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GENERAL COMMENTARY
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Commentary: Suboptimal Inspiratory Flow Rates With Passive Dry Powder Inhalers: Big Issue or Overstated Problem?

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A Commentary on

Suboptimal Inspiratory Flow Rates With Passive Dry Powder Inhalers: Big Issue or Overstated Problem?
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It is easy to forget that just a few decades ago, delivery of drugs by inhalation was at the periphery of medicine, even for the treatment of respiratory diseases. Today, it would be almost unthinkable that a patient with asthma, chronic obstructive pulmonary disease (COPD), or cystic fibrosis would not be taking some form of inhaled medication and, indeed, typically more than one daily (Anderson et al., 2022).

While the dominant inhalation technology invented in mid-1950s for decades were metered dose inhalers (MDIs), due to concerns over the environmental impact of propellants that provide the energy for the production of the aerosols, the pharmaceutical industry put a massive effort into reformulating drugs as dry powder inhalers (DPIs), particularly since the Montreal agreement signed in 1987 (Stein and Thiel, 2016). Instead of propellants, "passive" DPIs utilize the energy of the patients' inspiratory effort to pull the drug powder formulation out of the inhaler and disperse it into respirable particles.

In addition to the inspiratory effort, some considerable "mental" effort is needed to use any inhalation treatment correctly. The non-adherence to the instructions for use, including incorrect technique, is about 50%, and it has not improved much with time (Gonda, 2019 and refs. therein).

Additionally, in their ground-breaking publication that influenced much subsequent debate, Clark and Hollingworth (1993) pointed out that a fundamental attribute of each DPI was its flow resistance and that the inspiratory flow rate achieved through an inhaler depended on the patient's inspiratory effort and the device resistance. They also highlighted the subtle opposing impact of an increased inspiratory flow rate by a patient: while it will likely lead to better powder dispersion into smaller physical (and aerodynamic) size, the increased velocity of the drug-carrying particles will enhance deposition higher up in the respiratory tract. That suggested that with the right design, the regional dose delivery from a DPI can be quite inspiratory flow independent if these opposing factors are exquisitely balanced. However, it does not appear that the development of the majority of currently approved DPIs that use mostly technologies from several decades ago made a deliberate attempt to achieve such "flow independence." Does it matter?

In a recent publication in this journal, Weers (2022) presents his perspective that the concerns of certain physicians treating COPD patients with inhaled bronchodilators may be unwarranted regarding the inability of some patients to exert adequate flow rates through their devices. He provides a summary of clinical data with this class of drugs, showing that the safety and efficacy of the approved bronchodilator DPIs are adequate for the majority of the patients, despite the fact that in the "standard" *in vitro* tests, the DPIs appear to show "flow-dependent" performance.

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To understand the apparent lack of sensitivity of the clinical performance of inhaled bronchodilators vs. the dependence of their *in vitro* performance on inspiratory effort, it is also important to appreciate that this class of compounds is very safe at the prescribed dosing and that the therapeutic index is so wide that practically all patients are dosed on the right hand side of the upper plateau of the dose–response curve, that is, the variations in delivery make very little impact for these drugs with regard to their safety and efficacy in the majority of the target patients. Extrapolations to other drugs, disease, and patient populations are however unwarranted at this stage without further research effort. The debate on this front continues; the literature also includes concerns about another important part of the patients' inspiratory effort, namely, the inhaled volume they are capable of, in order to receive the full dose from their inhalers (Faria-Urbina et al., 2021; Sahay et al., 2021; Tiddens et al., 2006).

Weers (2022) also expresses justified frustration over the common (and unfortunately widely accepted) misinterpretation of cascade impactor data. To link the *in vitro* data to the regional deposition of aerosols in humans, one needs to consider both the size and the velocity of the particles. This is particularly pertinent for oropharyngeal deposition, as shown in the classic article by Stahlhofen et al. (1989). Not only is the deposition in this region wasteful and for some therapeutics can cause poor tolerability and other side effects, it is also the major cause of intra- and inter-subject variability. The requirements to strive for a combination of size and velocity that minimizes this effect were spelt out at least 30 years ago (Gonda, 1992), and these principles were applied in some technologies for systemic delivery of drugs with a narrow therapeutic index such as insulin and fentanyl (Cipolla and Gonda, 2011).

Weers (2022) prompts us to think about the reasons for the reluctance of major parts of the pharmaceutical industry to develop and commercialize passive inhalers whose regional deposition in the respiratory tract would be independent over a wider range of inspiratory efforts of patients. No doubt, the industry needs to consider the benefits of investment into reformulations and new devices that would be approved for old drugs vs. other technologies that solve the same problem in a different way, such as add-on devices that coach or guide patients to inhale correctly every time (Dundon et al., 2020; Gonda, 2019). The regulatory hurdles for the latter path seem to be much lower. However, it would be certainly important to consider the benefits of "minimum patient effort-dependent" products when developing new drugs and addressing new populations of patients with unmet or poorly met medical needs.

The opinion by Weers (2022) will hopefully provoke much interest in the development of new inhalation therapies that will recognize the obvious—in the end, to be safe and efficacious, they need to be used correctly applying some level of physical and mental effort achievable by the target patient populations. To make the devices simple to use by the patients correctly is a highly desirable goal. This applies not just to DPIs but also to any other inhalation products.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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