

The regulatory landscape for OINDPs—the biggest shake-up in a generation?

A review of ways in which globalization and generics are shaping regulation and practice

Mark Copley, MEng and Anna Sipitanou, BSc, MSc
Copley Scientific Ltd

The regulatory landscape for orally inhaled and nasal drug products (OINDPs) has altered markedly in recent years and change is continuing at an unprecedented rate. These changes can be linked to a transformation in the industry. Making effective, economically accessible products, particularly for the treatment of asthma and chronic obstructive pulmonary disease (COPD), is a high priority and abbreviated new drug applications (ANDAs) now significantly outnumber their new drug counterparts. The generics industry is truly global and is maturing for service to domestic markets, as well as for export. Overlaying these trends are well-documented, industry-wide shifts towards outsourcing, shared risk joint ventures and licensing, and a move away from fully integrated “big pharma” company structures. Today, inhaled products, novel and generic, are developed and manufactured by many companies across the globe, including contract research and manufacturing organizations (CROs and CMOs).

In this article, we look at recent changes in the regulatory framework, summarizing changes in United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance, the pharmacopeias, and in localized regulations from regions of growing importance for drug development and manufacture, such as Brazil and China. A key aim is to provide insight into how the overall approach to inhaled product testing and development is evolving.

A changing industry

2017 was a record year for new generics, with 843 full and 184 “tentative” approvals by the FDA, across all dosage forms.¹ This contrasts with 46 new drug

approvals (NDAs) for the same year, the highest total since 1996 (which had 59), a period fueling much of today’s generic activity.² These figures underline the extent to which ANDAs now dominate submissions to the FDA. Making first and subsequent generics available as quickly as possible, within the constraint of strictly safeguarding clinical safety and efficacy, is a vital defense against spiraling healthcare costs.

The rising global incidence of respiratory illness and patent expirations have made the drugs routinely used for treating asthma and COPD popular generic targets. These include fluticasone propionate (FP) and salmeterol, the active ingredients used in combination in Advair®/Seretide®, an off-patent product still commanding \$4 billion in annual sales, due to the difficulty of replication.³ However, there has recently been a significant breakthrough with the first generic version of Advair in the US: Wixela™ InHub™ from Mylan—approved in January 2019, following sustained investment over many years.⁴

Inhaled products are classified as complex generics because the success of drug delivery relies on both the formulation and the device, with the additional influence of patient technique and physiology resulting in unique complexity.⁵ It is extremely challenging to deliver drugs efficiently via the pulmonary route and products were initially commercialized largely as a result of significant investment by just a handful of large, blue-chip pharmaceutical companies—principally 3M, GlaxoSmithKline, AstraZeneca, Novartis, Sanofi and their predecessors.

The experts pioneering the commercialization of OINDPs within these companies essentially formed a relatively close-knit, predominantly US- and European-centric community that was closely

involved with developing the analytical techniques needed to characterize inhalers. Critical quality attributes (CQAs) for OINDPs include delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD), which are used to infer *in vivo* deposition behavior. Multi-stage cascade impaction is the technique of choice for APSD measurement because it measures aerodynamic particle size, a metric intuitively relevant to inhaled drug delivery, specifically for the active pharmaceutical ingredient (API(s)) within a formulation. Despite these unique merits, cascade impaction is a lengthy and predominantly manual technique, with data quality easily influenced by the skills of the operator.⁶

In recent decades, well-documented pressures on the pharmaceutical industry have led to a transformation in its structure.⁷ Much of the experience associated with inhaler development now resides with CROs, scientific consultants and consortia, (reflecting the broader industry switch to outsourcing), as well as smaller, generic pharmaceutical companies. Cross-industry expert groups such as the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) and the European Pharmaceutical Aerosol Group (EPAG) have therefore become vital reservoirs of expertise, working collaboratively to build consensus across the industry. At the same time, inhaled products are now routinely developed and manufactured across the globe, mirroring the proliferation of the generics industry. India, China, Mexico and Brazil, for example, all have flourishing inhaled product activity, much of it generic, serving the domestic market but also for export. Many of these companies are relatively small and resource-lean, and have limited experience with inhaler technology.

In summary, in the inhaled product area, the difficulty of dealing with an exponential rise in ANDA submissions is therefore exacerbated by the following issues:

- complex technology and testing techniques;
- the dissipation of large pharmaceutical company groups with detailed understanding of inhaler technology and testing;
- geographical diversification and the associated need to transfer specifications from lab-to-lab, across the globe.

Most directly in the US, recent changes in the regulatory framework can be linked to a desire to accelerate progress towards a more cost-effective product portfolio by reducing obstacles to the approval of complex generics and improving the efficiency and predictability of the FDA generic review process.⁵

A rapid rise in product-specific guidance

Since 2013, the FDA has released more than 42 product-specific guidance documents for inhaled drugs. These reinforce the fact OINDPs are now tested as combination products* (the delivery device and drug formulation together) and reflect a signaled policy change in June 2010 to adopt a more proactive approach to the provision of support for bioequivalence (BE) studies.⁸ More specifically, they indicate the prioritizing of complex generics.⁵

In a clinical setting, generic products are prescribed interchangeably with a reference listed drug (RLD). Demonstrating BE between a test (generic) and reference (RLD) is therefore central to a generic submission, with product-specific guidance indicating the application of both *in vitro* as well as *in vivo* (pharmacokinetic (PK) and pharmacodynamic (PD)) tests in most cases. These guidance documents are specific both to an API and its form—inhalation aerosol or inhalation powder, for example, and typically reference test methods in the general chapters of the US Pharmacopeia (USP).

The pharmacopeias are collections of standards and quality specifications for medicines and describe tests to quantify quality via characteristics such as strength and purity. In contrast with the situation within the European Union, they may operate independently of regulatory authorities; for example, the USP is a discrete and separate body from the FDA. Although in this instance, there is no formal obligation to adhere to compendial methods in the preparation of a submission, FDA regulatory guidance frequently references the USP. It is therefore common practice to adopt the methods the USP includes, to reduce the risk of an inadequate data submission. It is worth noting that the FDA actively encourages pre-submission discussions and correspondence to ensure that testing strategies will effectively support a proposed ANDA to minimize this risk.^{9,10}

In recent years, a growing number of product-specific USP monographs have been developed and the latest version of the USP includes five with a further one in draft.^{11,12} These cover:

- FP inhalation aerosol
- FP inhalation powder
- salmeterol inhalation powder
- FP and salmeterol inhalation aerosol
- FP and salmeterol inhalation powder
- albuterol inhalation aerosol (draft)

These monographs are typically contributed by the companies responsible for the RLDs to which they relate, and they can include test methods and equip-

*The description of OINDPs as “combination products” is used here to highlight the dependence of performance on the device and formulation, not to refer to formulations containing more than one active ingredient. Those are referred to as “dual active” products.

ment that are different from those in the general USP chapters (Figures 1 and 2). Such tests use set-ups implemented by innovator companies 20 years or more ago to deal with the nuances of unique products, rather than those associated with the refined best practice that general compendial methods seek to capture. Their value to generics developers is in eliminating a test

set-up as a possible source of difference when it comes to demonstrating BE and moreover the inclusion of acceptance criteria, which are particularly useful for product release testing. However, differences between the product-specific monographs and the general chapters are also now a potential source of confusion when it comes to determining the test set-up to be used.¹³

Figure 1

Product-specific monographs call for the use of glass sample collection apparatus for fluticasone propionate and salmeterol inhalation powders (separately and in combination, where applicable) (left) and inhalation aerosols (right) that is different from that specified in the general USP Chapters.

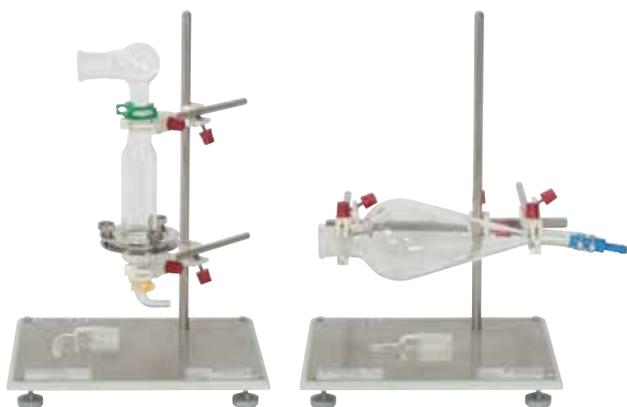


Figure 2

Product-specific monographs call for the use of a modified induction port in combination with a modified preseparator (left) for fluticasone propionate and salmeterol inhalation powders (separately and in combination, where applicable) and modified inlet cone for fluticasone propionate inhalation aerosols (right).



Better methods...

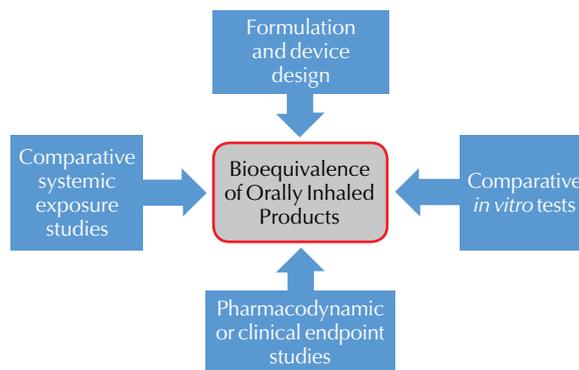
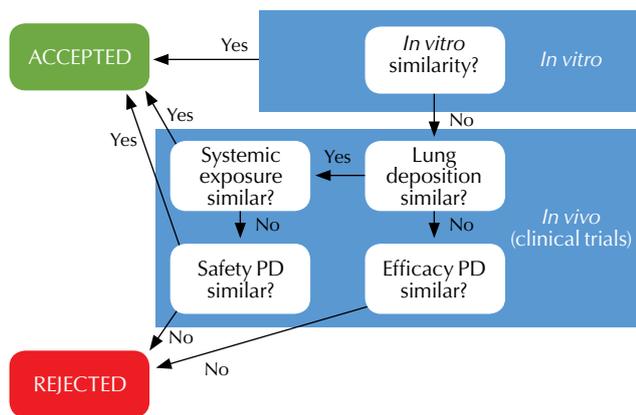
In vitro methods are the simplest approach to testing for the demonstration of BE. Easy to use and validate, they are highly repeatable and relatively inexpensive. PK studies typically track drug concentration in the blood plasma or urine and are a cornerstone of BE studies for systemic drugs. However, for drugs that work by localized action—the vast majority of OINDPs—their relevance can be more questionable.¹⁴ PD studies potentially offer the highest degree of clinical relevance since these quantify the biological and physiological effect of the drug. However, comparative PD studies can be costly, lengthy and relatively insensitive to differences between formulations⁵ and to differences in delivered dose and/or aerodynamic particle size.

The European Medicines Agency (EMA) does not currently offer product-specific guidance for generic OIP submissions, but rather offers general guidance that is in the process of being updated.^{15, 16} A stepwise approach is described which, in theory, allows a submission to succeed based on *in vitro* data alone (Figure 3). However, a high degree of formulation and device sameness between test and RLD products is required. Historically, robust correlations between *in vitro* data for OINDPs and *in vivo* behavior (*in vitro/in vivo* correlations—IVIVCs) have proven somewhat elusive and, as the concept paper makes clear, the rigorous process of demonstrating BE via *in vitro* testing alone is difficult in practice.¹⁶ When it comes to *in vivo* options, PK studies are noted to be “simpler, shorter and more discriminative” for demonstrating similar efficacy; the difficulty of achieving biomarker sensitivity in PD studies is highlighted.^{14, 16}

The FDA currently offers no comparable, formalized, general guidance to complement product-specific guidance documents, but the FDA 505(j) and 505(b) (2) pathways for OIP submissions call for a “weight of evidence” approach (Figure 3). These are the pathways used for generics and “supergenerics”—“improved therapeutic entities derived from known generics,”¹⁷ respectively. A minority of the product-specific guidance documents (mainly for nasal sprays) allow for the demonstration of BE via *in vitro* testing alone, but there is no indication with these generalized pathways that *in vivo* testing can be avoided. The FDA has, however, highlighted a need to improve the clinical realism of *in vitro* testing, through the implementation of strategies such as those described below, to reduce reliance on *in vivo* studies.⁵ Such improvements would likely prove beneficial with either regulatory approach.

Figure 3

EMA guidance (summarized at left) indicates a “stepwise” approach to testing to support a generic OIP submission, while FDA guidance (summarized at right) outlines a “weight of evidence” approach.



Enhancing the clinical relevance of *in vitro* tests also supports the implementation of Quality by Design (QbD), since this relies on developing a robust understanding of the correlations between critical material attributes and CQAs, the properties that define clinical efficacy. QbD is now relatively well-established across the pharmaceutical industry but adoption has been slow for OINDPs due to their complexity. Better IVIVCs make it easier to understand the clinical impact of formulation and device changes, thereby improving the science of product development—for both novel and generic products.

Against this backdrop, significant effort and FDA funding^{18, 19} has been invested in the development of novel, more clinically relevant *in vitro* techniques. Progress in this area was recently summarized in an FDA workshop⁵ which highlighted advances including the use of the following:

Breathing simulators

In compendial methods for APSD measurement, an OINDP is subject to a constant flow rate quite unlike the inhalation profile applied by a patient. This approach to testing is particularly problematic for dry powder inhalers (DPIs), where aerosol generation is typically driven by the inhalation maneuver of the patient. It is also an issue for products that are operated with a tidal breathing pattern, such as nebulizers and metered dose inhalers (MDIs) with spacers/valved holding chambers. Though breathing simulators are currently only specified in the compendial methods for dose uniformity testing for this latter group of products,^{20, 21} there is significant potential for more general application to improve the clinical relevance of the impactor-sized dose in APSD measurement.

With a breathing simulator, it is possible to investigate the impact of inhalation strength—the ramp rate to peak inspiratory flow rate (PIFR), for example—and lung volume to gain a clearer understanding of the likely impact of physiology on DPI performance. It is also possible to confirm that a test product retains BE

to an RLD across a range of relevant physiologies and flow parameters. A test set-up incorporating a breathing simulator for more clinically relevant APSD measurement is shown in Figure 4.

More representative mouth-throat models

The standard USP/Ph. Eur. induction port used to interface an OIP with an impactor has a simple, right-angled geometry that facilitates reproducible drug recovery for routine APSD measurement. It was originally conceived as a quality control (QC) tool to facilitate reproducible transport of the aerosol into the impactor, with little attempt to reflect real human geometry, but is now used widely in R&D. Unfortunately, this induction port is known to capture less of emitted dose than would be deposited in the mouth-throat region during clinical use.^{22, 23}

A more realistic mouth-throat model ensures that the mass sized by the impactor is closer to being representative of the dose that would enter the lung—in terms of total mass and size distribution—and is an important

Figure 4

More clinically realistic APSD measurements can be made using a breathing simulator to apply a patient-specific profile to a product during testing, in combination with a more representative mouth-throat model (e.g., the Alberta Idealised Throat, as shown).



step towards better IVIVCs. That said, moves towards greater realism must necessarily be balanced against the need to retain repeatability, and must also recognize that a cascade impactor is a high reproducibility particle aerodynamic size classification tool, not a lung simulator. Early efforts in this area include work by the Oropharyngeal Consortium²⁴ with more recently commercialized, alternative inlets such as the Alberta Idealised Throat [Copley Scientific Ltd, UK] which has a standard, idealized geometry, shown to robustly meet current industrial requirements²⁵ (Figure 4).

Dissolution testing

Following deposition in the lung, drug particles dissolve and permeate the lung tissue, thereby reaching their intended site of action. The dissolution behavior of inhaled drugs and the development of a test for its prediction has therefore been a subject of interest for some time. However, dissolution testing for inhaled drugs is a complex issue. The volume of fluid in the lungs is extremely limited, for example, and its composition varies according to the disease state and region of the lung. Methods proposed for dissolution testing include the McConville/Copley methodology,²⁶ but currently there are no compendial methods available. While many inhaled drugs are highly soluble, making dissolution almost instantaneous, studies have shown that dissolution testing can distinguish between formulations of the same drug and has significant potential for investigating modified release formulations and low solubility compounds. Work continues to develop robust methods, suitable for general use for all formulations.⁵

Morphologically Directed Raman Spectroscopy (MDRS)

Morphologically Directed Raman Spectroscopy (MDRS) enables the secure differentiation of API and excipient particles in a formulation via chemical identification, and the associated generation of component-specific particle size and shape information. It has proven particularly useful for BE studies of locally acting suspension nasal sprays, which involve confirmation of a comparable API particle size distribution in the test

and reference products. These sprays contain excipient and API particles that cannot be robustly differentiated based on size and/or shape alone. With MDRS, morphological data is gathered to direct and minimize the application of Raman spectroscopy, such that only particles of questionable provenance are chemically analyzed to make measurement times practical.⁵

MDRS also has potential for investigation of the dispersion behavior of suspension and dry powder OIP formulations as a non-destructive technique for chemical identification, and can also be used in combination with cascade impaction (Figure 5). Using an appropriate method to identify individual particles, it is possible to determine whether an API is completely dispersed or agglomerated and/or to see whether one active disperses differently than another in a dual active* product.²⁷ MDRS has also been used to rationalize observed differences in dissolution behavior between test and reference products.

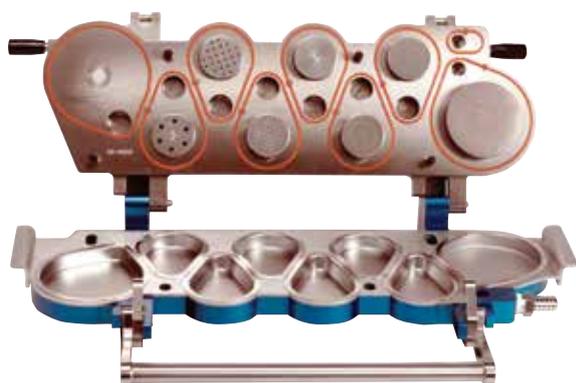
...best practice

Beyond the specific goal of greater clinical realism, recent changes reflect a move towards improving and safeguarding data quality, and the establishment of best practice. Extended FDA guidance and new USP Stimuli to the Review Process documents in these areas are particularly helpful for those with less experience but, as has been previously noted, ensuring “good science” reduces risks for all stakeholders. Expert training is highly complementary to the growing body of regulatory documentation, with the services provided by leading equipment vendors especially valuable to newer, less experienced researchers and analysts.

2018 saw the first update in 20 years of the FDA draft guidance document, “Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products—Quality Considerations Guidance for Industry,” with the inclusion of Parametric Tolerance Interval Testing (PTIT) for DDU a notable highlight.²⁸ PTIT is a statistical approach that provides a more rigorous assessment of quality by making more efficient use of DDU test data.

Figure 5

The Glass Disc Cup for the NGI (Copley Scientific) makes it possible to capture particles within a particular aerodynamic particle size fraction for analysis by MDRS, for the detailed study of dispersion behavior.



It is claimed that improved levels of protection for the patient can be achieved while simultaneously mitigating the risk of false rejection of an acceptable product.²⁹ The new draft guidance identifies PTIT as “more relevant for assuring the overall quality of the entire batch of an MDI or DPI” than traditional counting methods and its incorporation provides an incentive to improve product quality since this enables the reduction of sample size requirements; with PTIT, the producer chooses a test plan to match the specific product.

The latest thinking on various aspects of testing is also captured in a series of USP Stimuli to the Revision Process documents, which may go on to form the basis of informational USP chapters on the topics of:

Data interpretation³⁰

A multi-stage cascade impactor separates a delivered dose into a series of sized fractions which are analyzed, typically by HPLC, to determine particle size information for the API. This USP Stimuli to the Revision Process systematically considers presentation and interpretation of the resulting data including cumulative size distributions, stage groupings and the calculation of optional metrics. The original guidance relating to data analysis was removed from the USP in 2012 because it did not reflect the actuality of FDA requirements, leaving sponsors to work directly with the regulators to determine which metrics to report for a specific product.³⁰

Stage mensuration³¹

Mensuration is the process of measuring all the critical dimensions of a cascade impactor, notably the diameter of every nozzle on each stage, to assure suitability for use. These dimensions define the particle size fractionation performance of an impactor at any given flow rate and therefore the accuracy of the APSD parameters measured. Routine mensuration is therefore an element of Good Cascade Impactor Practices (GCIP) and is a surrogate for formal recalibration with standard particles. This USP Stimuli to the Revision Process proposes a procedure for mensuration that generates results to support the robust assessment of APSD measurement accuracy. A proposed informative chapter on GCIP will also cover other aspects of maintenance, method development and in-use testing to assure valid determinations of APSD.

Abbreviated Impactor Measurement (AIM) and Efficient Data Analysis (EDA)³²

AIM and EDA are two separate, but related, concepts. In simple terms, AIM streamlines the collection of APSD data by replacing a full resolution, seven- or eight-stage cascade impactor with a single- or twin-stage unit that divides the dose into just two or three fractions—the large- and small-particle mass (LPM and SPM, respectively) or the coarse, fine and extra-fine particle masses (CFM, FPM and EFPM, respectively), depending on the application. The induction port and pre-separator (where used)

are retained. AIM is designed to complement, rather than replace, the full resolution multi-stage cascade impactor, by accelerating measurements in formulation screening trials, for example, or in product QC.

EDA, which can be applied with either full resolution or AIM data, derives just two metrics from the impactor sized mass—LPM and SPM. The ratio LPM/SPM and sum LPM + SPM are used together to detect shifts in both mass concentration and size of the underlying APSD. Both AIM and EDA potentially improve data quality while at the same time alleviating the considerable analytical burden associated with OINDPs.

AIM and EDA were first introduced in the mid-2000s and there is some consensus in support of their adoption as compendial methods, providing there is sufficient evidence of validity from peer-reviewed studies.³² However, there is currently concern expressed by the FDA about the loss of resolution/information compared with full resolution APSD measurements, balancing the potential gains in analytical throughput.³³ This stance is broadly echoed by a Pharmeuropa enquiry of August 2014.³⁴

A changing geographical landscape

The drive to export to major markets, such as the United States and European Union, makes FDA and EMA regulations relevant across the globe, but localized regulatory guidance is also now advancing, bringing further complexity to the regulatory landscape. As noted earlier, the FDA and the EMA are not harmonized with respect to generic submissions and the picture is similar when it comes to the USP and the European Pharmacopoeia (Ph. Eur.). A new draft of USP <601>,³⁵ the general chapter relating to OINDPs, is currently in review and there is evidence of a further shift towards alignment with the FDA, at the cost of the harmonization with the Ph. Eur. A major change is the proposed removal of both the Marple-Miller Cascade Impactor and the Multi-Stage Liquid Impinger as recommended apparatus for APSD measurement, both of which are rarely used in the US due to their limited number of stages.

Brazil has an active inhaled generics sector, regulated by ANVISA (Agência Nacional de Vigilância Sanitária), the National Agency for Health Vigilance, and provides a good example of a more recently established regulatory framework. Estimates suggest that around 6.4 million Brazilians (over age 18) suffer from asthma, with mortality rates of approximately 2,500 per year.³⁶ A range of RLDs, both DPIs and MDIs, have been registered in Brazil and there are now several registered Pharmaceutical Equivalence Centres across the country for OIPs. ANVISA has very recently released new draft guidance on *in vitro* testing for nasal and oral inhalation medicines for the proof of therapeutic equivalence, supporting this work.^{37, 38} IPAC-RS, which has an established group in Brazil, has been assisting in the development of this regulation, which is closely aligned with US practice.³⁹

The Chinese Pharmacopeia (ChP) and the Chinese Food and Drug Administration (CFDA), which are more closely linked than the equivalent bodies in other geographies, are also making progress in establishing a localized framework. There is currently no regulatory guidance relating to OINDPs, making it difficult to take new products to market. However, the ChP, which is closely similar to the Ph. Eur., has a number of relevant chapters in the current version (2015).⁴⁰ These chapters refer to use of the Andersen Cascade Impactor (ACI), the Next Generation Impactor (NGI) and also cover nebulizer testing, and are currently under review in preparation for release of the 2020 edition.

In conclusion

It can be argued that the current regulatory framework lacks harmonization and is becoming more complex as localized regulatory structures become established. Conversely, decisive action has been taken to ease the task of developing generic products, as evidenced from the proliferation of product-specific guidance documents and USP Stimuli to the Revision Process articles on aspects of best practice. Such changes can be directly linked to broader shifts in the structure of the industry, which has changed dramatically in the last decade or so, and to the fundamental complexity of OINDPs, which continue to present scientific challenges that stimulate debate. The timely development of safe and efficacious products, novel and particularly generic, is an important goal for all stakeholders, from product developers and regulators through to patients. Evolution of the regulatory framework to streamline progress to a safe and cost-effective product portfolio for the treatment of respiratory diseases therefore looks set to continue.

References

1. Cook, K. "2017 was another record-setting year for generic drugs." FDA Voices. January 17, 2018. Available at: <https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm613832.htm>.
2. Mullard, A. "2017 FDA drug approvals." Nature Reviews Drug Discovery. 2018. 17:81-85.
3. Paton, J. "Glaxo's Advair is the \$100 billion asthma drug that won't die." Bloomberg. May 3, 2018. Available at: <https://www.bloomberg.com/news/articles/2018-05-04/glaxo-s-advair-is-the-100-billion-asthma-drug-that-won-t-die>.
4. "Mylan announces FDA approval of Wixela™ Inhub™ (fluticasone propionate and salmeterol inhalation powder, USP), first generic of Advair Diskus® (fluticasone propionate and salmeterol inhalation powder)." Mylan press release. Available at: <http://newsroom.mylan.com/2019-01-31-Mylan-Announces-FDA-Approval-of-Wixela-TM-Inhub-TM-fluticasone-propionate-and-salmeterol-inhalation-powder-USP-First-Generic-of-ADVAIR-DISKUS-R-fluticasone-propionate-and-salmeterol-inhalation-powder>.
5. FDA Workshop "New insights for product development and bioequivalence assessments of generic orally inhaled and nasal drug products." January 9, 2018. Recordings available at: <https://www.fda.gov/Drugs/NewsEvents/ucm576064.htm>.
6. Bonam, M. et al. "Minimizing variability of cascade impaction measurements in inhalers and nebulizers." AAPS PharmSciTechnol. 2008. 9(2):404-413.
7. "What are pharma's core competencies?" Pharmafile. May 2, 2009. Available at: <http://www.pharmafile.com/news/what-are-pharmas-core-competencies>.
8. FDA Guidance for Industry "Bioequivalence recommendations for specific products." Available at: <https://www.fda.gov/downloads/GuidanceComplianceRegulatoryInformation/Guidances/UCM072872.pdf>.
9. FDA Guidance for Industry "Controlled correspondence related to generic drug development." Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm583436.pdf>.
10. FDA Guidance for Industry "Formal meetings between FDA and ANDA applicants of complex products under GDUFA." Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm578366.pdf>.
11. USP Pharmacopeia 2018—(USP 41 – NF 36), May 1, 2018.
12. USP Pharm Forum 44(1) Albuterol inhalation aerosol. January 8, 2018.
13. Mitchell, JP. "Old throats for new: The curve ball posed by new USP product monographs." Presentation delivered at RDD 2017 Symposium, Antibes, France, April 2017.
14. Copley, M and Sipitanou, A. "Optimising the application of *in vitro* test methods for the demonstration of bioequivalence in orally inhaled products." Copley Scientific whitepaper. Available at: https://www.copleyscientific.com/files/ww/articles/COPJOB416_v0.3%20BE%20article%20whitepaper.pdf.
15. EMA. "Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents." Issued January 2009.
16. EMA. "Concept paper on revision of the guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the treatment of asthma in children and adolescents." Issued February 2017.

17. Stegemann, S. et al. "Improved therapeutic entities derived from known generics as an unexplored source of innovative drug products." *European Journal of Pharmaceutical Sciences*. 2011. 44: 447-454.
18. "Development of *in vivo* predictive dissolution method for orally inhaled drug products (U01)." US Food and Drug Administration and Center for Drug Evaluation Research (CDER), Office of Generic Drugs. 2013. Available at: <http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-014.html>.
19. "Development of clinically relevant *in vitro* performance test for generic OIDs: Physiologically relevant models for aerodynamic particle size distribution analysis (U01)." US Food and Drug Administration and Center for Drug Evaluation Research (CDER), Office of Generic Drugs. 2014. Available at: <https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-14-022.html>.
20. USP Chapter <1601> Products for Nebulization—Characterization Tests.
21. USP Chapter <1602> Spacers and Valved Holding Chambers Used with Inhalation Aerosols—Characterization Tests.
22. Zhang, Y. et al. "*In vivo*—*in vitro* comparison of deposition in three mouth-throat models with Qvar® and Turbuhaler® inhalers." *Journal of Aerosol Medicine*. 2007. 20(3): 227-235.
23. Weers, J. et al. "*In vivo*—*in vitro* correlations observed with indacaterol-based formulations delivered with the Breezhaler." *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. 2015. (in press).
24. Burnell, P. et al. "Studies of the human oropharyngeal airspaces using magnetic resonance imaging IV—the oropharyngeal retention effect for four inhalation delivery systems." *Journal of Aerosol Medicine*. 2007. 20(3):269-281.
25. Copley, M. "Improving the realism and relevance of mouth-throat models for inhaled product testing." *OnDrugDelivery Magazine*. 2015. 57:32-37.
26. Copley, M. et al. "Dissolution testing for inhaled drugs." *Pharmaceutical Technology Europe*. 2010. 22(11).
27. Kippax, P. "Faster de-formulation of dry powder inhalers." *Manufacturing Chemist*. 2014.
28. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products—Quality Considerations. Guidance for Industry. (Draft). U.S. Department of Health and Human Services Food and Drug Administration and Center for Drug Evaluation and Research (CDER), April 2018, Pharmaceutical Quality/CMC, Revision 1.
29. IPAC-RS. "A parametric tolerance interval test for improved control of delivered dose uniformity of orally inhaled and nasal drug products." November 15, 2001.
30. USP Pharm Forum 43(3). Stimuli to the revision process. "Proposals for data interpretation in the context of determination of aerodynamic particle size distribution profile for orally inhaled products." October 31, 2017.
31. USP Pharm Forum 40(1). Stimuli to the revision process. "Stimulus to revision: A rational approach to cascade impactor mensuration in a good cascade impactor practice (GCIP) environment." March 19, 2014.
32. USP Pharm Forum 44(4). Stimuli to the revision process. "The application of abbreviated impactor measurement and efficient data analysis in the lifecycle of an orally inhaled product: A roadmap." October 11, 2018.
33. Peri, P. "Assessing quality of inhaled products and links to efficacy and safety." Presentation delivered at IPAC-RS 2011 Conference. Rockville, Maryland, US. March 2011.
34. Pharmeducation Enquiry. "Abbreviated impactor measurements and efficient data analysis—A reliable tool for the quality control of inhaled drug products?" August 2014.
- 35 USP Pharm Forum 44(5). In-Process Revision: <601> Inhalation and Nasal Drug Products—Aerosols, Sprays and Powders—Performance Quality Tests. September 2018.
36. Valdares, BN. "Pharmaceutical equivalence of inhalation in Brazil." Presentation delivered at IPAC-RS/RDD 2016 Symposium. Phoenix, Arizona. US. April 2016.
37. ANVISA CP 490 Proposal for DRC providing for trials to prove equivalence therapy for nasal medications and oral inhalants. Issued March 26, 2018. Available at: <http://portal.anvisa.gov.br/documents/10181/3178137/CONSULTA+P%C3%9ABLICA+N%C2%BA+490+GGMED.pdf/383ff9a9-1289-415e-9802-be4d411796ce>.
38. ANVISA CP 491 Proposal for a normative ruling on *in vitro* performance tests of nasal drugs and oral inhalers. Issued March 26, 2018. Available at: <http://portal.anvisa.gov.br/documents/10181/3178137/CONSULTA+P%C3%9ABLICA+N%C2%BA+491+GGMED.pdf/cd05f3de-e97b-4603-9917-24f93c6109a2>.
39. Information on IPAC-RS global regulatory review outreach relating to Brazil is available at: <https://ipacrs.org/strategic-initiatives/general/global-regulatory-review-and-global-outreach-grro-h1/>.
40. Chinese Pharmacopeia 2015. Chapters 0111, 0112, 0113 and 0951.

Mark Copley, MEng is CEO and Anna Sipitanou, BSc, MSc is Business Development Manager, Copley Scientific Ltd., Colwick Quays Business Park, Private Road No. 2, Colwick, Nottingham, NG4 2JY, United Kingdom, Tel.: +44 1159 616229, m.copley@copleyscientific.co.uk, www.copleyscientific.com.