Point of View: Recommendations to a young scientist to pursue inhalation research

In this "letter to students," the author sees exciting opportunities ahead for young scientists willing to take on the challenges in inhalation therapy research and development.

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Many years ago, as a young faculty member, I was sitting at a postgraduate course dinner across the table from the guest of honor, a very famous pharmacy professor who asked me, "What do you do for living, young man?" When I responded that I taught pharmacy (which at the time occupied most of my time, as I was busy preparing lectures and exam questions), he clarified that he was asking me about my research. I replied, "Inhalation aerosols." His reaction should have been expected—his fame and fortune came from oral dosage forms—and he advised me to "Do tablets!" instead of wasting my time on a "totally irrelevant dosage form."

I am glad that I did not listen to his advice! Indeed, many of his younger colleagues who were skilled powder technologists realized later that there were many unexplored areas in properties of powders for inhalation products and much room for improvement, coupled with the move to replace CFC-propellant inhalers with alternative delivery systems. In contrast, the state-of-the-art in oral dosage forms was already well-developed and there was less scope in which to make additional, far-reaching advances.

Now I am asking myself: What advice would I give to a young inhalation scientist today? Have we reached the stage of development in the oral inhalation and nasal delivery (OINDP) area where we will be generating small incremental improvements, instead of making the enormous leaps that have resulted in the treatment of many respiratory diseases being dominated by inhalation products—notably asthma, COPD and cystic fibrosis? Of course, the ultimate question is "How can we contribute to improving the lives of patients?"

I am convinced there is much to be done in OINDP research and development, to give patients better tools to manage their health and to meet unmet needs in preventing and treating some very severe conditions.

Treating additional diseases

There are multiple respiratory infections that require better treatment. These include tuberculosis, with its multi-drug resistance complications; non-tuberculous mycobacteria, which in the United States is now a bigger problem than tuberculosis;[1, 2] *Pseudomonas aeruginosa* related to cystic fibrosis; and fungal infections for which current treatments are unsatisfactory. Many severe chronic respiratory diseases, such as emphysema, non-cystic fibrosis bronchiectasis and idiopathic pulmonary fibrosis have largely unmet therapeutic needs because existing therapies have modest efficacy coupled with severe side effects. Discovering and developing better drugs using devices and formulations tailor-made for these populations can be a very rewarding journey. However, it is not for the faint-hearted, as it may take multiple attempts over a long period of time to move from generation of a product concept to a marketed product.

However, rather than looking for new molecules, which could have inherent risks of failure (such as safety issues or other developmental challenges), it may be possible to repurpose drugs already approved

for other indications or administered by other routes. Such drugs may be able to treat severe respiratory diseases via inhalation while reducing the risks and timelines required to accumulate knowledge about new chemical entities.[3]

There are excellent examples of success with this approach, including inhaled antibiotics for cystic fibrosis, where drugs previously approved as injections for acute infection treatment were developed as chronic inhaled prophylactic and palliative treatments (e.g., tobramycin, aztreonam and colistin). The most recent success is the US approval of inhaled liposomal amikacin (ALIS, Insmed) for the treatment of patients who have refractory lung infections with *Mycobacterium avium*.

But beware, as the former CEO of Genentech, Kirk Raab, remarked, "The longest path to get a drug approved is a shortcut."[4] The repurposing approach still requires thorough safety studies focused on the inhaled route of administration, proof of efficacy in the new indication and demonstration of well-controlled quality of the product.

Getting involved with patients

A constructive, collaborative approach among industry, healthcare professionals, regulators and payors—with patient advocacy groups at the center of the dialogue—would be the most promising and impactful way to develop and supply the correct medications for the appropriate indications at an affordable cost to society. The intensive participation of patients in clinical trials must be matched with their presence in making decisions about development of new products. Getting them involved early, for example, through participation in focus groups, could help identify product attributes that are important for patients using a particular therapy. It is very encouraging that the United States Food and Drug Administration (FDA) has been actively involved in this process.[5]

The ultimate goal should be about improving patients' quality of life; therefore, their voices need to be reflected in setting targets for the balance of safety and efficacy. I believe this approach can profoundly accelerate the process of making accessible, precise and individualized therapies. An example of this type of collaboration and a "step in the right direction" are the recent European Respiratory Society Guidelines on management of bronchiectasis, which represent the collective views of patient representatives and key opinion leaders.[6]

So, budding OINDP scientists, get on with research in the most challenging areas. And get to know patients and their aspirations to have better lives. You will be infused with motivation like you have never felt before. There are many ways to learn and get involved. Read blogs on the web where patients communicate (for instance, www.PatientsLikeMe.com, www.COPDFoundation.org, www.CFF.org and www.NTMir.org). Contact and volunteer for patient advocacy groups such as the Alpha-1 Foundation, COPD Foundation, Cystic Fibrosis Foundation, NTM Info and Research Inc. and the PCD Foundation in the US, and similar organizations in other countries. At conferences, go to sessions where patients are speakers. Find physicians who treat these patients, ask them to introduce you, then invite those patients to your institution to tell their stories. Use all that knowledge and emotional energy for bold assessment of critical attributes of new products, then share that information with your colleagues in the regulatory bodies, compendial and professional organizations such as the United States Pharmacopeia, European Pharmacopoeia, the American Association of Pharmaceutical Scientists (AAPS), the International Society of Aerosol in Medicine (ISAM), the American Thoracic Society (ATS) and the European Respiratory Society (ERS), as well as with those in cross-industry groups like the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), the European Pharmaceutical Aerosol Group (EPAG), etc.

With regard to regulations, have an open mind and examine existing draft and final guidelines to see if they are still appropriate, or if changes should be made in line with our current scientific knowledge, including the nature of the target diseases and critical safety and efficacy issues for patients. You can also offer to serve on standards and pharmacopeial committees, where public expert participation is usually welcomed.

Determining aerodynamic particle size distribution

An "impactful" contribution can be made in this area, which is unique to pharmaceutical aerosols because aerodynamic size distribution is the key determinant of their biological impact. As you will see, there are significant opportunities to advance this field for the benefits of many.

Size fractionation by cascade impactor

Prior to the use of impactors or impingers, the "regulatory" method was optical microscopy. However, it did not provide information about "aerodynamic" properties of inhaled medications that related to their deposition and biological effects in the respiratory tract. Often it could not distinguish between the drug and the non-volatile excipients and, in the absence of electron microscopy, it could not quantify sub-visible particles. Today of course, electron microscopy is much more accessible and in conjunction, for instance with single particle spectroscopic methods, can be a powerful tool in inhalation formulation develop-

ment.[7] Nevertheless, it still lacks the ability to determine the aerodynamic size distribution.

The introduction of inertial impaction methods in the 1980s for the then-new type of products—suspension metered dose inhalers and carrier-based dry powder products—was a big step in the right direction. Cascade impaction is still the only general method, accepted to date, which can provide aerodynamic size distribution for the components of pharmaceutical inhalation aerosols that relates to their regional deposition in the respiratory tract. That is the great strength of this method; it is uniquely suitable for complex aerosol systems in which the drug and excipient concentrations—in particles or droplets of different sizes—are not the same, or where the structure and shape of the particles are such that their optical properties cannot be readily transformed into aerodynamic size.

Yet anyone who has done cascade impaction will appreciate it is a very laborious method that requires considerable knowledge and experience, as well as a fair amount of maintenance and control, if the equipment is to be used correctly.[8] It also can be challenging to use it in certain circumstances. For example, it was shown years ago[9-12] that cascade impaction could be an unreliable method to determine drug aerodynamic size distribution for nebulized aqueous solutions because their propensity for rapid evaporation and condensation is very difficult to control. Aqueous droplet size is highly sensitive to relatively small fluctuations in temperature, especially if the aerosol is relatively dilute.[9,10] Indeed, the cascade impaction method for nebulized aqueous systems originally introduced by Mercer, et al.[13] was based on deliberate, complete evaporation of water (and other volatile components) prior to entry into the impactor. But that approach has other challenges, as density of the solid residues needs to be determined and will likely be different from that of water. Furthermore, the particle dynamic shape factor may not be unity, as is the case for spherical particles. Both parameters need to be established in order to ascertain particle aerodynamic size.

Laser diffraction as a sizing method

So are there alternatives that may be easier to use and more appropriate for such volatile systems with drugs in solution? Laser diffraction as a sizing method for solution aerosols was elegantly validated against cascade impaction by Clark.[14] Laser diffraction is an ideal method for these types of aerosols, where the concentration of the drug in each droplet is the same and the optical size distribution can be readily converted into aerodynamic size distribution. It also has the advantage of measuring the size distribution at the exit from the mouthpiece, mimicking the entry into the oral cavity. Laser diffraction is also simple and quick to use. Regulators will consider this method but typically will require comparison against cascade impaction to prove its validity.

Still, laser diffraction, in its present state, is not suitable for the more complex aerosols for which cascade impaction was originally adapted. While considerable effort is being made in the design of "engineered" particles for inhalation, there is a gap between the pace of product development and the development and regulatory acceptance of alternative methods for aerodynamic sizing or other techniques that can reliably predict particle deposition distribution following inhalation.

Developing and validating methods for fast, detailed analyses of complex inhaled systems that could provide information related to their respiratory tract deposition and disposition[15] to understand the critical attributes affecting local and systemic effects of inhaled products would be a very significant advance.

Oropharyngeal deposition: Understanding it or avoiding it?

The human oropharyngeal cavity is a complicated and dynamic structure, with inter- and intra-subject variability in its anatomy and airflow patterns, making particle deposition within it a very complex phenomenon. Oropharyngeal deposition can be also highly dependent on the way a patient uses an inhaler. I am impressed by the increasing sophistication of both the physical/anatomical and computational models for this problem. Nevertheless, are there still opportunities to make the science of oropharyngeal deposition more predictive, more precise, more patient-oriented? Of course, there is always room for improvement!

But let me offer some different perspectives, with which I believe we can all agree: Deposition of orally inhaled products in the oropharynx is invariably wasteful; it can contribute to adverse events and is the biggest source of intra- and inter-subject variability in pulmonary deposition.[16, 17] Variable loss of medication to the oropharynx is a limiting factor for drugs with a narrow therapeutic index.

Therefore, my suggestion to the new generation of inhalation scientists, who may be interested in fluid dynamics, devices and formulations, is to find practical ways of minimizing oropharyngeal deposition, rather than devoting their talents to further refinements of oropharyngeal deposition modeling. I believe existing tools to measure oropharyngeal deposition in humans, including gamma scintigraphy and laboratory and computational methods, which have been, or can be, validated against human data, are now adequate for this task.[18]

Luckily, we know that controlling particle size, shape and velocity, as well as time of delivery during the inspiration portion of a patient's breathing, can min-

imize oropharyngeal deposition. This could eliminate much of inter- and intra-individual variability in delivery of drugs to the thorax and, as a consequence, improve delivery efficiency and reproducibility to the lung. This outcome was, indeed, demonstrated in humans some time ago.[19]

In this context, I believe we need more than just outstanding R&D—we also need evidence-based regulatory incentives that motivate companies to remove this wasteful and potentially toxic portion of the aerosol cloud, which can lead to unnecessary systemic exposure. The European developments in this respect are somewhat encouraging, in that the sponsors of generic versions of inhaled corticosteroids are at least not penalized for reduction of the systemic exposure to the drugs compared to the reference product. In the US, the requirements for "sameness" between the original reference product and the generic substitute have certainly not resulted in a rapid introduction of generic inhaled products. Research that would substantiate changes in the regulatory paradigm and result in incentives to improve the safety and efficacy of approved inhaled drugs would be very valuable for the global community at large, as it would provide easier access to better medicines.

Improving nasal delivery

This article would be incomplete if I did not comment on airborne particle deposition in the nasopharynx. In contrast to the oropharynx, the nose is a frequent target organ for locally acting drugs and vaccines, and more recently as the portal for systemic delivery of drugs or delivery of drugs to the brain. Modeling and understanding regional deposition in the nose is at least as challenging as with oropharyngeal deposition. So we need better understanding, as well as delivery devices and formulations that maximize "productive" regional delivery and disposition based on the desired location in the nose, while minimizing escape of drug beyond the nasopharynx, which is not only wasteful but a safety concern as well.[20]

Nasal delivery is arguably less well-developed and therefore has at least as much potential for exciting innovations as do orally inhaled drugs. The FDA is encouraging and sponsoring efforts in basic understanding of nasal delivery.[21] And when you see headlines like, "Nasal drug delivery technology market is expected to exceed US $64 billion by 2023,"[22] you young scientists should pay some attention! I can smell a lot of exciting opportunities in this area!

Targeting orally inhaled products with narrow therapeutic indices

Goals are universal for the delivery of any therapeutic dosage form: minimize toxicity and maximize efficacy and tolerability. At present, these attributes can only be reliably established largely through human clinical development. Once approved, quality control of the product should be based on that empirical body of evidence, which may (and often will) vary from product to product. It is not just the mean target values but also the margins of variability in product specifications that should depend on the product's preclinical and clinical performance.

A drug that is administered at doses well to the right of the plateau of the dose-response curve, and is safe and tolerable at those doses, would not need to have the same narrow *in vitro* specifications as a drug with a narrow therapeutic index with significant side effects at higher doses, which could outweigh the drug's benefits. In the case of delivery to the lungs for topical or systemic effect, accurate targeting to the desired regions of the respiratory tract would assist in achieving the required therapeutic benefit(s) for narrow therapeutic index drugs.

At the same time, it is highly desirable to minimize deposition elsewhere. There is no absolute regional selectivity, even for the delivery of monodisperse aerosols, but substantial shifts in the proportion of dose depositing in central or peripheral airway regions can be achieved with particle size control.[23] The control of breathing (inspiratory flow rate) and placement of a drug-containing-aerosol "bolus" in different parts of inspired volume may have equally dramatic impact.[19, 23, 24] Incorporation of these findings, based on good scientific principles, into modern inhalation systems tailored at specific patient populations is certainly a goal that is within our reach.

Closing thoughts

Before you pursue any of these exciting research opportunities, please conduct a thorough literature review. You do not want to spend your precious time and talent to later learn that you were "reinventing the wheel."

No matter which of these exciting opportunities (or others) in inhalation you pursue, using your talent to help enhance the lives of patients through your research can be one of the most inspiring and rewarding career journeys you can make.

References

1. Prevost DR et al, (2010) Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am. J. Respir. Crit. Care Med. 182:970-976.

2. Strollo SE et al, (2015) The burden of pulmonary nontuberculous mycobacterial disease in the United States. Annals ATS 12:1458-1464.

3. Cipolla D and Gonda I, (2011) Formulation technology to repurpose drugs for inhalation delivery. Drug Disc. Today: Therap. Strat. 8:123-130.

4. Bugos GE, (2003) G.Kirk Raab, CEO at Genentech 1990-1995, http://digitalassets.lib.berkeley.edu/roho/ucb/text/RaabBook.pdf. (Accessed November 29, 2018).

5. Patient-Focused Drug Development: Disease Area Meetings Held in Fiscal Years 2013-2017 (2018), https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm347317.htm. (Accessed November 29, 2018).

6. Polverino E et al, (2017) European Respiratory Society guidelines for the management of adult bronchiectasis. Eur. Respir. J. 50:pii1700629.

7. Paudel A et al, (2015) Raman spectroscopy in pharmaceutical product design. Adv. Drug Deliv. Rev. 89:3-20.

8. Bonam M et al, (2008) Minimizing variability of cascade impaction measurements in inhalers and nebulizers. AAPS PharmSciTechnol. 9(2):404-413.

9. Phipps PR and Gonda I, (1990) Droplets produced by medical nebulizers: Some factors affecting their size and solute concentration. Chest. 97:1327-1332.

10. Phipps PR and Gonda I, (1994) Evaporation of aqueous aerosols produced by jet nebulizers: Effects on particle size and concentration of solution in the droplets. J. Aerosol Med. 7:239-258.

11. Finlay WH and Stapleton KW, (1999) Undersizing of droplets from a vented nebulizer caused by aerosol heating during transit through an Anderson impactor. J. Aerosol Sci. 30:105-109.

12. Kwong WTJ et al, (2000) Comparison of nebulized particle size distribution with Malvern laser diffraction analyzer versus Andersen cascade impactor and low-flow Marple personal cascade impactor. J. Aerosol Med. 13:304-314.

13. Mercer TT et al, (1968) Operating characteristics of some compressed-air nebulizers. Am. Ind. Hyg. Assoc. J. 29:66-78.

14. Clark AR, (1995) The use of laser diffraction for the evaluation of the aerosol clouds generated by medical nebulizers. Int. J. Pharm. 115:69-78.

15. Gonda I, (1988) Drugs administered directly into the respiratory tract: Modeling of the duration of effective drug levels. J. Pharm. Sci. 77: 340-346.

16. Grgic B et al, (2004) *In vitro* intersubject and intrasubject deposition measurements in realistic mouth-throat geometries. Aerosol Sci. 35:1025-1040.

17. Stahlhofen W et al, (1989) Intercomparison of experimental regional aerosol deposition data. J. Aerosol Med. 2:285-308.

18. Martin AR et al, (2018) Models of deposition, pharmacokinetics, and intersubject variability in respiratory drug delivery. Opinion on Drug Delivery, DOI: 10.1080/17425247.2018.1544616.

19. Farr SF et al, (2000) Comparison of *in vitro* and *in vivo* efficiencies of a novel unit-dose liquid aerosol generator and a pressurized metered dose inhaler. Int. J. Pharm. 198:63-70.

20. Gonda I, (1998) Mathematical modeling of deposition and disposition of drugs administered via the nose. Adv. Drug Deliv. Rev. 29:179-184.

21. FY2016 Regulatory Science Report: Locally-Acting Orally-Inhaled and Nasal Drug Products (2016), https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549167.htm. (Accessed November 29, 2018).

22. Market Watch (2018) Nasal drug delivery technology market is expected to exceed US$ 64 billion by 2023, https://www.marketwatch.com/press-release/nasal-drug-delivery-technology-market-is-expected-to-exceed-us-64-billion-by-2023-2018-09-07. (Accessed November 29, 2018).

23. Usmani OS et al, (2005) Regional lung deposition and bronchodilator response as a function of ß2-agonist particle size. Am. J. Respir. Crit. Care Med. 172:1497-1504.

24. Farr SJ et al, (1995) Aerosol deposition in the human lung following administration from a microprocessor controlled pressurised metered dose inhaler. Thorax. 50:639-644.

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