IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

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Transition to Low Global Warming Potential Propellants in Metered Dose Inhalers: Proposed Pathways to US FDA Approval

INTRODUCTION

This document presents several regulatory scenarios to stimulate robust discussions of regulatory options for submitting technical information related to metered dose inhaler (MDI) propellants transitioning to Low Global Warming Potential (LGWP) propellants. Presented in this paper are three scenarios for regulatory pathways to address MDI products utilizing LGWP propellants. The presented scenarios are for brand-name and generic MDI products, i.e., those:

- Already approved and marketed under the US FDA New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs),
- Currently in development on an ANDA track, or
- Currently in development on an NDA track.

These scenarios are depicted graphically in the flow chart in Appendix 1. The first scenario addresses the regulatory pathway for already approved and marketed MDI products that wish to transition under their current market authorizations. This scenario incorporates transition to a LGWP propellant under a prior approval supplement (PAS) pathway for both NDA and ANDA products because these products are already approved and the product's transition to LGWP propellant is a chemistry, manufacturing and controls (CMC) change[1] in the product. Further details that support this transition as a post-approval CMC change are provided in the following sections. The second scenario addresses new applications submitted for Abbreviated New Drug Applications (ANDA) to incorporate an LGWP propellant before the Reference Listed Drug (RLD) does so. The timing of filing of an ANDA product containing an LGWP propellant before the RLD enables availability of generics in a timely fashion in consideration of the global transition away from higher global warming potential HFA propellants and takes into consideration the allowance of a difference in inactive ingredients per 21 CFR 314.94(a)(9), discussed later in this paper. The third scenario addresses original New Drug Applications (NDA) submitted incorporating an LGWP propellant.

All scenarios are dependent on the FDA already having assessed and evaluated the new LGWP propellant(s) as being safe for use. The requirements for the nonclinical and clinical data supporting approval of the initial NDA with a certain LGWP propellant are not addressed in this

[1] FDA Guidance, '*Changes to an Approved NDA or ANDA*', Apr 2004.

paper considering the anticipated predecessor of FDA review of safety data of the propellant and clinical expectations being product specific.

As companies develop the LGWP MDIs, it is critically important for them to know the data requirements and which particular regulatory path is accepted by FDA. Clarity about regulatory expectations for the transition of existing products and development of new products is urgently needed. As was observed in the previous transition from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) propellants, the timeline of the transition will be influenced by the regulatory pathway as well as external factors outside of manufacturers' control, and the regulatory approvals will need to keep pace with these external factors due to the phasedown of the higher global warming potential hydrofluoroalkane propellants. In today's transition, it is notable that as industrial uses of HFA-134a and HFA-227ea decline, the availability of those propellants in the refined pharmaceutical grade may be reduced. In a worst-case situation, this may result in drug shortages of existing MDIs.

Preliminary insights from FDA regulators on what data may be required for the transition of the current MDI products to the LGWP propellants have been presented at recent conferences[2,3]. However, further open scientific discussions among regulators, manufacturers, and academia on concepts and product-specific aspects are desired to facilitate the issuance of needed FDA guidance providing for a viable and transparent submission pathway, clarity of technical requirements, and clinical requirements (if any) to support an expedient propellant switch program for MDI drug products.

To frame the topics of consideration for a propellant switch program: propellants provide the force for aerosolization and bulking volume in the formulation's liquid state inside the pressurized canister. Therefore, the primary matters of concern in a propellant switch program are (a) the similarity of the physicochemical properties of the new propellants to the currently used HFA propellants and (b) comparability of the performance of the product leading to adequately similar drug delivery mass of properly sized particles or droplets. As described in USP <5> *Inhalation and Nasal Drug Products – General Information and Product Quality Tests*, MDI drug product tests are divided into two categories: General Quality tests and Product Performance tests. Taken together, these tests ensure the identity, strength, quality, and purity of inhalation drug products. The General Quality tests assess the integrity of the dosage form, whereas the Product Performance Quality tests, i.e., delivered dose uniformity (DDU) and physical characteristics such as aerodynamic particle size distribution (APSD), assess delivery of the drug and other attributes that may relate to in vivo dose performance, and therefore are

[2] IPAC-RS Workshop held 11Oct2023. '*Metered Dose Inhalers (MDIs)/Inhalation Aerosols with Lower Global Warming Potential (LGWP) Propellants – New Drug Quality Perspective*', Dr. Craig Bertha, Office of Pharmaceutical Quality, Office of New Drug Products, CDER, US FDA.

[3] Respiratory Drug Delivery Conference 2024. '*FDA Perspectives on Scientific and Regulatory Considerations for MDIs Transitioning to a Low Global Warming Potential Propellant'*, Drs Bryan Newman and Markham Luke, Division of Therapeutic Performance 1, Office of Research and Standards, Office of Generic Drugs, CDER, US FDA.

the critical performance attributes that would determine the impact on the patient of changing to a LGWP propellant.

Terminology is used herein to set the background to the present transition.

> **First generation** (**1st gen**): MDI propellants are the previously phased-out chlorofluorocarbons
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> **Second generation** (**2nd gen**): MDI propellants are HFA-134a and HFA-227ea
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> **Third generation** (**3rd gen**): MDI propellants are HFA-152a and HFO-1234ze(E)
>
> **In vitro comparability**: product performance as a self-to-self comparison, pre and post switch to LGWP propellant (not to another product); meets pre-defined ranges for critical product performance attributes when compared to pre-change product.
>
> **Critical product performance attribute(s)**: delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) as quantifiable in vitro aspects of MDI performance that support the safety and efficacy of the drug product.
>
> **Quality attribute**: quantifiable in vitro aspects of MDI performance which demonstrate that quality standards are consistently met and which in part are established to support critical product performance attribute targets (i.e., DDU and APSD). Quality attributes of this type include metered volume, metered mass (aka shot weight), and the concentration of active ingredient(s) in the MDI formulation.
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> **In vivo equivalence**: In the context of changing the propellant in an approved MDI this is defined as pharmacokinetic equivalence as a self-to-self comparison, pre and post switch to LGWP propellant (not to another product).

The regulatory scenarios which follow are based on categorization of the propellant as an inactive ingredient (excipient) from both the technical and regulatory perspectives. Moreover, the first approval(s) of MDIs with the new propellants can occur under either a prior approval supplement to an NDA or in a new NDA application if the safety has been demonstrated. As such, preclinical and clinical safety would have been demonstrated and supporting data would be available within the applications or from the propellant manufacturers' Drug Master Files.

These scenarios are being offered for consideration to facilitate open, expedient discussions to ensure patients have continued access to MDI products. IPAC-RS looks forward to ongoing dialogue between FDA, Industry, and academia to reach appropriate targets and provide timely guidance.

SCENARIO 1. Prior Approval Supplement: Approved MDI drug product under an NDA (i.e., an approved RLD) or ANDA (i.e., an approved generic)

In this scenario, the goal is to match the same critical product performance attributes (i.e., delivered dose uniformity (DDU) within and across batches and aerodynamic particle size distribution (APSD)) between the pre-change product (i.e., the approved RLD or approved generic) and the post-change product (i.e., the product that includes a new 3rd generation propellant). Quality attributes that may be adjusted to achieve the DDU and APSD targets include metered volume, metered mass (aka shot weight), and the concentration of active ingredient(s) in the MDI formulation. The strength of an MDI product is defined by the labeled delivered mass of the API(s) from the actuator (delivered dose, aka emitted dose); not by the concentration of API(s) inside the canister. Therefore, to accommodate differences in propellant density, delivered volume, etc., the API concentration in the formulation may vary pre to post propellant change.

In addition, minor changes to valve or actuator dimensions, as well as revised materials of construction (MOC), and addition/revision of other excipientss and levels, as may be necessary, are also included. Spray pattern (SP) / plume geometry (PG) characteristics with the 3rd generation propellant may be different from what is currently approved with the existing propellant, as a result from deliberate and purposeful dimensional changes to the actuator, mouthpiece, etc. While SP is still controlled (e.g. as part of the actuator release specification[4]) to ensure consistent performance, differences in SP/PG post propellant change may be justified because of better matching the more patient-relevant performance attributes of DDU and APSD.

Note that for an approved generic, the applicant is proposing changes to their currently approved product hence it is not required to compare to the RLD as the basis for approval of the ANDA supplement because the ANDA is already approved.

The following bullets propose the recommended submission pathway and quality/CMC product development considerations. Additional information that may be needed such as labeling or human factors assessments are also listed.

- Submission pathway recommended: Prior approval supplement (PAS) to the NDA/ANDA. This is proposed because the product is already approved and the product's transition to LGWP propellant is a chemistry, manufacturing and controls change to the product. IPAC-RS proposes that Product Specific Guidances (PSGs) do not define the requirements for these product transitions. PSGs apply to new ANDA products, not CMC changes to existing approved applications.

[4] Baxter, S., et.al., '*Spray Pattern and Plume Geometry Testing and Methodology: An IPAC-RS Working Group Overview*', AAPS PharmSciTech, (2022) 23:145.

- Quality / CMC requirements: recommend a science-based and risk-based approach with justification and supporting data for formulation and device adjustments needed to accommodate the change of propellant, such as valve dimensions, mouthpiece orifice, etc.

- Critical Product Performance Attributes assessed are within sponsor-defined ranges based on their approved product understanding and data. The following attributes will be compared for the pre-change to the post-change product:
    - Aerodynamic Particle Size Distribution (APSD)
    - Delivered Dose Uniformity (DDU)

- Additional information as needed:
    - Data supporting labeling changes (excluding label claim changes)
    - Human factors data, if device user interface changes

- In vivo requirements, when applicable (both NDA and ANDA): The prior approval supplement pathway is available for products needing to demonstrate pharmacokinetic equivalence.[5,6] If clinical studies are required, that would fall under Scenario Two (pharmacodynamic or comparative clinical endpoint) or Scenario Three (as defined by the specific application). The circumstance(s) of when pharmacokinetic equivalence would be pursued is the case of lack of in vitro comparability, in a stepwise approach (similar to EMA's guidance[7]).

Remarks on Supporting the Success of Scenario 1 (existing products)

In practice, the application of the top-level guidance for existing products will be justified based on the degree of similarity between a given propellant and its replacement and the in vitro comparability of critical product performance attributes between the existing and proposed product. It is a company's assessment of these two factors along with the corresponding FDA requirements that will assist in justification of a prior approval supplement to revise a currently approved product.

In terms of potential FDA policy, IPAC-RS believe it is appropriate for FDA to accept a prior approval supplement (where scientifically justified) to an existing NDA or ANDA, resulting in shorter development and review timelines, minimizing time delays, loss of therapeutic options, potential drug shortages, and cost increases. The PAS pathway focuses on CMC and, where appropriate, bioequivalence (PK) data to meet the product's approval requirements. The

[5] FDA Guidance, '*Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*', Dec 2004.
[6] Lostritto R, '*A Regulatory Roadmap for the Transition to Low Global Warming Propellant Pressurized Metered Dose Inhalers: A Proposal for Discussion*'. Respiratory Drug Delivery 2024.
[7] European Medicines Agency, Committee for Medicinal Products for Human Health, Draft Guideline, '*Requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)*', EMA/CHMP/101453/2024, 04Apr2024.

timeline benefit will also address maintenance of therapeutic options for patients in the evolving space of access to 2nd generation propellants.

In terms of scientific considerations, it is proposed that comparability metrics[6] such as meeting existing approved performance specifications and statistical approaches assessing mean and variability can be considered for a 3rd generation propellant MDI transitioning from a 2nd generation propellant under a prior approval supplement.

From a timing perspective and for the prior approval supplement pathway to be effective, it is requested that more frequent interactions and meetings with the FDA are needed. The current general correspondence pathway afforded to approved products is not specific enough to discuss product aspects and enable timely and targeted completion of the development activities. Specific interactions will help facilitate first pass regulatory approvals of the prior approval supplements.

SCENARIO 2.
ANDA in Development

In this scenario, the ANDA product being developed uses any 3rd generation propellant independent of the corresponding RLD. The ANDA product may also include formulation changes to accommodate the inherent physicochemical properties of the 3rd generation propellants including for example, adjustment of the API concentration and the addition/revision of other excipients. Other changes may be needed to the container closure system, e.g., revised materials of construction for the valve (to be compatible with the new propellant), adjustments to the metered volume/valve delivery/shot weight, mouthpiece orifice geometry, etc. as compared to the RLD, all to accommodate in vitro comparability, and in vivo equivalence as needed.

- Submission pathway recommended: new ANDA, with options for the RLD being
    - RLD using current 2nd generation propellant
    - RLD using the 3rd generation propellant

- Quality / CMC requirements: Follow PSGs. Note that some in vitro requirements as currently stipulated in PSGs may not be applicable or achievable, such as spray pattern and plume geometry which may change due to the change in propellant and/or other changes required to be made to the product. Priming/repriming will need to be characterized and may also change.

- In vivo requirements: Follow PSGs.

It is worth noting that 21 CFR 314.94 *Content and format of an ANDA* does not require that inhalation aerosol products are Q1 same as the RLD. Regulation 21 CFR 314.94(a)(9)(iii) through

(a)(9)(v) provides restrictions on changes that can be proposed regarding inactive ingredients for parenteral, ophthalmic, otic, and topical products. Of consideration in the determination of Q1 sameness for inhalation aerosols, is the role of the propellant in the dosage form. It is not intended to have a pharmacologic effect and has been demonstrated as well tolerated[8]. Propellant is utilized to provide an energy source and atomize the API for inhalation into the lungs. It may be completely evaporated during inhalation. When considering other dosage forms, the inactive ingredients are those ingredients which may afford the medium for contact and absorption at the site of action. This unique feature is proposed for consideration on whether Q1 sameness has a role or if the propellant may instead be considered to be essentially a device constituent in regard to its inherent expansion at room temperature and pressure.

Also worth noting are the comments presented in the Orange Book. In the case of an ANDA product where a new RLD and a new ANDA are required, the Orange Book Preface addresses therapeutic equivalent products as those which are pharmaceutical equivalents for which bioequivalence has been demonstrated and can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. A pharmaceutical equivalent product focuses on the following being the same:

Dosage form
Route of administration
Amount of active ingredient
Salt/ester of the API
Compendial or other applicable standards of identity, strength, quality, and purity
Also, where applicable, content uniformity.

Again, these pharmaceutical equivalent products do not necessarily contain the same inactive ingredients, packaging, expiration date, and within certain limits, labeling.

In the case where the ANDA product being developed starts by using a 2nd generation propellant and switches to a 3rd generation propellant the in vitro comparability and in vivo equivalence topics in PSGs are of consideration. It is proposed that as with EMA's guidance[7], a stepwise approach could be considered for an ANDA product submission if in-vivo equivalence was demonstrated during the development program with the 2nd generation propellant. Potentially the applicant would want to consider the FDA Draft Guidance explained in the Bridging Strategy section of this paper. These approaches would benefit from discussion between the applicant and FDA. The opportunity to meet with FDA regarding the submission and data strategies on ANDA products are described in guidance[9]. However, expediency in receiving feedback is crucial given the criticality of maintaining access to generic medicines. The current GDUFA meeting framework results in up to four and a half months before feedback is received and

[8] Kuehl PJ, Corr S., Leach CL, '*Safety, tolerance and Pharmacokinetics of HFA-152a in Healthy Volunteers'*. Respiratory Drug Delivery 2022; 87-96.
[9] FDA Guidance, '*Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*', Oct 2022, Rev. 1.

product development cannot stop while waiting for feedback, nor are switches in regulatory strategy after that period of time easy to adopt. Other mechanisms to accelerate action have been utilized during other times of crisis such as COVID-19 Pandemic in order to advance availability of necessary medicines to the American public. It is proposed that dialogue in a timely manner will advance the development and approval of the products submitted under the ANDA pathway.

Also in terms of a timing perspective for continued access to MDIs for patients, if FDA mandates the new NDA pathway for RLD drugs, then corresponding generics will still be able to reference the previous (2nd gen) RLD in their applications provided the RLD is not withdrawn for reasons of safety or efficacy. However, the affected ANDA applicants may have difficulty sourcing sufficient quantities of the RLD for the studies required in either their original ANDAs or ANDA supplements. Flexibility and timeliness in the designation of any necessary reference standards will be key to enable ongoing availability of generics. Navigating this will be crucial to avoid drug shortages and reduced therapeutic options for patients.

SCENARIO 3.
NDA in Development

In this scenario, the NDA product being developed started with a 2nd generation propellant and switches to a 3rd generation propellant prior to original NDA submission. The final product may also include addition/revision of other excipients, revised materials of construction for the valve (to be compatible with the new propellant), adjustments to the valve delivery/shot weight, mouthpiece orifice geometry, etc. as compared to the early development product, all to accommodate in vitro comparability, and in vivo equivalence as needed, to the 2nd generation propellant NDA product where clinical safety and efficacy had been previously demonstrated.

- If the switch to 3rd generation propellant occurs during the early Investigational New Drug Application (IND) stages (Phase 1) then a bridging strategy is in vitro based and easier, being before pivotal clinical studies are conducted. Pivotal safety and efficacy studies will be conducted with the 3rd generation propellant MDI in this scenario.

- If the switch to the 3rd generation propellant MDI product occurs after the 2nd generation MDI product has completed dose escalation studies, the clinical and CMC bridging strategies in pivotal safety and efficacy trials become more complex. The in vitro bridging studies to link to the previous dose escalation studies should be defined (see Bridging Strategy Section).

- Repeat of studies including recharacterization, revalidation of manufacture, new specifications, and new clinical studies may be required on a case-by-case basis supported by appropriate risk assessment and risk ranking tools as a propellant switch

timing approaches the NDA submission. Or, where possible, it should be explored where in vitro bridging studies may be used (see Bridging Strategy Section).

The PDUFA meetings afforded to applicants of NDA products can be utilized to clarify expectations as the development process progresses. These meetings have relatively short response time windows in order to provide timely feedback on regulatory strategy and requirements in time windows that enable implementation of the recommendations in sync with the development program. Depending on the meeting type, the meetings may occur within 30 days to 75 days of meeting request.[10]

Bridging Strategy Considerations for Scenarios 2 and 3

Assumptions to the framework from the FDA Draft Guidance, *Bridging for Drug-Device and Biologic-Device Combination Products*, December 2019[11] are described as follows:

- Bridging of information related to a combination product that employs either a different device and/or drug constituent part as the previous combination product.
- Bridging refers to the process of establishing the scientific relevance of information developed in an earlier phase of the development program or another development program. Once the applicant has established the relevance, the applicant can leverage that information to streamline its development program. (Lines 32-34 of guidance) [11]
- In general, FDA would require additional data or information only if the information were needed to address additional questions of safety or effectiveness raised by the proposed use or function of a constituent part in a combination product. (Lines 98-101 of guidance)[11]
- The bridging strategy framework identifies information gaps to inform a bridging and leveraging approach. (Lines 115-116 of guidance)[11]

Table 1. Bridging Strategy Framework per FDA Draft Guidance

Step Number	Explanation from Guidance	Applicability to Third Generation MDI products
1	Identify all differences between Products A and B, consider the potential effect of the individual and aggregate differences on the safety and effectiveness profile for Product B. Include a clear, comprehensive listing of the differences in device constituent part, drug constituent part and the combination product as a whole. Examples of	Several of the examples in this step may be applicable to 3rd generation MDI products. These changes could be assessed using this framework.

[10] FDA Draft Guidance, '*Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products'*, September 2023, Rev. 1.
[11] FDA Draft Guidance, '*Bridging for Drug-Device and Biologic-Device Combination Products'*, December 2019.

Step Number	Explanation from Guidance	Applicability to Third Generation MDI products
	changes to use this framework are listed in guidance[12].	
2	Identify existing information for Product B (prior knowledge, studies, assessments) – compare to the safety and effectiveness submission requirements necessary for approval.	Extensive knowledge is available regarding the safety and effectiveness of MDI products and these drug substances in these dosage forms. Information regarding 3rd generation MDI products will be applicant specific.
3	Identify and explain how and why existing information on previous product can be bridged and leveraged to support approval of Product B.	Steps utilize considerations in Step 1 and information gathered in Steps 2-4.
4	Focus on any information gaps remaining from Steps 2 and 3. Consider if other existing information can be reviewed and used to address these gaps for the proposed regulatory pathway (see Step 5).	
5	Compare findings from Step 2 through 4 and identify the remaining gaps in information that needs to be addressed in the product application. Meet with the FDA to discuss the new information or studies to support.	

The examples discussed in this guidance for user interface, manufacturing process, dose accuracy, and biocompatibility have the potential to be adapted for the MDI propellant transition and adopted for submission strategies.

CONCLUDING SUMMARY

Both FDA and Industry are interested in ensuring uninterrupted access by patients to safe and efficacious MDI products. The common aim therefore is to have clarity on the various scenarios applicable to regulatory pathways for NDA and ANDA products. Expedited approval pathways, with options to utilize existing tools (e.g. stepwise approaches and bridging data sets), are welcomed and certain to assist in continued availability of this critical dosage form for patients.

[12] See lines 142-165 of FDA Draft Guidance, '*Bridging for Drug-Device and Biologic-Device Combination Products*', December 2019. Examples of changes include change in formulation, manufacturing process, user interface, lung deposition, extractables/leachables.

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Appendix 1