Point of view: Overcoming barriers to affordability of orally inhaled products while protecting innovation

Aligning incentives for innovators and generic developers of orally inhaled products

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Respiratory diseases are a major worldwide healthcare problem[1] and their prevalence is likely to increase due to a multitude of factors, including air pollution, the incidence of smoking and vaping, and aging of the population. The rapid global spread of the COVID-19 infection has been a stark reminder of our vulnerability to life-threatening respiratory diseases and the need for an industry that can quickly and effectively respond to such crises.

Chronic obstructive pulmonary diseases (COPDs) are one of the leading causes of morbidity and mortality in many countries.[1] Influenza and asthma also affect large populations and contribute to enormous and rising healthcare costs. Tuberculosis remains a painful reminder, especially in developing countries, that respiratory infections of the past could come back with a vengeance in the form of multi-drug resistant strains and become endemic in parts of the world.[1]

Furthermore, there are many less-common respiratory diseases, including cystic fibrosis, bronchiectasis, pulmonary arterial hypertension and pulmonary fibrosis, as well as numerous severe chronic lung infections that contribute to the global burden of respiratory diseases.

Many patients around the world already benefit from inhaled treatments for these diseases, but for many more, they are unavailable or unaffordable.

Accessibility and affordability of inhaled medications (orally inhaled products or OIPs) should be an important focus for improving health care outcomes globally. While there are many factors that impact the availability and pricing of inhaled drugs, long development timelines and the associated cost and risk of drug development are significant components. This applies to innovative products as well as generic medications.

Development of new drugs in general and pulmonary drugs in particular, is a very risky endeavor. As an illustration, from 2006-2015 in the United States, the failure rate for all respiratory products (including biologics) from Phase I to approval was almost 90%.[2] Even the failure rate of products in late stage development (Phase III to approval) was significant, at 33.7%. Failure rates for inhaled products are likely to be even greater, as biologics are included in these statistics and, typically, these have markedly higher success rates.[3] It is therefore natural that the innovator companies and their investors look for long periods of protection to be rewarded for the risk, length and cost of respiratory product development.

The patent laws no longer provide adequately long periods of exclusivity to reflect the increasing length of innovative pharmaceutical product development; i.e., the twenty-year patent life begins at the time of patent filing, which is typically very early in product development and can be ten to fifteen years prior to product approval. Some estimates suggest that the remaining patent life after product approval is, in many cases, as low as seven to ten years.[4] Additional exclusivity, in the variety of regulatory rules introduced initially in the Hatch-Waxman Act, and more recently in the form of other initiatives (e.g., the Generating Antibiotic Incentives Now (GAIN) Act and the 21st Century Cures Act), is also possible.[5]

The barriers to entry of generic products are not just in the form of patent infringement and regulatory exclusivity. They also include regulatory hurdles associated with the nature and quantity of the evidence required to prove their equivalence to innovator reference products to have such generics approved.

For example, Wixela® Inhub® (Mylan, Canonsburg, PA, US), the only generic version to date of GSK's Advair Diskus® (Brentford, UK) approved in the United States, took "10 years of rigorous development."[6] Mylan reported[7] that their R&D expenditure for this generic development was more than $700 million US. No doubt, a significant portion of the length and cost was the preparation for and conduct of the 28-day "bioequivalence" trial that enrolled more than 1,000 patients.[8] The Novartis/Oriel program with their generic version of Advair has not yet succeeded in obtaining approval, despite extensive pharmacokinetic and efficacy trials to provide evidence of "bioequivalence" [9, 10] and has subsequently been suspended with a write-off of $442 million US.[11]

Clearly, innovators have an interest in obtaining the maximum protection through patents and regulatory exclusivity, while generic companies and the public have an interest in the earliest approval of "generic" products. The purpose of this article is to initiate a discussion among all key stakeholders to find ways to provide the general public with the best-possible inhaled drugs at an affordable cost while rewarding the industry for taking the risk of investing in the development of more efficacious and safer medicines. For illustration, we propose some examples of what might be done. As many companies would not develop new inhaled products without including the US in their potential market, we will focus on the US.

Can we improve accessibility and affordability of orally inhaled therapies while protecting incentives for the development of innovative products?

Improving accessibility while protecting innovation

The question is: Can we improve accessibility and affordability of orally inhaled therapies while protecting incentives for the development of innovative products?

We believe the answer is "Yes" and want to provide the important assurance that this goal should, and can be, achieved without any adverse impact on the quality, safety and efficacy of the products reaching patients. As we will outline in detail here, a combination of regulatory incentives for innovators, in return for their assistance preparing the necessary monographs, should enable sufficient risk reduction to allow generic products to be approved on the basis of compliance with the monographs, without the need for human clinical trials to prove equivalence.

We applaud the process of harmonization of compendial standards in the form of drug product monographs.[12-14] However, such standards could be used more extensively than that which appears to be currently contemplated, in order to be much more impactful for the public good.

The foundations of the post-approval quality of inhaled products, whose clinical performance is assumed to resemble the results of the pivotal clinical trials that justified their approval, are in the adherence to good manufacturing principles and quality control systems that focus on the critical attributes of these medicines. These systems ultimately reflect the Chemistry, Manufacturing and Controls (CMC) aspects of the product used in the pivotal trials. In principle, it can be reasoned that if an innovator is able to release their batches of commercial product based on *in vitro* assessment methods and specifications derived from a thorough understanding of the product, then a generic version of the product from another manufacturer that is made under GMP conditions, tested with the same methods and compliant with the same specifications as the innovator's product should be as safe and efficacious as the original product and therefore approved without any additional clinical studies.

Yet in the US, generic versions of OIPs—specifically pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs)—cannot be approved on the basis of *in vitro* studies only. This contrasts with EU regulations where this is possible in principle and an algorithm for the decision process starting with *in vitro* "bioequivalence" is available, which allows a generic product to be approved without conducting "bioequivalence" clinical trials.[15-17] This difference has enabled the approval in the EU of at least four generic versions of the Advair Diskus.

However, even in the EU, there are both practical challenges and logical inconsistencies in these regulations: there is no universal reference standard to which the generic company can compare their products. The generic company must pass bioequivalence studies against "randomly" selected reference batches, with no certainty that these are either "representative" of the batches on the market, or, indeed, of the properties of the batches that were used in the pivotal approval trials. Running complicated pharmacokinetic trials with multiple batches to provide evidence of bioequivalence seems even less meaningful in light of the findings that samples of the marketed reference product may fail bioequivalence tests against "itself" due to inter-batch variations.[18-20]

It therefore seems much more meaningful for generic products to meet the same "reference product" CMC criteria that the innovator is using to release their batches to the market.

Compendial product monographs should set the standards for generic product approval

There are already elements of legal framework in the US that could be adjusted to facilitate the process we are proposing: approval of generic products solely on the basis of *in vitro* tests in the form of compliance with product monographs, in conjunction with attractive concessions for innovators in return for providing the necessary product information in a timely fashion.

The Hatch-Waxman Act, which was introduced to accelerate the introduction of generic products, recognized the discrepancy between patent protection duration and length of new product development. To reflect that, it afforded increased regulatory exclusivity periods.[21]

We believe that additional exclusivity (e.g., similar to that for biologics) or attractive regulatory incentives such as priority review vouchers, could be used to compensate innovators for the mandatory publication of their quality control methods and specifications and provision of reference standards to enable the compendial product monographs.

This would require urgent implementation of the current regulatory[12,13] and compendial[14] efforts to have such monographs ready for use by the generic industry no later than five years prior to the anticipated first "legal" entry of a generic version of a product.

The approval of the generic product would then be subject to the ability of the sponsor to demonstrate compliance with specifications for the product using these published compendial methods, both at release and during the stability studies, as well as evidence of GMP compliance of the product's manufacturing facilities. No additional evidence of "bioequivalence" in the form of *in vitro* or *in vivo* studies would be required for approval of the generic products.

Marketing of such generic products would still only be possible under the existing patent laws applicable in the territory.

The suggested path would only apply to products approved as "generic" (through an Abbreviated New Drug Application (ANDA) in the US), as opposed to products that use the same active pharmaceutical ingredient (API) but have substantially different formulations or routes of administration relative to the innovator's product (e.g., products approved under the 505(b)(2) regulatory path in the US).

The future of OIP industry is what we will make it

Inhaled medications have many advantages over other routes of delivery, especially for locally acting drugs. It is in the best interest of all key stakeholders—patients, healthcare professionals and inhalation companies developing and marketing products as well as payors—to have these products accessible and affordable to all who need them. At the same time, it is necessary to continue to reward companies and individuals who work with innovator products for their efforts and investments that bring better inhaled medications to patients.

Both innovator and generic companies would be well served with such greater certainty about regulatory exclusivity. In conjunction with new incentives, the innovator industry may invest more effort on fundamentally new approaches to OIPs versus extension of patent protection for old products. Much of academic and industrial research could be redirected from bioequivalence studies to investigations aimed at development of new OIPs with improved efficacy, safety and convenience for patients. All of these efforts should result in better respiratory healthcare. Approval of multiple generic versions of OIPs would result in greater affordability and accessibility through lower pricing and availability in all segments of the US healthcare system as well as those of other countries. The incentives for innovators would both stimulate and accelerate development and approval of new valuable therapies.

Join the discussion!

We hope that this short opinion piece will stimulate constructive discussion. We invite readers to use the Inhaled Drug Delivery Specialist LinkedIn blog to participate: https://www.linkedin.com/groups/69806/. We are also seeking proposals for participation at conferences to facilitate a vigorous exchange of ideas and paths to implement them.

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