical procedures is available in the ICH guidances (Q2A) *Text on Validation of Analytical Procedures* (March 1995) and *Q2B Validation of Analytical Procedures: Methodology* (November 1996) and CDER's guidance on *Submitting Samples and Analytical Data for Methods Validation* (February 1987). CDER's 1987 guidance will be superseded by the guidance on *Analytical Procedures and Methods Validation*, when finalized. A notice of availability for a draft version of this guidance published in the *Federal Register* on August 30, 2000 (65 FR 52776).

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protective packaging, as applicable. The specifications should include dimensional measurements, particulate matter, physicochemical parameters, and individual and total extractables as outlined above in #3 under the discussion of the routine extraction studies. In addition, the specifications should include performance attributes of the pump (e.g., functionality, pump or spray weight delivery, particle/droplet size distribution, spray pattern, minimum actuation force to achieve desired spray characteristics). Data should be collected using defined actuation parameters (e.g., force, speed, hold and return times). All proposed acceptance criteria should reflect the test results of the pumps used in the submitted drug product batches (e.g., critical clinical, primary stability, biobatch, and production batches, all using same pumps). If the information outlined above is generated by the pump manufacturer through authorized DMFs and is reported by certificate of analysis, applicants should also develop or have access to the analytical and other procedures to verify the reliability of the supplier's test results at appropriate intervals (21 CFR 211.84).

For the extractables profiles and the physicochemical parameters, a reduced acceptance testing schedule can be considered once the applicant establishes the reliability of the supplier's test results. If a reduced acceptance testing schedule is proposed, the applicant should confirm the supplier's results by testing multiple incoming batches of individual components (e.g., container, closure, pump components), some of which were used in preparing the submitted drug product batches (e.g., critical clinical, primary stability, biobatch, production). Also, a commitment should be provided to test a predetermined number of batches of each component used in preparing postapproval drug product batches.

5. Semipermeable Container Closure Systems

Protective packaging (e.g., foil overwrap) is recommended for inhalation drug products packaged in semipermeable containers (e.g., low density polyethylene (LDPE)). The protective packaging mitigates conditions such as ingress of foreign contaminants, loss of solvent, exposure to oxygen. Furthermore, labeling of these products by embossing or debossing is recommended to avoid the potential ingress from other types of labels (e.g., volatile organic chemicals from inks, paper, adhesive components). The levels of the leachables originating from indirect exposure to labels or related materials should be determined with validated methodology that has suitable detection and quantitation limits for the potential leachables. The levels of leached compounds should be appropriately qualified and documented and acceptance criteria established.[14]

H. Drug Product Stability

[14] A draft guidance is under development and will publish soon. When finalized, this guidance will provide additional information on inhalation drug products packaged in semipermeable container closure systems.

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Stability studies provide a means for checking the physical and chemical stability of the drug product at various storage conditions, including the compatibility of the formulation with the components of the device, as well as performance of nasal and inhalation spray drug products. The application should contain (1) a complete, detailed stability protocol, (2) stability report and data, and (3) information regarding the suitability of the test procedures employed.

1. Protocols, Commitment, and Data Reporting

A stability protocol is a detailed plan described in an application that is used to generate and analyze stability data to support the retest or expiration dating period for a drug substance or the expiration dating period for a drug product.

The applicant should verify and ensure continued stability of the drug product by placing production batches into the applicant's routine stability testing program. The applicant should provide appropriate statements in the stability protocol committing to conduct and/or complete prescribed studies on production batches of a drug after approval.

For detailed information on the stability protocol, commitment, and data reporting, refer to *Submitting Documentation for the Stability of Human Drugs and Biologics* (the stability guidance) (February 1987).[15] For nasal spray and inhalation solution, suspension, and spray drug products, the stability report should also include the grade, batch number, and source of critical and novel excipients.

The following additional discussion elaborates on specific aspects of stability information for nasal spray and inhalation solution, suspension, and spray drug products that should be included in the application.

a. Specification

The stability test parameters, with appropriate acceptance criteria, should include those test parameters identified in the drug product specification (refer to section III.F) but can exclude the following: for nasal sprays, identity of the drug substance, spray pattern, osmolality, and net content; for inhalation products, identity, osmolality, net content, and content uniformity of the premetered dose units (SCU is not exempt). Test procedures should be stability indicating where applicable. For the parameter of drug content (assay), refer to information provided in sections III.F.1.c and III.F.2.c above. A single primary stability batch of the drug product stored under long-term stability conditions should be

[15] In June 1998, FDA made available a draft guidance document for industry on *Stability Testing of Drug Substances and Drug Products*. When finalized, this guidance will supersede the 1987 stability guidance.

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tested for antimicrobial preservative effectiveness at the proposed shelf life for verification purposes.

b. Test Time Points

The stability test intervals should be indicated in the protocol. For NDAs, long-term, accelerated, and, if applicable, intermediate test intervals should be used that are consistent with the recommendations in the ICH guidance *Q1AR Stability Testing of New Drug Substances and Products* (November 2000). For ANDAs, the long-term and intermediate intervals should be consistent with the ICH guidance, but intervals at 0, 1, 2, and 3 months can be used for accelerated testing. Tabular presentation of test intervals can be used to add clarity.

c. Container Storage Orientations

The stability of nasal and inhalation drug products can be affected by storage under differing orientations. For example, leachable levels, pump appearance, weight loss, assay, particle size distribution, and SCU can be affected by orientation. Primary stability studies should include storage under different orientations (e.g., upright and inverted or upright and horizontal) to characterize any differences in the behavior under storage and to define optimum storage orientation, if any. Once sufficient data demonstrate that orientation does not affect the product quality, routine stability studies can be conducted on product stored in only one orientation.

Stability storage under multiple orientations may not be necessary for some drug products (e.g., blow-fill mold unit-dose inhalation solutions).

d. Test Storage Conditions

Stability studies should be performed on the drug product with the packaging configuration (i.e., primary, protective) for which approval is sought, using the appropriate test storage conditions. CDER's recommendations on appropriate test storage conditions can be found in the ICH guidance *Q1AR Stability Testing of New Drug Substances and Products* (November 2000). A summary of these recommendations is provided below.

Usually, the test storage conditions in the stability protocol for a drug product intended for storage under controlled room temperature conditions should include (1) accelerated (40• 2°C/75• 5%RH), (2) intermediate (30• 2°C/60• 5%RH), if applicable, and (3) long-term (25• 2°C/60• 5%RH) conditions. Stability studies under the various storage conditions can be initiated concurrently. Accelerated stability

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studies alone may not be predictive of the product performance throughout the extrapolated expiration dating period.

For drug products packaged in semipermeable containers (e.g., low density polyethyelene) without protective packaging that are intended for storage under controlled room temperature conditions, the test storage conditions in the stability protocol should include (1) accelerated (40• 2°C/NMT 25%RH), (2) intermediate (30• 2°C/60• 5%RH), if applicable, and (3) long-term (25• 2°C/40• 5%RH). Additional approaches for testing of drug products packaged in semipermeable containers are described in the ICH guidance *Q1AR Stability Testing of New Drug Substances and Products* (November 2000).

For drug products intended for storage in a refrigerator, the test storage conditions in the stability protocol should include (1) accelerated (25• 2°C/60• 5%RH), and (2) long-term (5• 3°C).

For drug products using sealed glass ampules, humidity control during stability studies is not necessary.

For NDAs, the first three production batches manufactured postapproval should be placed in the accelerated, intermediate (if applicable), and long-term stability testing program using the approved stability protocol. If stability data for the first three production batches were submitted with the original application using the approved protocol and the above cited storage conditions, then it may not be necessary for the first three production batches manufactured postapproval to be placed on stability.

For ANDAs, refer to the stability guidance.

e. Batches, Manufacturing Process, Facilities, Components, and Container Closure System Considerations

To determine drug product stability, a minimum of three batches should be studied to provide an evaluation of batch-to-batch variability. The formulation and container closure system components of the three primary stability batches should be the same as those intended for distribution, which should be the same as those used in the other submitted batches (e.g., critical clinical, biobatch, production). For ANDAs, see the stability guidance for recommendations regarding the number of batches. Stability batches identified in the application should be described in terms of the size, manufacturing method, manufacturing site, testing procedures and acceptance criteria, and packaging. Applications should indicate the type, size, and source of various container and closure components that were used in generating stability data for the identified stability batches (e.g., IND, NDA, ANDA).

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f. Quality, Purity, and Source of Drug Substance and Excipients

Data should be provided to demonstrate the quality and purity of drug substance and excipient batches used in the drug product stability batches. The source (e.g., manufacturer, site) of the drug substance used in these drug product batches should be specified. The sources of the excipients used in these drug product batches should be specified where formulations are suspensions or the excipients have a direct impact on the drug product performance. The information on these drug substance batches should include but may not be limited to the purity, synthetic method, synthesis site, micronization site, micronization procedure, and testing. Similar information, such as purity, micronization site and procedure, and testing, should also be provided for excipients that affect the suspension and/or particle characteristics. For inhalation solution, suspension, and spray drug products, purity information should be provided for compendial excipients where purity is not controlled through the associated monographs. This information for the drug substance and the excipients can be duplicated in the stability report or referenced to the specific pertinent section or sections of the drug application.

g. Sampling Plans and Statistical Analysis Approaches and Evaluation

Refer to the stability guidance.

h. Expiration Dating Period

For NDAs, the expiration dating period should be based upon the accelerated, intermediate (if applicable), and long-term stability data from at least three batches of drug product. The data should be statistically analyzed, as appropriate. These primary stability batches should be manufactured, preferably, from three different batches of the drug substance and with different batches of container and closure components, to ensure a statistically acceptable level of confidence for the proposed expiration dating period. See the stability guidance for the determination of the expiration date and for additional recommendations regarding expiration dating periods for ANDAs.

2. Other Stability Considerations

Changes in the manufacturing facility; manufacturing procedure; source, synthesis, or micronization of the drug substance; source or type (design or composition) of container and closure components; or grade of excipient may affect the stability of the drug product. In addition, for excipients used in suspension formulations that may have direct impact on the performance, a change in the source of such excipients may affect the stability of the drug

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product. After such changes, additional stability data should be generated for the drug product so that comparability can be assessed and linkages established between the various batches.

If multiple manufacturing facilities, manufacturing processes, or sources of the components (container and closure or formulation) are intended to be used in the manufacturing of the drug product, adequate data should be provided to support the different facilities, manufacturing processes, and sources. See the stability guidance for additional guidance.

Appropriate bracketing and matrixing protocols can be used in stability programs for some of these drug products (e.g., solution-based formulations). However, additional justification should be provided for certain complex drug delivery systems where there are a large number of potential drug-device interactions. Applicants are encouraged to contact the appropriate review team for further guidance on bracketing or matrixing before implementing such protocols.[16]

For additional stability considerations, refer to section IV below on drug product characterization studies and the stability guidance.

IV. DRUG PRODUCT CHARACTERIZATION STUDIES

For nasal spray and inhalation solution, suspension, and spray drug products, certain studies should be performed to characterize the performance properties of the drug product and to provide support in defining the optimal labeling statements regarding use (e.g., storage, cleaning, shaking). Delivery systems for nasal and inhalation spray drug products can vary in both design and mode of operation, and these characteristics may be unique to a particular drug product. Studies to define these characteristics will help facilitate correct use and maintenance of the drug product and contribute to patient compliance. For the most part, these should be one-time studies, preferably performed on multiple batches (e.g., two or three) of drug product representative of the product intended for distribution. Additionally, this information will provide a baseline for comparison if, at a later time, the performance characteristics of a drug product are in question. For ANDAs, the applicability of each of the characterization studies outlined below for a given drug product can be discussed with the responsible review division.

[16] In September 2001 (66 FR 49029), the Agency made available a draft guidance on ICH *Q1D Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products*. Applicants can consult this guidance once issued by FDA in its final form.

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A. Priming and Repriming in Various Orientations

For multiple-dose nasal and inhalation spray drug products, studies should be performed to characterize the priming and repriming required for the product after storage in multiple orientations (upright and inverted or upright and horizontal) and after different periods of non-use. SCU and other pertinent parameters should be evaluated. The following information should be established:

- the approximate interval that can pass before the drug product should be reprimed to deliver the labeled amount of medication
- the number of sprays recommended to prime or reprime the unit

Multiple orientation studies should be performed with initial sprays and with sprays near the label claim number. Priming and repriming information will be used to support the proposed labeling statements.

B. Effect of Resting Time

For multiple-dose inhalation spray drug products, a study is recommended to determine the effect of increasing resting time on the first spray of unprimed units, followed immediately by the second and the third sprays. Units should be primed only before initiation of the study. After resting for increasing periods of time (e.g., 6, 12, 24, 48 hours), uniformity of the medication delivered in the first, second, and third sprays (no priming) should be determined. Testing should be performed on units that have been stored in different orientations (i.e., upright and inverted or upright and horizontal). To shorten the length of the study, testing can be performed concurrently on separate samples with progressively longer resting periods.

C. Temperature Cycling

For nasal spray, inhalation suspension, and inhalation spray drug products, a stress temperature cyclic study should be performed to evaluate the effects of high and low temperature variations that may be encountered during shipping and handling on the quality and performance of the drug product. Such a study can consist of 12-hour cycles, with temperatures ranging between freezer temperature (-10 to -20°C) and 40°C for a period of at least 4 weeks. Alternative conditions and duration can be used with appropriate justification. Periodically throughout the study, at the end of a predetermined number of cycles, the samples should be analyzed for appropriate parameters and compared with the control drug product. Test parameters for cycling studies should include, where applicable, droplet size distribution, particle size distribution, microscopic evaluation, appearance, color, clarity, assay, SCU, sterility, and functionality of pump components. A validated container closure integrity test, instead of sterility testing, can be used to assess sterility and demonstrate maintenance of the integrity of the microbial barrier

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provided by the container closure system. With regard to appearance of the nasal spray and inhalation drug products, one should consider, as applicable, the discoloration of the formulation, distortion of pump components, pump clogging, and adherence of the drug to the walls of the container, closure, and/or pump components.

D. In Vitro Dose Proportionality

For nasal and inhalation spray drug products with multiple strength suspension formulations, studies should address in vitro dose proportionality between strengths by determining SCU and particle/droplet size distribution.

E. Cleaning Instructions

For nasal and inhalation spray drug products, in-use studies should be performed to determine the frequency of cleaning and related instructions to be included in the labeling.

F. Device Robustness

Device robustness should be studied for nasal and inhalation spray drug products and should address the following:

- For devices that can be reused repeatedly with replaceable reservoirs, a study should be conducted to establish the product performance characteristics in terms of SCU and particle/droplet size distribution throughout the nominal number of sprays of the device.

- Limits of use related to failure of critical device mechanisms should be studied to determine the appropriate replacement intervals for the device.

- The performance characteristics of the device should be studied after different handling situations (e.g., dropping, shaking, vibrating).

For additional information on studies relating to device robustness, see documentation from the Center for Devices and Radiological Health (CDRH).[17]

G. Effect of Dosing Orientation

[17] Contact CDRH for additional guidance and copies of (1) *Reviewer Guidance for Premarket Notification Submissions* (November 1993), Anesthesiology and Respiratory Devices Branch, Division of Cardiovascular, Respiratory, and Neurological Devices and (2) *Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(K) Review* (August 1991).

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For nasal and inhalation spray drug products, studies should be undertaken to determine the comparative performance of the devices in terms of SCU and particle/droplet size distribution at various dosing orientations.

H. Effect of Varying Flow Rates

The effect of varying flow rate should be studied for inhalation spray drug products and should address the following:

- For breath-activated drug products or those that are intended to be marketed with an expansion or holding chamber, spacer, or similar component, a study should be undertaken to determine the SCU and the particle/droplet size distribution as a function of different testing flow rates at a constant volume. The total volume should be limited to 2 liters. This study assesses the sensitivity of the device to widely varying flow rates generated by patients of different age and gender and with different severity of disease.

- Another study for breath-activated products should assess the triggering ranges of flow rates that generate the amount of delivered dose and the corresponding particle/droplet size distribution.

- For drug products with an expansion or holding chamber, spacer, or similar component, a separate study is encouraged to assess the effect of increasing waiting periods (e.g., 0, 5, 10 seconds) between actuation and initiation of inflow, at a specified flow rate, on the SCU and particle/droplet size distribution.

I. Profiling of Sprays Near Container Exhaustion (Tail Off Characteristics)

For nasal and inhalation spray drug products, a study should be conducted to determine the profiles of SCU and droplet (solution) or particle/droplet (suspension) size distribution of each individual spray after the point at which the labeled number of sprays have been dispensed until no more sprays are possible (i.e., the container is empty). SCU testing can be replaced by pump delivery testing for solution formulations. These studies help determine if the target fill and any proposed overfill of the containers are justified, since the tail off characteristics can vary as a function of pump design, container geometry, and formulation. A graphical representation of the findings is also recommended. Refer to sections III.F.1.g, III.F.1.i, III.F.2.o, and III.F.2.q.

J. Effect of Storage on the Particle Size Distribution

For suspension spray drug products, the stability studies on the primary stability batches should determine the effect of storage time and conditions on particle size

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distribution through unit life (beginning to end for device-metered products). If stability studies demonstrate an effect on the particle size distribution within unit life, then the routine stability protocol should include particle size distribution testing through unit life. Refer to sections III.F.1.j and III.F.2.m.

K. Plume Geometry

For nasal spray drug products, plume geometry of the spray should be characterized. For discussion of this test, refer to section III.F.2.p for inhalation sprays. Plume geometry does not distinguish between drug substance particles and formulation droplets in the spray or indicate any density gradient for the drug substance, but determines the shape of the entire plume. Therefore, this test is complementary to the spray pattern test (see section III.F.1.h and III.F.2.p). The plume geometry characteristics can be used as a baseline to compare similar nasal spray drug products by different manufacturers or when certain changes are introduced to an already approved drug product.

L. Preservative Effectiveness and Sterility Maintenance

If preservatives are used in the formulation, the minimum content limit should be demonstrated as microbiologically effective by performing a microbial challenge assay of the drug formulated with an amount of preservative equal to or less than the minimum amount specified. For details for this characterization, see the stability guidance.

For device-metered, aqueous-based inhalation spray drug products (as defined in section II.C), studies should be performed to demonstrate the appropriate microbiological quality through the life of the reservoir and during the period of reservoir use. Such testing could assess the ability of the container closure system to prevent microbial ingress into the formulation and/or the growth inhibiting properties of the formulation.

M. Characterization of Nebulizer Specified in the Labeling

For inhalation solution and suspension drug products, a study should be undertaken to determine the delivered dose and the particle/droplet size distribution as per the specified operating parameters and ranges for a given nebulizer.

N. Photostability

Photostability studies should be performed using appropriate test conditions, if warranted by the immediate container, i.e., the formulation in the primary container can receive light exposure. These studies should be conducted in the absence of any additional packaging (e.g., foil overwrap). For additional

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guidance, applicants can refer to the ICH guidance *Q1B Photostability Testing of New Drug Substances and Products* (November 1996).[18]

O. Stability of Primary (Unprotected) Package

For a drug product labeled for storage at room temperature, if additional packaging (e.g., foil overwrap for LDPE-contained product) is used to protect the drug product from degradation and/or evaporative effects, adequate stability data conducted at a minimum of 25°C and a maximum of 40 percent RH should be generated for these units without the protective packaging for pertinent parameters. This data can support the establishment of the maximum length of time for product use after the protective packaging is removed. Drug products both newly manufactured and near the end of the proposed expiration dating period should be evaluated.

V. LABELING CONSIDERATIONS

To achieve consistency and uniformity in the content, the product title, and the format of the labeling of nasal spray and inhalation solution, suspension, and spray drug products, the following pertinent information is recommended in the labeling. These comments are not all inclusive, and they are directed mainly at labeling issues unique to NDAs for prescription nasal spray and inhalation solution, suspension, and spray drug products. For additional information regarding the labeling of drug products, see part 201 (21 CFR part 201). In general, labeling for ANDAs should be the same as the reference listed drug.[19]

A. Nasal and Inhalation Spray Drug Products

1. Product Title

To standardize the nomenclature for oral inhalation sprays, the established name of all such drug products should include the designation *(Drug Substance) Inhalation Spray*. For nasal sprays, the drug product would include the name *(Drug Substance) Nasal Spray*. The established name should be followed by a phrase such as *For Oral Inhalation Only*, or *For Nasal Use Only*, as appropriate.

2. Label

The label should bear the following information:

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[18] Additional information on photostability testing will be available in FDA's forthcoming guidance for industry *Stability Testing of Drug Substances and Drug Products* (draft published June 1998) when it is finalized.

[19] For additional information regarding labeling for ANDAs, see § 314.94(a)(8) (21 CFR 314.94(a)(8)).

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- Established name of the drug product
- Amounts of the drug substance delivered from the pump nasal actuator or mouthpiece
- Number of medication sprays per container
- Net content (fill) weight
- Usual dosage
- Excipients (established names)
- Route of administration
- Recommended storage conditions including any warning statements regarding temperature or light exposure
- Manufacturer's and/or distributor's name and address
- "Rx Only" or "• Only" statement
- Lot number
- Expiration date
- Use period once drug product is removed from protective packaging (if applicable)
- Instructions regarding shaking of suspension drug products
- NDC number (recommended)

For nasal and inhalation spray drug product devices that can be reused repeatedly with multiple reservoirs, each reservoir should be labeled adequately.

In the case of small labels, only some of the information listed above must be included in the label (21 CFR 201.10(i)). However, all labeling information required by the Federal Food, Drug, and Cosmetic Act (the Act) and the regulations in Title 21 of the Code of Federal Regulations must be included on the carton, outer container, wrapper, and leaflet as appropriate.

3. DESCRIPTION Section of the Package Insert

In addition to the information typically required by FDA regulations for the description of the drug substance and formulation (21 CFR part 201), the package insert should include the following information that is specific for nasal and inhalation spray drug products:

- The medication dose delivered to the patient should be expressed by a statement in this section, such as: *Each spray delivers •x• mcg of drug substance in •w• mg of suspension or solution equivalent to •y• mcg of drug substance base (if applicable) from the nasal actuator or mouthpiece.* The term *approximately* should not be used to modify the medication dose delivered.
- For suspension formulations, if the drug substance forms solvates or hydrates, this formation should be clearly specified with proper conversion for the active drug shown.
- A list of all excipients should be included. Substances should be identified by their established names.

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- The number of priming sprays before using the unit for the first time should be included. The number of priming sprays for a unit that has not been used for more than a specified period of time (e.g., 24 hours, 48 hours) should be included.

4. HOW SUPPLIED Section of the Package Insert

The following should be included in nasal and inhalation spray drug product labeling:

- The net content (fill) weight of the container should be stated.
- The number of medication sprays expected throughout the shelf life of the drug product should be indicated for each container fill weight. Qualifying terms such as *at least* and *approximately* should not be used.
- The color and appearance of the container, closure, and pump components should be included.
- A statement should be provided that the correct amount of medication in each spray cannot be ensured after the labeled number of sprays from the unit even though the unit may not be completely empty. In addition, for reusable devices with replacement cartridges or refill units, a statement should be included that these units should be discarded when the labeled number of sprays have been dispensed and this labeling should be applied to these unit, not the device. The device should be labeled with an appropriate replacement or service interval.
- Storage conditions should be clearly stated including any warning statements regarding temperature and light exposure.
- Any preferred storage orientation should be indicated.
- If protective packaging (e.g., foil overwrap) is warranted to ensure product quality and is used for the drug product, this should be clearly stated. In addition, appropriate statements should be included that the contents of the protective packaging should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed. The length of time specified should be supported by data in the application (refer to section IV.O).
- A statement should be included regarding recommendations for shaking, if warranted (i.e., for suspension products).
- NDC number or numbers (recommended)

5. Patient Package Insert

The instructions to the patient should include the following if applicable:

- Detailed, step-by-step, appropriately illustrated instructions for patient use should be included. The following information is also recommended:

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- A figure that displays the various elements of the container closure system.
- Instructions for initial priming and for repriming of the unit.
- A statement cautioning against spraying the eyes with the formulation.
- For inhalation spray drug products, a statement instructing the patient to confirm the absence of foreign objects in the mouthpiece before using the product and after removing the protective mouthpiece cap, where applicable.

- Storage conditions should be clearly stated, including any warning statements regarding temperature and light exposure. A statement should be included regarding recommendations for shaking, if warranted (i.e., for suspension products). Any preferred storage orientation should be noted.
- If protective packaging was used for the drug product, appropriate statements should be included that the contents of the protective packaging should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed (refer to section IV.O).
- Appropriate cleaning instructions should be included (if applicable).
- A statement should be included that the correct amount of medication in each spray cannot be ensured after the labeled number of sprays even if there is evidence that the unit is not completely empty. A statement instructing the patient to keep track of the number of sprays used from the container should also be included unless a counter mechanism is incorporated into the device.

B. Inhalation Solutions and Suspensions

1. Product Title

To standardize the nomenclature for inhalation solutions, the established name of all such drug products should include the designation *(Drug Substance) Inhalation Solution*. For inhalation suspensions, the drug product would include the name *(Drug Substance) Inhalation Suspension*. The established name should be followed by a phrase such as *For oral inhalation only*.

2. Label

The label should bear the following information:

- Established name of the drug product
- Amount of the drug substance per container and concentration of drug substance in the formulation
- Net content (fill) weight
- Usual dosage

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- Excipients (established names)
- Route of administration
- Recommended storage conditions including any warning statements regarding temperature and light exposure
- Manufacturer's and/or distributor's name and address
- "Rx Only" or "• Only" statement
- Lot number
- Expiration date
- Use period once drug product is removed from protective packaging (if applicable)
- Instructions regarding shaking of suspension drug products
- NDC number (recommended)

In the case of small labels, only some of the information listed above must be included in the label (21 CFR 201.10(i)). However, all labeling information required by the Act and the regulations in Title 21 must be included on the carton, outer container, wrapper, and leaflet as appropriate.

3. DESCRIPTION Section of the Package Insert

In addition to the information typically required by FDA regulations for the description of the drug substance and formulation (21 CFR part 201), the package insert should include the following information that is specific for inhalation solution and suspension drug products:

- For suspension formulations, if the drug substance forms solvates or hydrates, this formation should be clearly specified with proper conversion for the active drug shown.
- A list of all excipients should be included. Substances should be identified by their established names.
- Delivered dose and description of particle/droplet size distributions that could be expected from an identified nebulizer under specific and defined operating conditions should be provided (refer to section IV.M).

4. HOW SUPPLIED Section of the Package Insert

The following should be included in inhalation solution and suspension drug product labeling:

- The net content (fill) weight of the container should be stated.
- Storage conditions should be clearly stated including any warning statements regarding temperature and light exposure.
- A statement should be included indicating that the contents of any partially used container should be discarded (e.g., unit dose presentations).
- If protective packaging (e.g., foil overwrap) is used for the drug product, this should be clearly stated. In addition, appropriate statements should be

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included that the drug product should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed. The length of time specified should be supported by data in the application (refer to section IV.O).

- A statement regarding any recommendations for shaking should be included, if warranted (i.e., for suspension products).
- Any preferred storage orientation should be noted for inhalation suspensions, if applicable.
- NDC number or numbers (recommended)

5. Patient Package Insert

The instructions to the patient for inhalation solution and suspension drug products should include the following if applicable:

- Instructions for proper opening of containers and transfer of formulation to the specified nebulizer should be included.
- A statement that the contents of any partially used container should be discarded should be included in this section.
- Storage conditions should be clearly stated, including any warning statements regarding temperature and light exposure. A statement should be included regarding recommendations for shaking, if warranted (i.e., for suspension products).
- Any preferred storage orientation should be noted for inhalation suspensions, if applicable.
- If protective packaging was used, appropriate statements should be included that the drug product should not be used after a specified number of days (e.g., 2 weeks, 30 days) from the date the protective packaging was removed.

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GLOSSARY OF TERMS

Acceptance Criteria: Numerical limits, ranges, or other criteria for the test described.

Batch: A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2)).

Container Closure System: The sum of packaging components that together contain, protect, and deliver the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product (e.g., foil overwrap). The container closure system also includes the pump for nasal and inhalation sprays. For nasal spray and inhalation solution, suspension, and spray drug products, the critical components of the container closure system are those that contact either the patient or the formulation, components that affect the mechanics of the overall performance of the device, or any protective packaging.

Drug Product: The finished dosage form and the container closure system.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body (21 CFR 314.3(b)).

Excipient: Any intended formulation component other than the drug substance.

Extractables: Compounds that can be extracted from elastomeric or plastic components of the container closure system when in the presence of a solvent.

Expiration Dating Period: The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Inhalation Solutions, Suspensions, and Sprays: Drug products that contain active ingredients dissolved or suspended in a formulation, typically aqueous-based, which can contain other excipients and are intended for use by oral inhalation. Aqueous-based drug products for oral inhalation must be sterile (21 CFR 200.51). Inhalation solutions and suspensions are intended to be used with a specified nebulizer. Inhalation sprays are combination products where the components responsible for metering, atomization, and delivery of the formulation to the patient are a part of the container closure system.

Leachables: Compounds that leach into the formulation from elastomeric or plastic components of the drug product container closure system.

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Nasal Sprays: Drug products that contain active ingredients dissolved or suspended in a formulation, typically aqueous-based, which can contain other excipients and are intended for use by nasal inhalation. Container closure systems for nasal sprays include the container and all components that are responsible for metering, atomization, and delivery of the formulation to the patient.

Overfill: For the purposes of this guidance, the excess of theoretical deliverable volume or weight of the drug product formulation that ensures (1) transfer of the dose of drug product declared in the labeling (unit dose) or (2) delivery of the number of dosage units declared in the labeling (multiple-dose).

Packaging Component: Any single part of a container closure system.

Placebo: A dosage form that is identical to the drug product except that the drug substance is absent or replaced by an inert ingredient.

Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.

Primary Stability Batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in an application for the purpose of establishing the expiration dating period.

Primary Stability Data: Data on the drug product stored in the proposed container closure system for marketing and under storage conditions that support the proposed shelf life.

Protective Packaging: The secondary packaging component that provides protection essential for product quality. This packaging (such as a foil overwrap) can provide, for example, protection from light, ingress of moisture, oxygen, foreign contaminants, or loss of solvent.

Pump: All components of the container closure system that are responsible for metering, atomization, and delivery of the formulation to the patient.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in the approved application to confirm the quality of drug substances, drug products, intermediates, raw material reagents, components, in-process materials, container closure systems, and other materials used in the production of drug substances or drug products.

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Specified Impurity: An identified or unidentified impurity that is selected for inclusion in the drug substance or drug product specification and is individually listed and limited to ensure the reproducibility of the quality of the drug substance and/or drug product.

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