PUBLIC INTEREST & INCENTIVES FOR INNOVATORS OF INHALED PRODUCTS

In this article, Igor Gonda, PhD, Chief Executive Officer & Founder of Respidex; David Cipolla, PhD, Vice-President, Research, Insmed; and Philippe Rogueda, PhD, Chief Business Officer & Co-Founder, Merxin, discuss the changes needed to increase the number of approved generic orally inhaled drug products (OIDPs) whilst providing additional incentives to innovators to meet the needs of the general public.

The debate about how to reduce healthcare costs is on everyone's mind but one key question remains unanswered – how can we accommodate the needs of the general public for accessible and affordable healthcare whilst preserving the motivation for innovators to make large, long-term and risky investments to discover and develop new therapies?

We will start with the opportunity to decrease healthcare costs through the approval of generic OIDPs. One of the key factors is naturally the effort required to obtain approval of a generic version of an OIDP, especially in the US as this is potentially the biggest market with the highest drug prices. Remarkably, the push to bring these prices down is one of the very few areas upon which the US president and his political opponents seem to agree!

The impact of generic product introduction in the US is indisputable: according to a US Association for Affordable Medicines (AAM) report, generic medicines saved US$253 billion (£206 billion) in 2016.[1] Considering that the total US retail cost of prescription drugs that year was about $389 billion, this is certainly no small change – representing a 40% reduction. Whilst prescription drugs represented less than 12% of the total annual US healthcare costs in 2016 of $3.3 trillion, increasing the availability of generics is clearly one of the ways to contain the seemingly unsustainable growth of healthcare costs.

The challenge for society and its leadership is to maintain a responsible balance between lowering the cost of drugs whilst supporting the existence of an innovative industry[2] with its impressive achievements in recent history.[3,4] Let us not forget that it is this industry that has enabled us to deal successfully with diseases, notably many types of cancer and HIV, whose diagnosis not so long ago was the equivalent to a death sentence and can now be cured or treated with dignity as a chronic disease – if the patient can afford the treatment. Inhalation products contributed significantly to the increased life expectancy of cystic fibrosis patients and made living with chronic diseases – asthma and COPD – much more bearable.

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WHAT IS THE CURRENT STATUS FOR OIDPS?

Respiratory diseases already constitute one of the highest global health burdens and are on the rise.[5] The existence of an innovative industry that can successfully deal with existing problems as well as swiftly respond to new and often sudden crises, such as the COVID-19 pandemic, is crucial for the wellbeing of all. Although the immediate focus is on oral therapy for the management of the current crisis, the transmission of the virus can occur by inhalation and the key aspects of its morbidity and mortality are respiratory complications. It is possible that locally acting agents administered by inhalation may ultimately be most suitable both for prophylaxis and treatment of this and other viral infections affecting the respiratory tract.

Let us take a more focused look at the competition from generics among

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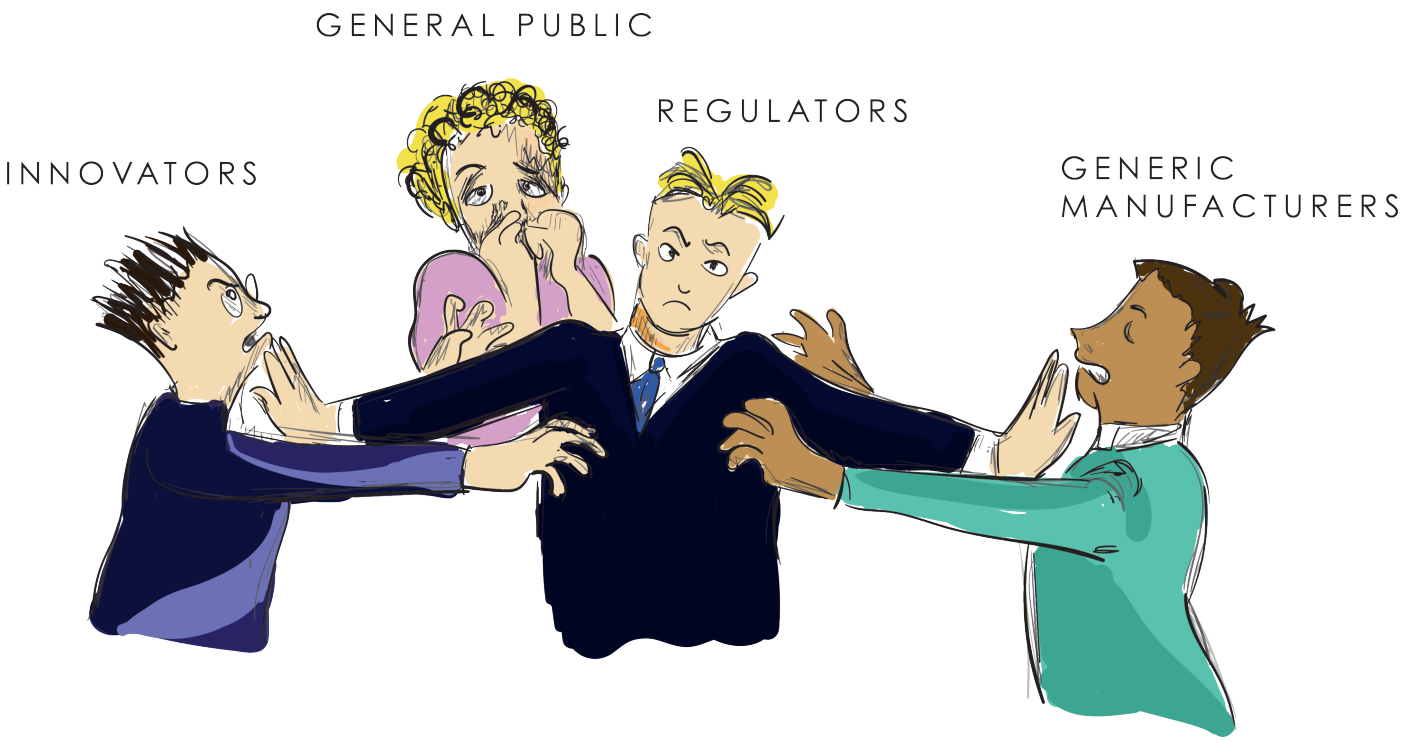

Figure 1: Regulatory hurdles, formalised in the requirements of the amount of evidence deemed adequate for approval, represent an obstacle to generic OIDP approvals, affecting various stakeholders.

respiratory products: the availability of generics in this category contributed $7.4 billion savings in the US in 2016.[1] Although this is significant, it represents less than 3% of the overall annual impact of the introduction of generics. Interestingly, the biggest contributor to this number was the genericised version of Merck & Co's Singulair (montelukast), which ranked as the eighth highest generic cost saver at $4.7 billion. Whilst Singulair is indicated for asthma, it is given orally and ingested, not inhaled. Yet the asthma inhaler market in the US is much bigger than oral asthma drugs. Based on the above figures for the total impact on savings from all other generic respiratory products, the savings from generic inhalers in 2016 represented only about 1% of the total savings.

POTENTIAL CAUSES OF LOW NUMBER OF GENERIC OIDPS

There is no doubt that the size of the market for an innovator's product is a major attraction for generic manufacturers to develop substitutes. The generic industry weighs that against the cost, risk and time to obtain approval of such generics. Whilst patent protection and the potential impact of litigation play an important role, other key factors include the regulatory hurdles formalised in the requirements of the amount of evidence deemed adequate for approval (Figure 1).

These challenges are recognised by the US FDA. Upon the approval of the first generic version of Teva's ProAir HFA (albuterol solution metered dose inhaler (MDI)), the FDA commissioner said: "MDIs like these are known as complex generics, which are traditionally harder to copy because of their complex formulation or mode of delivery. As a result, too many complex drugs lack generic competition even after patents and exclusivities no longer block generic approval. Supporting development and approval of generic copies of these complex medicines so that these products can get to patients has been a major focus of our efforts to improve competition and access and to lower drug prices. Getting more generic copies of complex drugs to the market is a key priority for how we'll help bring new savings to consumers."[6]

The multiple facets of the importance of generic OIDPs for the general public *vis a vis* the difficulties with the regulations of their entry were expressed by the FDA in conjunction with the approval of Mylan's Wixela – the generic version of Advair – in 2019, 19 years after the US approval of GSK's NDA:[7] "Advair was the only dry powder inhaler combination product available for many years, and its manufacturer earned about $5 billion a year in revenue for this one treatment. Because it is a combination of two drugs administered by an inhaler (the device component), it is a very complex product to copy." The public interest could not have been better exemplified than by the quote from a patient, published in the FDA's Office of Generic Drugs Annual Report: "Thank you so very, very much for this — you have no idea how this generic brand will change the lives of untold numbers of people who were struggling to pay for their asthma medicine. I paid $398.96 for my inhaler back in January and today, when the cashier at the pharmacy told me that my total was only $188.65, I almost broke down in tears! Again, thank you from the bottom of my heart!"[7]

Although these two approvals of generic versions of important inhalation products in the US may signal that more are probably coming, the barriers to entry are currently still very high as per current product specific guidances (PSGs) issued by the FDA. As of March 2020, these guidances for MDIs and dry powder inhalers (DPIs) mandate successful conduct of PK and PD clinical trials in addition to extensive *in vitro* studies, often requiring "dauntingly large numbers of patients to demonstrate bioequivalence (BE)" – the quoted expressions are from an FDA presenter at a recent workshop on harmonisation of approval of generic products:[8] These BE studies must be carried out with variable reference products and against statistical criteria that fail to acknowledge the variability of the reference products.

To illustrate the associated hurdles at present for generic manufacturers of OIDPs in concrete numbers, development of Wixela took more than a decade and $700 million.[9,10] This represents a big effort even for a large pharmaceutical company – Novartis gave up on its programme towards a generic Advair inhaler after many years and a write-off of about $442 million.[11] The financial details of the Perrigo-Catalent programme that resulted in the approval of their generic version of the ProAir HFA are not publicly known but they received three complete response letters from the FDA during their long ANDA process, confirming long time lines and likely high development costs.[12]

The FDA has invested a substantial effort in its internal research as well as funding extramural activities to provide a scientific basis for approval of OIDPs, and more specifically MDIs and DPIs. When summarising the achievements to 2017 and the path forward, the FDA Generic Drug Products report stated with reference to OIDPs: "In the next five years of generic drug product user fee amendments (GDUFAs), there are a few overarching goals for OIDPs. The first goal will be to build on the research of the first five years of GDUFA to create clear pathways to establish BE, without the need for comparative clinical endpoint studies."[13]

The concerns about the inability to ascertain equivalence solely on the basis of *in vitro* testing seems to be driven primarily by the lack of consensus on the impact of the rate of dissolution for poorly soluble locally acting inhaled drugs. To quote from the above cited report: "There is no standardised, validated method to measure drug dissolution. Additionally, there is no clear understanding of how *in vitro* parameters might correlate with *in vivo* dissolution for these products; i.e. lack of an *in vitro* to *in vivo* correlation. Understanding the dissolution process could eventually predict therapeutic behaviour based on these *in vitro* characteristics."[13]

We certainly think that the equivalence of *in vitro* test results between the generic and reference products for other critical aspects of the performance of OIDPs – notably those related to the regional deposition in the respiratory tract and systemic exposure – should be sufficient for approval without the need for human studies.

Unfortunately, the sentiments about the lack of scientific consensus for poorly soluble inhaled drugs do not seem to be relevant in the context of drugs that are highly water soluble and/or delivered in a solution formulation, such as the ProAir HFA, and yet it would appear that both human PK and efficacy studies are still required for ANDAs for this product.[14] Let us hope that the FDA will achieve its goal to remove the requirements for ANDAs to contain human studies for the majority of OIDPs by 2022 and subsequently for all of them. Perhaps the new beclomethasone MDI PSG which provides some wiggle room for a waiver of human studies if the *in vitro* package is convincing enough, is a sign of more enlightened times to come.[15]

Faster and more cost-effective generic product development, however, will require more than just changes in the US regulatory hurdles. To show equivalence, even *in vitro*, it is necessary to have access to the reference materials (API and drug products) as well as the methods and specifications. In an ideal world – which we believe can be achieved in this respect – there would be internationally accepted reference standards as well as API, and critical excipient and drug product monographs containing all the information required to show adequate quality of the generic product through compliance with the same standards as the innovator product.[8]

After all, the innovators do not have to conduct a clinical trial every time they release a new batch of drug product. Neither do they need to run clinical trials in many other circumstances – e.g. changes of sources of the API or manufacturing facility,[16] that would be subject to a supplemental NDA. In those situations, *in vitro* tests used for the product release and in-process checks are usually adequate for such supplemental approvals to mitigate many of the risks similar to those posed by the introduction of generic substitutes. Of course, both the innovator and the generic companies are and should continue to comply with the high standards of good manufacturing practice (GMP).

COMPENDIAL MONOGRAPHS AND REFERENCE STANDARDS

There is a strong correlation between the existence of USP monographs and the availability of generic products; not surprisingly, inhalation products have the smallest proportion of monographs relative to the total that are eligible for generic substitution of OIDPs based on the Orange Book (19.4% monographs for inhalation versus the highest category – oral dosage forms – with 79.4% of eligible orals).[17]

> "We do not believe that the relationship between the number of generic products and availability of monographs is just a spurious correlation."

We do not believe that the relationship between the number of generic products and availability of monographs is just a spurious correlation. We think it is reflected in the lack of approvals for MDIs and DPIs and caused in part by the very onerous ANDA approval hurdles and the absence of relevant monographs. It should be a major risk mitigation for the general public and the FDA to waive the requirement for human studies for bioequivalence if the generic products are made to comply to the battery of tests used in quality control systems of the innovators. Such monographs also have the advantage of resulting from a consensus process subjected to continuous public scrutiny by all key stakeholders.

POTENTIAL WIN-WIN-WIN PATH FORWARD

Today, there is neither a stick nor a carrot available to the FDA or the USP to facilitate the availability of product-specific monographs and reference standards. The history of FDA regulations suggests that meaningful regulatory incentives are a powerful motivation for innovator companies.[2,18] The US Hatch-Waxman Act that was introduced in 1984 to accelerate the introduction of generic products recognised the discrepancy between the patent protection duration and the length of new product development – and to reflect that, it afforded increased regulatory exclusivity periods.[1] Extension of regulatory exclusivity and acceleration of product approval provided a variety of attractive stimuli for industry – e.g. priority review vouchers for the development of orphan indications, breakthrough drugs, paediatric indications and novel antibiotics.

We suggest that similar incentives from the FDA could be used to motivate innovators to provide timely assistance to publish the relevant monographs and enable provision of critical reference standards for regulators and generic manufacturers (Figure 2).

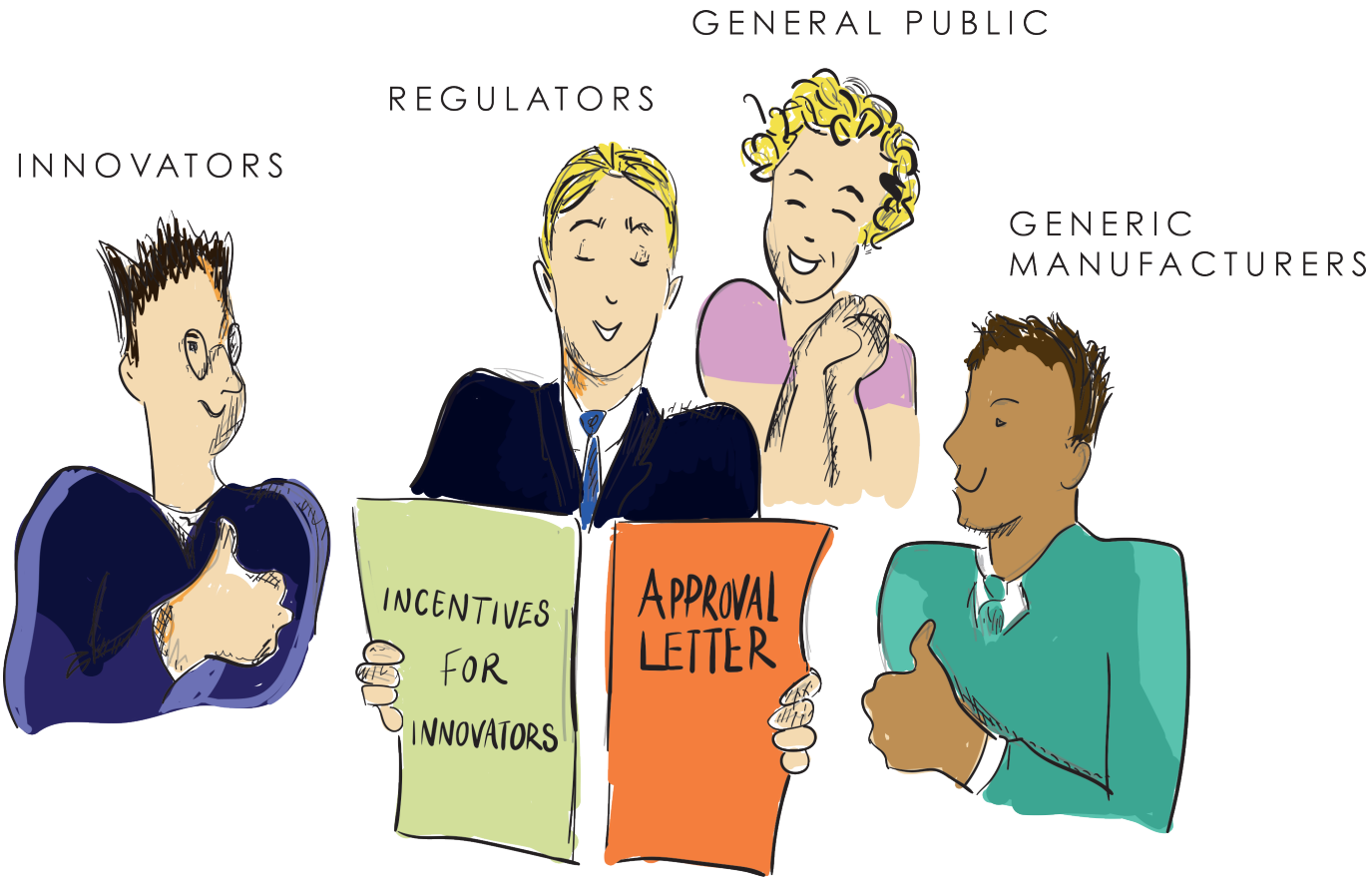

Figure 2: Regulatory incentives would prompt more generic OIDP developments and there could be benefits for innovators too, representing a win for all stakeholders.

> "The absence of monographs for many important OIDPs is the likely reason why even companies with significant resources are reluctant to attempt to develop the first and then a second and subsequent generic products."

The USP already has the right to develop monographs with third parties if the innovator is unwilling to do so.[19] However, there appear to be no incentives at present for generic or innovator companies to work with the USP to develop such monographs. The absence of monographs for many important OIDPs is the likely reason why even companies with significant resources are reluctant to attempt to develop the first and then a second and subsequent generic products.

The economic impact of the presence of monographs as a causal factor for a greater availability of generics was estimated to be more than $6 billion in cost savings to US healthcare in 2016;[17] the cost savings to the generic manufacturers would likely be highly significant. Given the size of the inhalation market in the US and the sparsity of inhaled generics for the major inhalation products that are off patent, the opportunity seems very significant.

We believe that some additional exclusivity (e.g. similar to what was implemented for biologics) or attractive regulatory incentives, such as priority review vouchers, could be used to compensate the 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 compendial[19] and regulatory[20,21] efforts to have such monographs ready for the generic industry no later than five years prior to the anticipated first legal entry of a generic version of the product.

Similar incentives for publication of monographs could be provided to the first-to-approval generic manufacturers if the innovator did not participate in a timely collaboration with USP. Marketing of such generic products would still only be possible under the existing patent laws applicable in the territory.

For the innovators, the regulatory incentives may outweigh the losses due to the earlier entry of generic competitors. But perhaps they will also save them substantial costs incurred to protect their markets through litigation against generic manufacturers. And they will be able to refocus those efforts on what they are best appreciated for – innovative research leading to approval of superior therapies.

REGULATORY HURDLES FOR INHALER DEVICES

An important development in the context of generic OIDPs that is also likely to have a positive impact on innovators is the FDA's greater flexibility in approaching the question of equivalence of devices. The recently issued draft guidance[22] appears to allow more flexibility and a much more relevant decision-making process than the strictly legalistic definition of the device sameness: it allows human factors studies to provide evidence that the device for the generic product is equivalent to the innovator's product from a perspective that is highly relevant to the patient.

The approval of Wixela as a generic substitute of Advair is an example of the flexibility afforded by the FDA for a device which not only looks different from the innovator's product but is also operationally different, in at least one respect – the device resistance – that is generally viewed as a critical attribute of an OIDP, especially a DPI.[23]

Exercising such meaningful, carefully considered flexibility would also assist innovators in bridging between devices during development as well as post approval, thus reducing the length, cost and risk of development of new inhalation therapies.

ABOUT THE COMPANIES

Respidex is a consultancy helping pharmaceutical companies in their R&D activities, regulatory strategy, financing and commercialisation of products for prevention, diagnosis and treatment of diseases. Respidex clients include small early preclinical companies as well as enterprises in late-stage clinical development.

Insmed is a global biopharma company developing treatments for patients with serious and rare diseases. Its first commercial product, ARIKAYCE® (amikacin liposome inhalation suspension), is the first therapy approved in the US for the treatment of refractory *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options. Insmed's earlier-stage clinical pipeline includes INS1007, a novel oral reversible inhibitor of dipeptidyl peptidase 1 with therapeutic potential in non-cystic fibrosis bronchiectasis and other inflammatory diseases, and INS1009, an inhaled formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension.

Merxin designs and supplies generic and customised inhaler device platforms, including multidose dry powder inhalers, capsule dry powder inhalers, soft mist inhalers, no heat no PG vaping devices and devices tailored to cannabinoid delivery to the lungs and nasal cavities. Customers combine Merxin device platforms with their drug formulation to make final dosage forms that are supplied to users and patients. Merxin has been assessed and certified as meeting the requirements of ISO 13485:2016 for the Design, Development and Supply of inhalers. Established in the UK in 2015, with manufacturing capacity across the globe and an international client base, the company is adding more products to its portfolio and expanding rapidly.

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ABOUT THE AUTHORS

Igor Gonda, PhD, is the Founder of Respidex, a San Francisco-based consulting company. Dr Gonda has held a variety of executive positions in US and Australian private and public pharmaceutical and biotech companies. His research focus was primarily in the area of drugs and biologics administered to the lung and nose conducted in industry and, prior to that, in universities in England, Australia and the US. Dr Gonda's current interests additionally include the prevention and cure of the COVID-19 respiratory infection, the involvement of patient advocacy groups in pharmaceutical R&D, venture philanthropy and the regulatory process to accelerate availability of cures for their diseases, and in opportunities for making individualised precision medicines faster and cheaper.

David Cipolla, PhD, has >25 years of experience with a focus on the development of formulation and drug delivery technologies to support pharma product development. Dr Cipolla is Vice-President, Research at Insmed, where he is part of a team developing novel, targeted therapies to help serve the critical unmet needs of patients battling serious rare diseases. Prior to joining Insmed in 2018, he was Vice-President, Preclinical Research at Aradigm covering all phases of product development and before that he worked at Genentech developing and characterising the delivery of protein aerosols to the airways, culminating with the approval of Pulmozyme® rhDNase for the management of cystic fibrosis in 1993. Dr Cipolla holds a chemical engineering degree from MIT (SB) and UC Davis (MS) and a pharmacy degree from the University of Sydney (PhD). He served as chair of IPAC-RS, chair of the ISAM Regulatory Affairs Working Group and ISAM Board Member.

Philippe Rogueda, PhD, FRSC, CChem, CSci, CIng, EURIng, Co-founder and Chief Business Officer of Merxin, is a Fellow of the Royal Society of Chemistry and OINDP expert with an accomplished track record delivering technology and global projects across R&D and commercial industrialisation. Dr Rogueda has held a number of positions in the inhaled drug delivery space, starting as a formulation scientist in the pMDI formulation labs of AstraZeneca; as a principal scientist at Novartis designing DPI, nasal and nebulised inhaled therapies; as an Executive Director of Inhaled Products R&D at Actavis/TEVA; before setting up Merxin to make inhaler technology accessible to a wider audience. Rogueda is principal consultant at Aedestra (Hong Kong), founder of Inhalation Asia (Hong Kong), and of Anthocan (UK) a company dedicated to the formulating of inhaled cannabis therapies.

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