Point of view: A proposal to regulate propellants as device components in metered dose inhalers

This approach is better aligned with propellant function in pMDIs and, as a more efficient and relevant regulatory approach, could facilitate propellant switch programs in approved and emerging pMDIs.

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This opinion article represents the author's views as an independent consultant. He does not represent any organization, company or health authority.

Abstract

Currently, HFA-134a and HFA-227 are the propellants used in pressurized metered dose inhalers (pMDIs). Although ozone-sparing, they have significant global warming potential compared to candidate 3rd generation propellants (3GP), HFA-152a and HFO-1234ze(E), which are considered to be low global warming potential (LGWP) propellants [1, 2]. Propellants serve as the physical driving force for aerosolization and drug delivery from pMDIs. Supported by multiple precedents, a pMDI propellant may be feasibly regulated as a device component in these drug-device combination products.[1] The propellant acts analogously to a spring in an auto-injector combination product, or an elastomeric infusion pump, or simply an ordinary syringe used to deliver drug. Note that with a syringe (plunger) or an elastomeric bag (container), the driving force for drug delivery is in direct contact with the drug formulation. Therefore, there is no prohibition against the aerosolization driving force device component being in contact with the formulation. Furthermore, heparin lock flush solution is regulated by the United States Food and Drug Administration (FDA) as a device, despite the fact that heparin exerts a pharmacological effect (anticoagulation) even when distributed at the molecular level within the product and then within the body when used as labeled [3, 4]. Therefore, there is precedent for an active pharmacological agent to be regulated as a device. This particular precedent supports that a device (or device components) can be distributed at the molecular level within the formulation or human body. Taken together, these and other well-established precedents (e.g., barium sulfate suspension as a device used in radiology) support that pMDI propellants can be regulated as device components and not as formulation components. In the FDA combination product review model for pMDIs, the Center for Drug Evaluation and Research (CDER) could continue to lead the pMDI review, and the Center for Devices and Radiological Health (CDRH) could review, from an engineering perspective, the propellants' physical aerosolization function.

1 Per Section 201(h)(1) of the Food, Drug, and Cosmetic Act, a device is: An instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is: (A) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

A more relevant assessment of propellant function on aerosolization performance in pMDIs would benefit from CDRH's engineering approach. Furthermore, this new paradigm may apply particularly well when an applicant for an approved pMDI combination product provides a submission to switch the propellant to an LGWP propellant (3GP) via the prior approval supplement (PAS) pathway.[2]

Introduction

Pressurized metered dose inhalers (pMDIs) are drug-device combination products where the drug exerts the primary mode of action (PMOA), almost always to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). In any pMDI, the propellant, formulation and other components simply serve as the mechanical force (via propellant expansion) to generate the inhalable aerosol from the liquid contents inside the pMDI canister through a metering valve and then through one or more actuator component(s), allowing for oral inhalation [5]. The United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) is the lead review center in these cases and the Center for Devices and Radiological Health (CDRH) provides an assessment of device components, as needed, particularly if those device components are novel in terms or composition, manufacture or function [4].

For an approved pMDI product, the switch to the next generation of pMDI propellants (3GP) is novel and fraught with many complexities [6]. These include delivered dose uniformity (DDU) and the aerodynamic particle size distribution (APSD) over the life of the pMDI product. Encouragingly, the currently used propellants, HFA-134a and HFA-227, are physicochemically more similar to 3GPs than the currently used propellants were to the CFCs phased out in the 1990's [5, 7, 8].

Furthermore, the officially designated and longstanding dosage form name for pMDIs is "inhalation aerosol" [8, 9]. This definition is based on the material that *exits* the pressurized pMDI container[3] and not on the material form in the container. This atypical dosage form definition is notable, points directly to the importance of the generated aerosol and is agnostic as to the physical form inside the container.[4]

Typically, a drug product is labeled to the form it exists in the commercial container-closure system, even if the drug changes form in use (e.g., powder for injection, etc.) For inhalation aerosols, this means that the labeled critical aspects of safety, efficacy and quality are (appropriately) very clearly focused on the generated aerosol and not on the form inside the canister. That is, the entirety of the pMDI system: the active pharmaceutical ingredient (API) formulation, propellant, canister, valve, actuator, etc.) all exist to generate the inhalable API aerosol (solution or suspension) with the proper particle or droplet characteristics to assure safety and efficacy over the life of the pMDI. As propellants change in response to LGWP influences, this distinction is an important consideration in developing novel regulatory theory, which can support a rational, transparent and science-based propellant switch process for pMDI drug products that are already approved and which maintains safety and efficacy [5, 7 ,8].

Regulating propellants as device components may be a tool to help shift the regulatory emphasis to a more agnostic approach that focuses on the properties of the inhalable aerosol (i.e., DDU, APSD, spray pattern) rather than which propellant(s) are used. In this agnostic framework, applicants would be free to choose their own propellant or propellant mix as they switch propellants for already-approved products (reference listed drugs (RLDs) as well as generics) under a lesser regulatory burden as a prior approval supplement (PAS) without sacrificing the science-based performance requirements of the generated aerosol itself.

Theoretical basis

The propellant in a pMDI serves as the driving force for aerosolization by creating a pressure differential that provides the necessary physical energy to generate an aerosol. That is its purpose and the propellant is intentionally pharmacologically inert.[5] Furthermore, a recent FDA presentation depicted formulation factors and propellant properties as *separate entities* [10].

The propellant in a pMDI is analogous to the delivery spring in a spring-loaded syringe inside a drug autoinjector combination drug product or an elastomeric infusion container. The exact composition of the spring or elastomer in contact with the drug formulation would not matter as long as it met criteria for performance, compatibility with the formulation and material safety.

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2 Any new 3GP propellant must independently be shown to be safe in terms of human toxicology. An analysis of these safety aspects is beyond the scope of this work and is not presented here. This paper is based on the (likely) possibility that those safety concerns are (or will be) satisfactorily met.

3 The performance of the pMDI product in terms of DDU and APSD is in reference to the active pharmaceutical ingredient (API) and is independent of propellant species, mass or concentration.

4 For example, suspension versus solution (i.e., inside the container) pMDIs are not differentiated by "inhalation aerosol."

5 Toxicological acceptance in the US is pending. However, one 3rd generation propellant (HFO-1234ze(E)) now appears in a pMDI that has been approved in the UK and has received a positive recommendation for approval in Europe.

In the case of pMDIs however, not only is the propellant in contact with the formulation, it is molecularly dispersed throughout that formulation. *Is the molecular dispersion of the propellant inside the canister allowable for its consideration as a device component?* The answer appears to be yes, largely based on the precedents described below.

1. The FDA regulates *heparin lock flush solution* as a device: Although acting at the molecular level (dissolved heparin) and being pharmacologically active [11], heparin lock flush solution has been regulated as a device in the US since 2006 [3, 4]: "*The transfer of lead review responsibility to CDRH is based on FDA's determination that the primary mode of action for these heparin catheter lock flush solution products is that of the device part of the combination. The transfer provides consistency and efficiency in the regulation of these combination products by treating like products similarly.*"

Given that pMDI propellants are pharmacologically inert and provide no therapeutic function inside the body, they can easily be envisioned as a device constituent part in pMDI combination drug products more easily than heparin in a lock flush syringe or oral barium sulfate in radiological studies.

2. The FDA was ordered to regulate barium sulfate and other products as devices. Genus Medical Technologies, LLC v. FDA, 994 F. 3d 631 (D.C. Cir. 2021): The Court ruled that the FDA's classification as a drug was inconsistent with the Federal Food, Drug, and Cosmetic Act (FDCA) and the Administrative Procedure Act (APA).

Congress subsequently enacted the Food and Drug Omnibus Act of 2022 (FDORA) (Public Law 117-328), which added Section 503(h) to The Act, which deemed contrast agents to be drugs. Note that 503(h) applies to outsourcing pharmacy compounding activities and does not apply to propellants used in pMDIs or to any individual device component within a combination product.

Practicality of the theory

Some non-propellant molecules, such as heparin and barium sulfate, when dispersed at the molecular level (heparin lock flush solution) or as a suspension (barium sulfate oral suspension) and used inside the human body to either aid in the diagnosis of disease (barium sulfate) or exert pharmacological action (heparin per labeling) have been and/or are currently treated as devices outright.

Even though the FDA effectively obviated (through new legislation) the Court's ruling of 2021 for barium sulfate products, the original thinking may still apply for propellants as device components because 503(h) of The Act applies to outsourced compounded products and does not apply to propellants on their own or as used in pMDI products, in terms of defining the drug-device status of the overall pMDI product. However, the thinking and rationale that a molecular entity dissolved or disbursed in a drug formulation may act as a device component remains intact. Therefore, the theory of propellants serving as device components is not legislated against by 503(h) and remains a viable possibility.

These precedents support the theoretical foundation for the proposal that current or 3GP pMDI propellants that claim no therapeutic or diagnostic effects and are otherwise inert may be regulated as molecularly distributed device components in pMDIs.

The value in treating pMDI propellants as device components

There are a number of practical regulatory, technical and public health advantages to regulating pMDI propellants as devices, which are enumerated below.

1. An agnostic approach to the propellant used. The shift is a focus to performance (e.g., DDU, APSD, etc.) that directly supports quality, safety and efficacy over the life of the pMDI product.

2. An agnostic regulatory framework for propellant choice also provides a more flexible prior approval supplement (PAS) pathway for propellant switches for approved pMDIs. In such a framework, approved pMDIs under a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) may more easily change to a 3GP propellant via a PAS to the existing NDA or ANDA application number [5, 7, 8]. The PAS approach is low risk considering that all relevant data requirements (safety (e.g., propellant), efficacy (e.g., bio) and quality) may be fulfilled via the PAS pathway. In contrast, requiring new NDAs or ANDAs to be submitted is labor intensive (for the industry to develop and the FDA to review), untimely (PAS review timelines are a fraction of new NDA timelines), and expensive to develop. Furthermore, requiring new NDAs would eliminate existing RLD links to generic pMDIs.

3. A generic pMDI can more easily support the use of a different propellant (as a device component) from the RLD no matter when or if the RLD changes its propellant. Furthermore, there would be nothing to stop a generic pMDI from independently adopting a 3GP before its RLD made that switch.

4. Generic pMDI BE studies (*in vitro* or *in vivo*) would not be constrained to use the same propellant (or propellant mixture) as the RLD during development or after approval. Note that this is already an option for new ANDAs seeking initial approval.

5. Generic pMDI development and marketing could not be blocked as easily if the independent use of a propellant were allowed or encouraged in order to avoid or circumvent so-called "gray" practices [12, 13].

6. Despite this, FDA product specific guidances (PSGs) for pMDI products recommend (but cannot

mandate) the same propellant be used as in the RLD. The applicants' justification for not following the FDA-recommended Q1/Q2 option in pMDI PSGs may become bureaucratically impracticable in a vacuum of science-based justification by the FDA for this recommendation in the first place. However, relaxing this implied constraint and focusing on pMDI performance as the point where equivalence metrics are taken would support and facilitate the development and continuance of generic pMDIs during the era of propellant transition. This could bring substantial public health benefits in preserving the availability of therapeutic options along with corresponding controlled costs of pMDI medications.

Technical considerations

If the regulatory framework for pMDIs were agnostic with respect to the propellant used then the PAS change pathway for approved products under an ANDA or NDA would not include the propellants' chemical identity as a comparability consideration (i.e., before versus after propellant change [5, 7, 8]).

Note that approved ANDAs have already demonstrated pharmaceutical equivalence (PE) and bioequivalence (BE) to an RLD. In terms of comparability to support a propellant change, the requirements for an NDA should be the same for an ANDA, according to the FDA's similarity practices. Therefore, there is no science-based reason for the double jeopardy that would be imposed on generic pMDIs only by requiring approved ANDAs to redo PE or BE studies a *second time (i.e., post-approval)*. For ANDAs in development or future ANDAs, there should be no prohibition for the use of any propellant, provided the usual PE and BE requirements are met as for any initial ANDA approval.

Is it technically feasible to change the propellant in an approved pMDI product then expect the changed pMDI to be adequately comparable in critical performance to its former variant? Likewise, is it feasible to expect a generic pMDI with a different propellant from its RLD to meet PE and BE requirements?

During the 1990's, new NDAs were required to support new HFA propellant use [5]. Also, the generic program for pMDIs was just emerging. In addition, properties of the new (at that time) HFAs were radically different from those of the CFCs in use. Furthermore, there was much less understanding of the physical and chemical factors that influence DDU, APSD, compatibility, etc., as well as fewer analytical capabilities. The result is that today's propellant switch scenario to 3GPs is less drastic and better understood than that of the 1990's switch from CFCs to HFAs. Therefore, the requirement of new NDAs to support a 3GP switch for approved pMDI products based on 1990's and early 2000's experience is no longer relevant or necessary.[6]

Today's 3GP propellants are much more like HFA-134a and HFA-227 than these two HFAs were to the CFCs they replaced in the 1990's. Considering the recent UK approval of the reformulated Trixeo Aerosphere® pMDI (AstraZeneca, Cambridge, United Kingdom [14]), the practicality of this distinction is being made contemporaneously. Arguably, there remains no scientific or public health basis for a regulatory framework that prohibits a successful PAS submission pathway for a propellant change in already-approved pMDIs in the US. In previous publications, it has already been noted [5, 7, 8] that the PAS submission pathway can contain all the necessary technical and bioequivalence data to support a propellant change.

For example, owing to propellant density differences, shot weight and/or metered volume may differ to obtain DDU performance matching. In a propellant-agnostic framework, accommodating changes in shot weight and/or metered volume are inconsequential provided DDU, APSD and other critical performance criteria such as leachables are met [5, 7, 8].

The impact on aerosol quality with changes in formulation inactive ingredients (e.g., ethanol level) as part of a propellant change program for an approved ANDA or NDA pMDI carries more significance and should be evaluated to better support comparability pre- to post-change. For new ANDAs (in development or future), such changes should be studied to better support future PE and BE as well.

The quality and human factors data package to support a change in propellant will, of course, be significant [5-8]. However, the historically-based need for new NDAs and ANDAs to support that change does not appear to be justified at this time. *This was recently proven with the UK's approval and Europe's recommendation for approval of the reformulated Trixeo Aerosphere pMDI* [14, 15].

Regulatory engineering a propellant-PAS approach for approved pMDIs

The FDA's progress is often application-based. In pMDI propellant switch approaches, the FDA appears to be less progressive than other regions of the world and so far has spoken out in favor of requiring new NDAs for currently approved pMDIs. Given the public health and regulated industry stakes, as well as the science-based mission of the FDA, it seems unusual to base policy for all pMDI applicants for the next decade on what the first applicant may or may not creatively devise to solve their own propellant switch issues.

6 In Europe and the UK, there are mechanisms to manage propellant switch programs for marketed pMDIs as extensions of existing products rather than as new *ab initio* products. The first success has come from the UK's approval of AstraZeneca's Trixeo Aerosphere.

It will likely take an NDA or ANDA applicant to formally propose the PAS approach (on their own or as part of a group) for change to a new propellant, whether the propellant is proposed as a device component or not. However, putting *propellant as device component* on the table early may catalyze a productive shift in thinking about pMDI propellant switch and *ab initio* development programs. Recent FDA Guidance from the Office of Combination Products [12] addresses some of the principles that would need to be considered should the propellant in pMDIs be regulated as a device component (see the following excerpt).

"… for a combination product that is not device-led and includes a device constituent part, engineering, biocompatibility, performance data, and other design validation data would typically be necessary. Regardless of which center may have the lead and which application type may be appropriate, consistent with section 503(g)[7] *of the FD&C Act, FDA is committed to applying a consistent, risk-based approach to address similar regulatory questions, including scientific questions, similarly, utilizing relevant expertise from the lead and consulted centers... It bears noting that the data and information needed to address safety and effectiveness questions related to the non-lead constituent part of a combination product may differ from the data and information needed to obtain marketing authorization for that article as a stand-alone product that is not part of a combination product."*

Although this guidance is geared towards new combination products, there is no prohibition from applying this thinking to supplemental applications for approved pMDIs seeking to have a propellant change approved.

Several other factors may improve the possibility that a propellant-agnostic PAS approach would have merit for the FDA as it continues to holistically explore the propellant transition situation. These include:

- In June 2024, the US Supreme Court overturned the "Chevron Deference."[8] This has significant implications for the US Department of Health and Human Services (HHS) in that courts may no longer defer in favor of the HHS in ambiguous situations. This weakens the HHS's interpretative power of statute in any potential litigation as well challenges to any downstream regulation, guidance or policy.
- US Executive Order dated May 05, 2025: Promoting American-Made Prescription Drugs: The order directs the FDA and US Environmental Protection Agency (EPA) to reduce regulatory burdens and accelerate the approval of new or expanded pharmaceutical manufacturing facilities in the US. This executive order includes instructions to the FDA and EPA to identify and eliminate duplicative or unnecessary regulations that hinder domestic pharmaceutical manufacturing.
- May 2025: The US Federal Trade Commission (FTC) renewed a challenge to more than 200 improper patent listings. The FTC continues Orange Book listing disputes, marking the third round of FTC challenges to promote affordable drugs and generic competition.
- If the FDA were to allow pMDIs to be propellant agnostic, that could help mitigate some "gray" practices [13].
- Furthermore, a propellant-agnostic approach that allows for greater flexibility in terms of propellant choice and change approaches (i.e., PAS) may address ongoing concerns related to US supply chain resilience for US drug products [16], a pillar of the FDA's mission. Flexibility in terms of technical options and regulatory approaches could bolster that resilience.

Conclusions

1. The FDA has the authority to accept a PAS approach to propellant changes for approved pMDI products, no matter how the propellant is regulated (either as an inactive ingredient or preferably as a device component). This would allow an agnostic approach to the propellant used in pMDIs across the board. In addition, this would not put generic pMDIs in jeopardy due to loss of RLDs because new NDAs would be required for those RLDs. It also would not put generic pMDIs in *double* jeopardy by requiring approved ANDAs to repeat BE determinations as a result of a propellant change.

2. There is no science-based reason to treat *approved* generic pMDIs any differently than their corresponding RLDs with regard to propellant changes.

3. The theory that propellants in pMDIs may be regulated as device components has precedent within the FDA. This is a novel concept in pMDI thinking that may help satisfy a number of goals for the FDA, the Executive Branch of the US Government, the regulated industry, and the US public health as 3GP propellants emerge into pMDI usage.

4. Although the technical considerations for a propellant change are extensive, a propellant transition program for approved pMDIs may be facilitated by a more open and agnostic regulatory view of the propellant as a device component.

5. Reducing the focus on propellant chemical composition in the canister (i.e., propellant as an inactive ingredient) and increasing focus on *performance* of the generated aerosol, such as DDU and APSD,

7 503(g) of the FD&C Act is not impacted by 503(h); the latter applies to outsourcing compounding activities.

8 The Chevron Deference (established in 1984 and overturned by the US Supreme Court in 2024), required Federal Courts to defer to a Federal Agency's interpretation of ambiguous statutes that apply to that Agency.

over pMDI life[9] could facilitate science-based propellant change criteria. It could also better address public health needs by focusing more on the substance the patient inhales and less on criteria such as shot weight and metered volume.

6. *The UK (MHRA, [14]) recently approved and the EU (EMA, [15]) recently recommended approval of the* first LGWP version of a pMDI based on a product that was already approved. This is a triple fixed-dose combination! Hopefully, the FDA will consider this success story and provide a reasonable PAS approval pathway for currently approved pMDIs as they switch to 3GP propellants.

7. In terms of *similar therapeutic performance*, results for DDU, APSD, *in vitro* BE (or PK) matter the most. Other considerations matter too, such as spray pattern, priming, human factors, etc.

8. Contemporary issues such as the 2024 overturning of the Chevron Deference, recent US Executive orders, concerns over gray practices and supply-chain vulnerability may increase the visibility, timeliness and impact of regulatory actions that facilitate (or hinder) propellant changes for pMDI products in a more science-based manner than simply requiring new drug applications.

References

1. Koura: Zephex HFA-134a, HFA-227, HFA-152a product literature, https://www.kouraglobal.com/applications/medical-propellants.

2. Honeywell: Solstice Air HFO1234ze(E) product literature, https://advancedmaterials.honeywell.com/us/en/products/medical-propellant/solstice-air.

3. Heparin Lock Flush Solution, USP, label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/017037s154,055,156lbl.pdf.

4. The Federal Register: Responsibility from Center for Drug Evaluation and Research to Center for Devices and Radiological Health, August 17, 2006, 71 FR 47499.

5. Lostritto RT: MDI propellant switch in the 2020's compared to the propellent switch of the1990's: Commentary, perspective and recommendations. Inhalation August 2024, 18(4): 22-30.

6. US Food and Drug Administration: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations, Guidance for Industry (Draft), 2018.

7. Lostritto RT: A regulatory roadmap for the transition to low GWP pMDIs: A proposal for discussion, Respiratory Drug Delivery Asia (RDD-Asia) 2024, Invited speaker.

8. Lostritto RT: A regulatory roadmap for the transition to low GWP pMDIs: A proposal for discussion, Respiratory Drug Delivery (RDD) 2024, Invited speaker.

9. USP NF 2024, May 2024, Chapter <1151>.

10. Bielski, Elizabeth: FDA's current perspectives on the propellant transition: Work towards global harmonization, Slide 6, Respiratory Drug Delivery (RDD) Europe 2025, Invited speaker.

11. Swaminathan L et al.: Safety and outcomes of midline catheters vs peripherally inserted central catheters for patients with short-term indications. JAMA Intern Med 2022, 182(1): 50-58.

12. US Food and Drug Administration: Principles of Premarket Pathways for Combination Products, Guidance for Industry and FDA Staff, https://www.fda.gov/media/119958/download.

13. US Federal Trade Commission: FTC renews challenge of more than 200 improper patent listings, May 21, 2025, https://www.ftc.gov/news-events/news/press-releases/2025/05/ftc-renews-challenge-more-200-improper-patent-listings.

14. AstraZeneca: Trixeo Aerosphere approved in the UK as first inhaled respiratory medicine using next-generation propellant with near-zero Global Warming Potential, May 12, 2025, https://www.astrazeneca.com/media-centre/press-releases/2025/trixeo-aerosphere-approved-in-the-uk-as-first-inhaled-respiratory-medicine-using-next-generation-propellant-with-near-zero-global-warming-potential.html.

15. European Medicines Agency: First reformulation of an inhaled medicine with environmentally friendly gas propellant. EMA, July 25, 2025, https://www.ema.europa.eu/en/news/first-reformulation-inhaled-medicine-environmentally-friendly-gas-propellant.

16. US Chamber of Commerce: U.S. supply chain vulnerabilities and resilience, 2022, https://www.uscc.gov/sites/default/files/2022-11/Chapter_2_Section_4--U.S._Supply_Chain_Vulnerabilities_and_Resilience.pdf.

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9 This assumes acceptable safety of the propellant and the corresponding pMDI product including extractables and leachables.