IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

1500 K Street NW • Washington DC • 20005
Telephone +1 202 230 5607 • Fax +1 202 842 8465
Email info@ipacrs.org • Web www.ipacrs.org

Opportunities to Facilitate the Transition of pMDIs to Third-Generation Propellants

International Pharmaceutical Aerosol Consortium on Regulation & Science.
Alternate Propellants Working Group. 2025.

In October 2023, the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) hosted a workshop on the "Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers,"[1] in which industry speakers were joined by representatives from both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to discuss the current regulatory and technical aspects of the ongoing propellant transition for pressurized metered dose inhaler (pMDI) products. In response to the action by global environmental agencies to phase out the propellants currently used in approved pMDI products, industry had begun to develop alternative products using two new propellants, HFA-152a and HFO-1234ze(E), but faced significant challenges and business uncertainty arising from the lack of available guidance from regulatory agencies at the time of the meeting.

The currently used second-generation pMDI propellants, HFA-134a and HFA-227ea, have been used for the past several decades on the basis of their safety and low impact on the ozone layer compared to their first-generation chlorofluorocarbon (CFC)-based counterparts. However, HFA-134a and HFA-227ea have significant global warming potential and their use is in the process of being restricted as part of the initiatives related to the Kigali Amendment to the Montreal Protocol. Currently, third-generation propellants – namely, HFA-152a and HFO-1234ze(E) – are being introduced in pMDIs, which are both non-ozone depleting and have low global warming potential (LGWP).

Since 2023, global health regulatory agencies have organized and participated in several public workshops and conferences related to this topic.[2] The EMA issued a specific guidance[3] on this topic, which appears to be the basis for the approach also being taken in the UK and Canada. Encouragingly, product approvals by Medicines and Healthcare products Regulatory Agency (MHRA) in the UK[4] and EMA in Europe[5] during 2025 have been obtained for one product using HFO-1234ze(E), adding further momentum and precedent for a successful transition.

However, other major health regulators, including the FDA, have yet to provide clear guidance. Notably, although FDA are referring industry to Product Specific Guidances (PSGs) that are appropriate for development of generic pMDIs, these PSGs were not intended for, and are not considered by

[1] IPAC-RS 2023: Workshop on the Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers
[2] CRCG 2024: CRCG-FDA workshop Navigating the Transition to Low Global Warming Potential Propellants (4-5 Dec 2024); ISAM Congress 2025 (22-25 June 2025); RDD 2025 Europe (6-9 May 2025)
[3] EMA 2023: Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers
[4] EMA 2025: First reformulation of an inhaled medicine with environmentally friendly gas propellant.
[5] MHRA 2025: MHRA approves world's first low-carbon version of COPD inhaler Trixeo Aerosphere - GOV.UK

industry to be entirely relevant for propellant transition programs where the manufacturer and active pharmaceutical ingredients (APIs) are unchanged from the original product.

The aim of this paper is to offer recommendations to close these technical and regulatory gaps, which will assist in streamlining regulatory review, eliminate unnecessary use of limited development resources, and ultimately ensure that patient access to these important medicines is unencumbered.

1. Regulatory Pathway and Requirements to Establish Precedence for the Safety of a Novel Propellant and Dose

The regulatory pathways available for applicants with products employing third-generation propellants are dependent on whether the propellant is precedented at the time of the regulatory submission and the nature of the product itself.[6]

At several conferences to date, FDA has stated that, when the propellant is unprecedented, only the New Drug Application (NDA) pathway is designed to review the safety data required for a novel propellant.[2] This position is in contrast to the view stated in FDA Guidance[7,8] that permits new safety data to be submitted in support of a supplement to an approved application.

However, the FDA has stated that once a propellant is used in an approved product, and that propellant has been listed in the FDA's Inactive Ingredient Database (IID)[9] for inhalation use, other regulatory pathways such as supplemental NDA (sNDA), prior approval supplement (PAS) and abbreviated NDA (ANDA) become available. Access to these pathways is essential to support the efficient and timely transition of products from second-generation propellants to third-generation propellants.

Uncertainty remains, however, about the mechanism and burden of proof used by FDA to categorize a new inactive ingredient as precedented. During the Center for Research on Complex Generics (CRCG) workshop,[2] FDA speakers did not appear to have a consistent message on the requirements for listing of a new propellant on the IID. Speakers from the FDA's Office of New Drugs (OND) indicated that multiple NDA approvals would be required via a study arm to demonstrate whether or not the propellant increases the toxicity of the drug by its presence. In contrast, attendees from the FDA's Office of Generic Drugs (OGD) asserted that the safety of novel propellants could be established with reference to publicly available safety data on the propellant and therefore a streamlined approach can be applied. The latter position somewhat aligns with the EMA guideline,[3] where the safety of a novel LGWP propellant is considered to be established once it is used in any approved medicinal product with the same route of administration. The two positions are in conflict and industry requires clarification from FDA to confirm alignment with the latter approach.

Furthermore, the legal or policy basis for the FDA's position on review of supportive safety data has not been made clear. The third-generation propellants are biologically near-inert and their high volatility makes the risk of any drug-propellant interaction remote. The FDA did not provide data or case studies to show or illustrate a mechanism by which a specific propellant-induced drug toxicity could arise.

---

[6] IPAC-RS 2024: Transition to Low Global Warming Potential Propellants in Metered Dose Inhalers: Proposed Pathways to US FDA Approval

[7] FDA 2004: Guidance for Industry. Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees.

[8] Lostritto, R. Point of view: MDI propellant switching in the 2020's vs. 1990's: Commentary, perspective and recommendations. Inhalation, August 2024.

[9] FDA: Inactive Ingredients Database https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

IPAC-RS requests that FDA clarify their requirements to establish propellant safety and propose that once a new propellant has been used in an approved product that the safety of the propellant in subsequent products can be established based on safety data available in the public domain. IPAC-RS would also encourage FDA to align with EMA that a propellant becomes established following approval of any pMDI product utilizing that propellant.

In addition, inclusion of a new inactive ingredient in the IID is typically accompanied by either an amount in the formulation (maximum potency per unit dose) or dose (maximum daily exposure) of the inactive ingredient that is derived from the inactive ingredient exposure in the product for which the IID inclusion is based. For pMDI products, there is significant variation in the number of inhalations per day and the volume of metering valves available; and therefore, a first approval of a product with a smaller number of daily inhalations and smaller valve volume may not provide coverage for products with a greater number of inhalations or a larger propellant volume being developed with that propellant.

The available nonclinical safety data for both HFA-152a[10,11] and HFO-1234ze(E)[12,13] indicate large safety margins beyond any realistic clinical pMDI dose, which should provide confidence in the safety of using higher maximum daily dose. Requiring repeat studies of propellant safety in multiple filings would introduce unnecessary complexity and resources to both development and review without a material benefit to patients.

IPAC-RS requests that FDA set the Maximum Daily Exposure (MDE) to be the MDE supported by the available nonclinical safety margins and not limited to the exposure of the propellant used in the first approved pMDI.

2. Suitability of Option 1 (from PSGs) Q1/Q2 Requirement

In keeping with other dosage forms, FDA has issued Product Specific Guidances (PSGs) for pMDI products, which offer two options to demonstrate bioequivalence. The progression toward an alternative to comparative clinical endpoint (CCE) bioequivalence (BE) studies is welcomed by industry.

A pre-requisite for using Option 1 in a PSG – demonstrating BE without a clinical endpoint study – is generally that "the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) product that may significantly affect the local or systemic availability of the active ingredient."[14] Although it is not specified in the CFR[15] that inhalation products should have the same inactive ingredients as the Reference Standard, PSGs

[10] Mohar et al. Overview of Nonclincial Safety Program for 1,1-Difluoroethane (HFA-152a) as a Low Global Warming Potential Metered-Dose Inhaler Propellant. DDL2025, Poster #36.
[11] Kuehl et al. Safety, Tolerance and Pharmacokinetics of HFA-152a in Healthy Volunteers. Respiratory Drug Delivery 2022, 1-9.
[12] Giffen, P.S. et al. The Nonclinical Assessment of Trans-1,3,3,3-tetrafluoropropene (HFO-1234ze (E)), a Near Zero Global Warming Potential Propellant for Use in Metered Dose Inhalation Products. International J. Toxicology, 2024, p.4-18.
[13] Rusch, G.M. et al. The acute, genetic, developmental and inhalation toxicology of trans-1,3,3,3-tetrafluoropropene (HFO-1234ze). Drug and Chemical Toxicology, 2013, p.170-180.
[14] FDA 2024: Draft Guidance on Albuterol Sulfate and many other PSGs.
[15] US Code of Federal Regulations. CFR 314.94 (a)(9)

for inhalation products generally do go on to exemplify a Q1/Q2[16]-equivalent product as a means to satisfy "no difference in inactive ingredients".

By the nature of a product transitioning to a new propellant, Q1/Q2 equivalence is not possible, but FDA has provided limited specific guidance on how this situation could be resolved to enable an Option 1 BE pathway. During the December 2024 CRCG workshop,[2] FDA recommended that a justification could be based on formulation characterization data, product development history, comparative characterization studies, and/or scientific literature. Sponsors were also asked to demonstrate an understanding of the formulation design space with respect to critical inactive ingredients, their ranges, and their potential impact on bioavailability. FDA also recommended to consider optional *in silico* modeling studies to evaluate impacts on local regional drug delivery to establish biorelevant limits. Further discussion of *in silico* modeling is provided below in section 3.4.

PSGs were developed for scenarios other than a propellant change. By their nature, PSGs are intended as guidance for sponsors of ANDAs and do not address regulatory pathways themselves. While PSGs could be a useful reference for questions of bioequivalence, they may not be appropriate for applicants of a new NDA or supplemental NDA for a formulation with a new propellant.

IPAC-RS requests that FDA provide more specific guidance so that industry is clear on the requirements for an Option 1 BE package to sponsors seeking approval of a pMDI with a third-generation propellant.

3. Studies to Evaluate Comparability

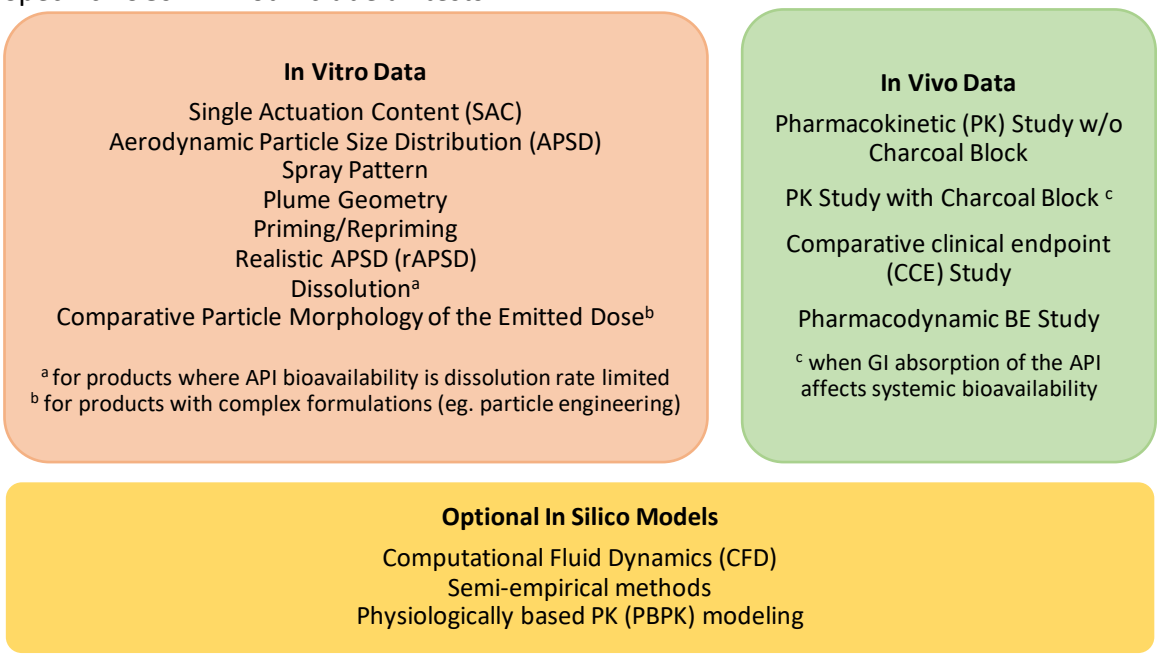
The transition to third-generation propellants coincides with a major change within the FDA regarding the requirements for demonstrating bioequivalence of inhalation products. For many years, PSGs for many inhalation products have included a requirement to conduct a comparative clinical endpoint (CCE) study as part of the *in vivo* BE requirements. The effectiveness of the CCE study as a means to determine bioequivalence specifically for inhalation products has been debated for many years, particularly in light of the high demand on sponsors conducting these studies and the poor discrimination power of such studies themselves.

In the last two years, PSGs for inhalation products, including pMDI products, have been updated to include two options to establish BE (Option 1, discussed above, and Option 2). While the alternative to the CCE study is welcomed by industry, the new BE options are new and carry additional uncertainty for sponsors at the same time as sponsors navigate the regulatory uncertainties and technical challenges associated with the propellant change.

During the CRCG 2024 workshop, FDA directed sponsors to the corresponding PSGs as a guide on agency views regarding tests required to establish bioequivalence. Product specific guidances for several pMDI products have been updated to include additional BE tests. A list of possible studies/data that can be used to support the establishment of bioequivalence of pMDI products is listed below:

[16] FDA describes Q1 as qualitative sameness, and Q2 as quantitative sameness (within ±5%), of inactive ingredients in a generic drug compared to the Reference Standard.

Figure 1. Inclusive List of Bioequivalence tests across pMDI Product Specific Guidances. Specific PSGs will not include all tests.



IPAC-RS considers that some of the above tests either appear to have little added value or have poorly defined test methods and therefore these tests constitute an unnecessary obstacle to a streamlined transition of an existing pMDI to a product reformulated with a third-generation propellant. The following sections discuss these tests in more detail.

3.1 Reduced Decision-Making Value of Spray Pattern and Plume Geometry

Well before the introduction of two options for demonstration of BE in recent PSGs, the relevance of spray pattern (SP) and plume geometry (PG) as bioequivalence tests had generated much criticism within the scientific community. It is well known that SP and PG measurements are highly susceptible to test design and that in general these tests lack clinical relevance.[17]

Discussion during the December 2024 CRCG workshop amplified the missed opportunity to remove BE requirements for SP and PG tests which add little value, do not have a clear clinical relevance, and are prone to numerous experimental variations. Furthermore, given the need to change to third-generation propellants and the different physico-chemical properties of the second and third-generation propellants, the requirement to provide a match for SP/PG introduces an unnecessary barrier to successful transition with no value in terms of safeguarding product safety or efficacy.

By contrast, other *in vitro* data included in the Option 1 pathway provide a higher degree of confidence in equivalence of performance under a variety of stressing conditions.

SP and PG assess the behavior of the plume in a situation that is not biologically relevant – namely, the expansion of the plume in the absence of airflow and in an unconstrained environment. During patient-use situations, the expansion of the plume is constrained by the mouth and throat of the patient and

[17] Gruenloh C. et al: Plume Geometry: examination of processing schemes and inter-analyst variability…We Can Do Better! at DDL 2023; and Dhapare S et al.: "Effects of Formulation and Actuator Design on Spray Pattern and Plume Geometry on Mometasone Furoate Metered Dose Inhalers (MDIs)" at the 2021 FDA Science Forum, Silver Spring, MD

the plume is entrained in the air flow associated with the patient's inhalation. Realistic APSD testing provides a more biologically relevant characterization than SP or PG in terms of how the pMDI plume interacts with the patient and where the drug is likely to deposit. Pharmacokinetic (PK) studies with charcoal block provide a direct measure of *in vivo* lung deposition. In the specific circumstances of the change from a second- to a third-generation propellant, we consider it appropriate to focus on meeting BE limits for the biorelevant tests of realistic APSD (at a constant flow rate, as discussed in section 3.2) and PK with charcoal.

Furthermore, different densities and other differences in physico-chemical properties may drive differences between second- and third-generation products in terms of the actuation weight, valve metered volume and actuator geometry. Appropriate flexibility to adjust these parameters during development can be achieved in a way that will not affect the more biorelevant BE tests. These parameters can be suitably controlled through standard component and finished product quality control testing.

Technical comparisons (pre- to post-propellant change) should focus on science-based approaches and not historical perspectives associated with the now-antiquated approaches from the CFC to HFA propellant change of the 1990s. What matters is what the patient gets in terms of delivered dose and aerodynamic particle size distribution (APSD). There are numerous contemporary methods suitable to demonstrate *in vivo* equivalence pre- to post-propellant change for an approved product.[8]

IPAC-RS requests that FDA clarifies, in the specific instance of a transition from a second to third-generation propellant, that difference in SP/PG parameters be permitted where required to achieve equivalent *in vitro* and pharmacokinetic performance and that spray pattern and plume geometry be removed as recommended tests to support this transition.

3.2 Clarity on the Meaning of Weak and Strong Breathing Profiles Specified in PSGs for Realistic APSD (rAPSD) Testing

The nature of flow profiles for conducting clinically relevant APSD testing depends on the product being tested. For example, the most appropriate inhalation profiles to use will be very different for dry powder inhalers (DPIs) compared to those for pMDIs or soft mist inhalers (SMIs). This is due to the very different nature of the aerosol generation from these products. For most dry powder inhalers, the patient's inspiratory effort provides the energy needed to generate the aerosol and thus the inhalation profile has a very large impact on the delivered dose (DD) and APSD. In particular, the flow rate ramp at the start of the inhalation profile can have a dramatic impact on the APSD and DD generated during testing of a DPI.[18,19] For pMDIs, the energy for aerosol generation is provided by the propellant vapor pressure and is independent of the patient's breathing profile. **Therefore, for rAPSD testing of pMDIs, it is suitable to test using a constant flow rate.**

[18] Chavan V, Dalby R: Novel system to investigate the effects of inhaled volume and rates of rise in simulated inspiratory air flow on fine particle output from a dry powder inhaler. AAPS Pharm Sci 2002, 4(2): E6. https://pubmed.ncbi.nlm.nih.gov/12102616/

[19] Mohammed H, Arp J, Chambers F, Copley M, Glaab V, Hammond M, Solomon D, Bradford K, Russell T, Sizer Y, Nichols SC, Roberts DL, Shelton C, Greguletz R, Mitchell JP: Investigation of dry powder inhaler (DPI) resistance and aerosol dispersion timing on emitted aerosol aerodynamic particle sizing by multistage cascade impactor when sampled volume is reduced from compendial value of 4 L. AAPS PharmSciTech 2014, 15(5): 1126-37. https://pubmed.ncbi.nlm.nih.gov/24871551/

3.3 Dissolution Testing

Recently published PSGs for pMDI suspension products have included in Option 1 a test for dissolution for some active ingredients. While the decision to include a dissolution test for an active ingredient appears to be related to lower solubility and the inference that slower dissolution could contribute to *in vivo* differences between the test product and reference standard, the rationale for including a dissolution test for a specific active is not transparent.

For solid oral dosage forms, there is a well-defined biopharmaceutics classification system (BCS), a corresponding FDA BCS database, and several BCS guidance documents that address biowaivers, the methodology (referencing USP approaches and apparatus), and acceptance criteria for immediate, delayed release, and extended-release solid oral dosage forms.

Although much more recent, the publication of a proposed inhalation BCS (iBCS)[20,21] had been in development for many years and represents a scientific framework for classification of inhalation drugs created with wide industry, academic and regulatory input.

It would be valuable for developers of both generic and brand-name drugs if FDA could be transparent about the decision-making process leading to the inclusion of a test for dissolution for pMDI suspension products, and particularly in light of the developed iBCS framework.

Furthermore, in the specific case of a pMDI product undergoing a transition from a second- to a third-generation propellant with no change in the material attributes of the active ingredient(s), dissolution testing should not be required. The propellant is highly volatile and cannot contribute to differences in the *in vivo* properties of the deposited dose. Given the other requirements of the Option 1 pathway, such as PK equivalence, Single-Actuation Content (SAC), impactor-sized mass (ISM), and realistic APSD, a further requirement for dissolution testing is redundant and unnecessary for pMDIs.

IPAC-RS recommends that dissolution testing be removed from BE guidance related to the propellant transition where the material attributes of the active ingredient(s) remain unchanged.

3.4 *In Silico* Modeling

IPAC-RS acknowledges FDA's invitation for sponsors to provide additional *in silico* modeling studies. These studies can be used to justify wider acceptance criteria for tests, including realistic APSD and plume geometry studies.[22] However, the requirements to establish an *in silico* model's credibility – including validation of the *in silico* model by comparing a model's predictions with data from *in vivo* and/or *in vitro* sources demonstrating the real-world accuracy of the model – adds significant complexity to the drug development process.

As described above, for tests mandated in PSGs, such as SP and PG, where the justification for clinical relevance is weak, IPAC-RS considers it unreasonable to suggest that complex *in silico* models be developed and validated in order to justify wider acceptance criteria – when other stronger tests (realistic APSD, PK without and with charcoal block) are already available.

---

[20] Hastedt, J.E. et al. iBCS: 3. A Biopharmaceutics Classification System for Orally Inhaled Drug Products. Mol. Pharmaceutics 2024, 21, 1, 164–172

[21] Forbes, B, et al. iBCS: 4. Application of the Inhalation Biopharmaceutics Classification System to the Development of Orally Inhaled Drug Products. Mol. Pharmaceutics 2025, 22, 4, 1740–1751.

[22] FDA 2024: Draft Guidance on Formoterol Fumarate; Glycopyrrolate.

Conclusions

In light of the seriousness and uniqueness of the need to make the switch to third-generation propellants to protect patient access to pMDIs, IPAC-RS asserts that the FDA can alleviate unnecessary barriers associated with that transition by issuing specific guidance that will provide industry with increased clarity and a stronger scientific foundation for testing requirements related to pMDIs with new propellants. In this white paper, IPAC-RS has identified several specific areas where FDA can provide clarity to streamline regulatory review and approval and allow to maximize efficient use of limited development resources, with the ultimate goal of maintaining patient access to these important medicines.