Point of view: Product development considerations for transition to LGWP propellants in MDIs: "Status Quo" versus a "Scientifically Rationalized Approach"

Ponderance on a resource-efficient pathway with possibility for regulatory appeal

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Abstract

Pressurized metered dose inhalers (MDIs) are drug formulations enclosed in container-closure systems. The latter serve to hold reservoir(s) of formulation(s) that are dispensed in the desired amount(s). Among the various constituents of the formulations, propellant(s) constitute the principal inactive ingredient both by weight and volume. Propellants provide the sole source of energy required for aerosolization and delivery of the drug.

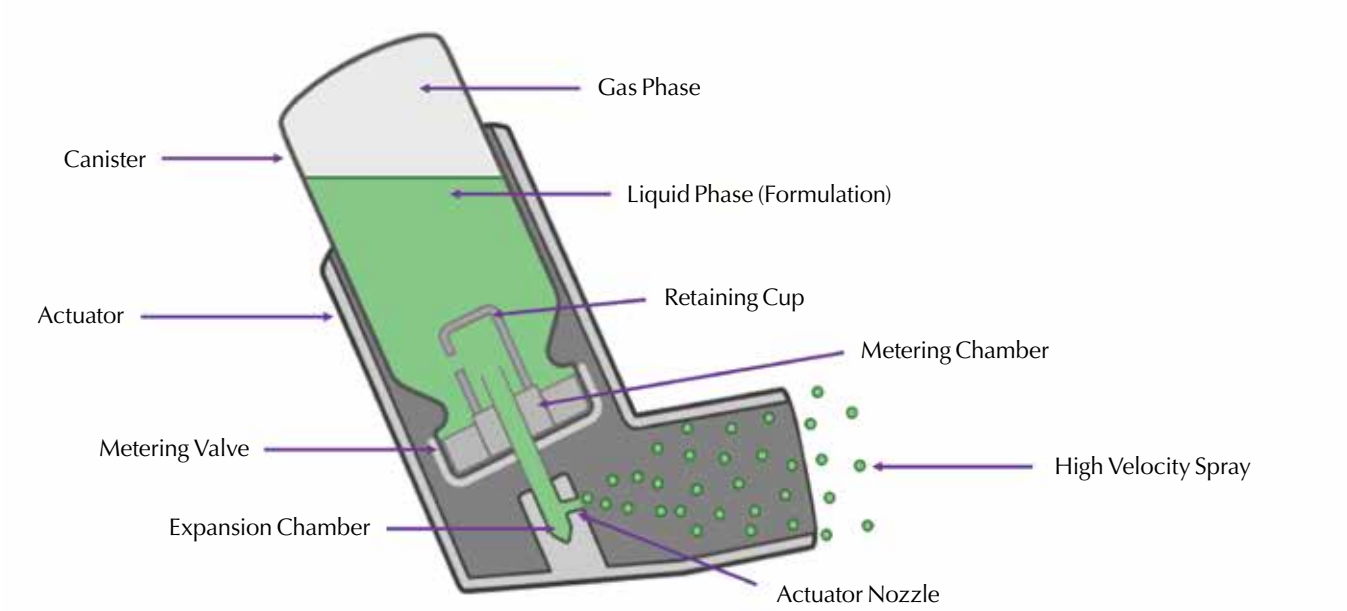
Since the introduction of the first MDI in 1956, the need to change propellants has arisen out of environmental concerns. Therefore, in the mid-1990's, substitution of chlorofluorocarbon (CFC) propellants with hydroflouroalkane (HFA) propellants was made to address the ozone depleting potential of CFCs. HFAs were considered acceptable until their identification and classification as global warming gases, which has triggered efforts for another change, this time to a new generation of low global warming potential (LGWP) propellants.

Introduction of the MDIs with HFA propellants was supported by full clinical development programs that were extensive, expensive and extremely time-consuming. As a result, several CFC-based drugs did not survive the transition, mostly for business reasons. This article considers lessons learned from that transition and the hitherto advances in the relevant sciences that could facilitate an efficient pathway to support the current transition to LGWP propellants.

The ongoing clinical developments to support transition to LGWP propellants can either follow the "Status Quo" or be streamlined by accommodating advances in the relevant scientific disciplines and exceptional scientific contributions from the Office of Generic Drugs (OGD), US Food and Drug Administration (FDA). If incorporated in product development, these advances could help expedite the LGWP propellant transition and potentially save millions of dollars spent on clinical programs. This article examines the Status Quo in view of relevant scientific advancements and regulatory devel-

Figure 1

Schematic representation of a metered dose inhaler.



opments and proposes a "Scientifically Rationalized Approach (SRA)" to impart both efficiency and cost-effectiveness to support the MDI transition to LGWP propellants. The proposed approach has certain parallels to the FDA's streamlining of programs for evaluation of the LGWP versions of the currently marketed HFA MDIs.

Introduction

The majority of the orally inhaled drug products indicated for treatment of respiratory diseases are metered dose inhalers (MDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs) and nebulizers. Among these, the MDIs are the most used inhalers, [1, 2] likely due to the lack of alternatives for delivery of reliever medicine(s) and the associated cost per dose. In global use of inhalers, DPIs rank second to MDIs, although the most widely used reliever medication (Albuterol) is available in DPI format [3]. DPI use may be limited by the inability of certain patient populations to achieve the inspiratory effort required for effective drug delivery [4-6]. SMIs have an advantage that can overcome this limitation. However, the extent of their use remains significantly lower than MDIs, probably due to higher cost per dose and absence of asthma reliever drugs in that format.

MDIs are complex drug products [7] made up of several components including container (canister), drug formulation, metering valve and actuator (Figure 1). Drug formulations can be suspended in the propellant or may contain additional excipients such as cosolvents, surfactants or engineered particles. In the MDI formulations, propellants (which are in gaseous phase at atmospheric pressure) are pressurized into liquid form within the MDI cannister. The propellent constitutes the principal inactive ingredient, both by weight and volume. It provides the force for dose delivery ex-valve and its subsequent aerosolization to deliver drug in the desired amount and particle size distribution suitable for pulmonary delivery.

Approved drug products occasionally undergo post-approval changes for a variety of reasons. However, post-approval changes in orally inhaled products are not common occurrences, with changes in propellants being most infrequent [8]. Since the introduction of the first MDI in 1956, [9] propellant change in approved products has not been motivated by business, technical or safety/efficacy reasons. Rather, propellant substitutions in approved MDIs have been prompted in response to environmental concerns. The first was the CFC-HFA change in the mid-1990s due to the ozone layer depleting potential of CFC propellants (CFC 11: trichlorofluoromethane and CFC 12: dichlorodifluoromethane) [10]. Another shift is currently underway [11], due to the global warming potential of propellants HFA-227 (1,1,1,2,3,3,3-heptafluoropropane) and HFA-134a (1,1,1,2-tetrafluoroethane) used in the approved MDIs that are transitioning to new LGWP propellants HFA-152a (1,1-difluoroethane) and HFO-1234ze(E) (trans-1,3,3,3-tetrafluoropropene) [12]. Figure 2 depicts the relative global warming potential of the CFC propellants used in the past, HFA gases currently used in the approved MDIs and the HFA and HFO propellants proposed as environmentally friendly substitutes. Replacement of HFA-134a and HFA-227 with either HFA-152a or HFO-1234ze(E) in the approved MDIs is expected to provide a substantial decrease in the carbon footprint per actuation (Figure 3).

Figure 2

Relative global warming potential of pMDI propellants. Data source [13].

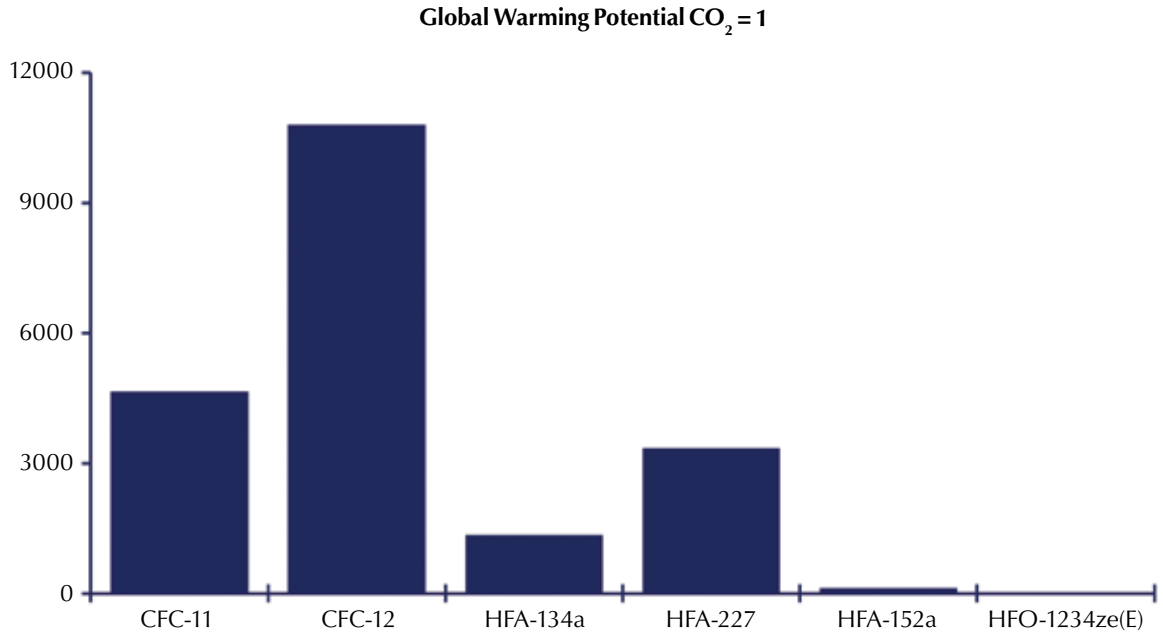
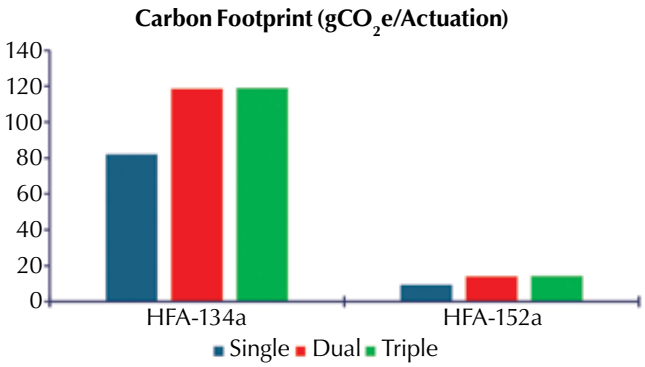


Figure 3

Carbon footprints of pMDIs containing formulations of drug alone (single) and its dual and triple combinations. Data source [13].



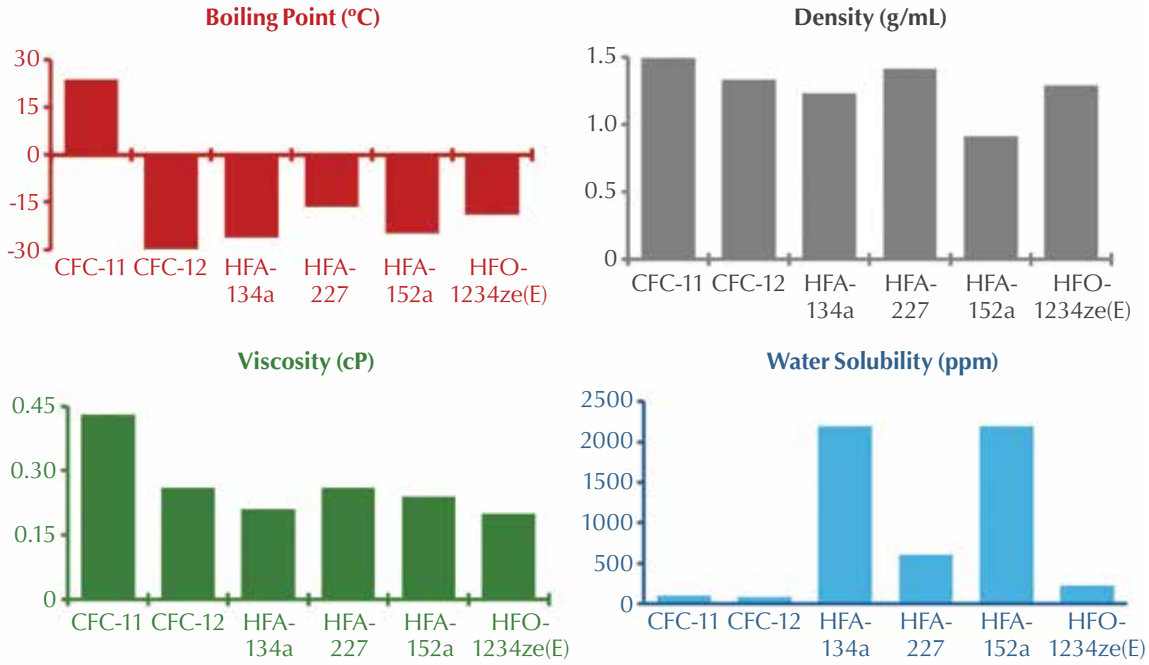
Propellant substitution in MDIs is not a simple excipient change, due to the propellant's participatory role in drug delivery, and possible influence on the delivered dose (DD), aerodynamic particle size distribution (APSD) and plume characteristics—all relevant to efficacy. In addition, propellant substitution also induces safety concerns based on the intrinsic safety of the propellent, its material compatibility and its impact on related substances and leachables. Therefore, due to the multifaceted impact of a propellant change on the safety and efficacy of approved MDIs, the CFC-HFA transition required full clinical programs. Whether the HFA-LGWP propellant change should also require the same resource-intensive product development, or can the clinical development programs be abbreviated in view of relevant advancements in science and regulatory arenas is an important and timely ponderance. This article examines the possibility of a "Scientifically Rationalized Approach (SRA)" that might impart both efficiency and cost effectiveness to clinical programs supporting the HFA-LGWP transition.

Product development considerations for the propellant switch

Pharmaceutical enterprises may reformulate their approved products for a variety of reasons including enhancement of product efficiency, change of route of administration, development to support new indication(s), etc. The extent of scientific data required to support the new formulation varies with the complexity of change in the formulation, route of administration and disease indication(s). For example, with drug products that are delivered to the site(s) of action via the systemic circulation, demonstration of pharmacokinetic (PK) bioequivalence (BE) between the existing and revised formulations might support therapeutic equivalence—a recognized surrogate for safety and efficacy. The PK-BE approach is limited to reformulations that utilize approved inactive ingredients for the same route of administration and within the range previously used and found in the US Food and Drug Administration (FDA) inactive ingredient database [15], provided the nonclinical evaluations of the previously approved drug products are deemed adequate by the current applicable regulatory standards. Regulatory approval of formulation improvisations beyond this level may require

Figure 4

Key chemical attributes of propellants relevant to substitution. Data sources [1, 14].



additional studies. Inhaled medicines for lung diseases are locally acting; consequently, systemic PK by itself may not be a reliable surrogate for demonstrating efficacy at the site of action. The extent of data required to support safety and efficacy of the revised products depends upon the nature of the modification(s) to the approved product. For extreme and/or complex changes, the regulatory requirements to support safety and efficacy of the modified products may include new nonclinical studies and full clinical programs to include Phases 1, 2 and 3. This article also explores the extent of nonclinical and clinical data that might be required to support the expected transition to LGWP propellants.

Nonclinical studies

Formulation modifications that introduce inactive ingredient(s) previously not approved for the same route of administration, and/or if the concentration of an approved excipient used in the new formulation exceeds the previously approved levels, may require nonclinical and clinical studies to determine safety of the new ingredient for administration to man. For the inhalation route of administration, the extent of testing will also include consideration of chronic administration by inhalation. The nonclinical data to support formulation change may include long-term studies [16].

Nonclinical studies to support the introduction of HFA propellants were accomplished by two consortia (IPACT-I and IPACT-II) that were formed by a number of pharmaceutical companies to generate a package of safety data on pharmaceutical-grade propellants [17]. However, no such consortium has been formed for development of safety data packages for the prospective LGWP propellants. Instead, safety studies for the HFO-1234ze(E) propellant from Honeywell (Charlotte, North Carolina, US) and the HFA-152a propellant from Orbia (formerly Koura, Mexico City, Mexico) have been undertaken by propellent suppliers and drug product manufacturers.

Drug delivery attributes of MDIs with LGWP propellants

As stated above, MDIs are drug-device combination products. The currently approved MDIs are classified as "press and breathe," with the exception of breath-actuated devices that depend upon the patient's inspiratory effort to trigger the actuation (e.g., QVAR® RediHaler®, Teva Respiratory, Tel Aviv, Israel). Irrespective of device design, MDI formulations contain either drug suspended in volatile liquid propellants or additional excipients, including engineered particles, ethanol, lecithin, oleic acid, citric acid, polyethylene glycol and HCl. However, the propellant constitutes the largest inactive ingredient in volume and by weight, and provides the energy to atomize droplets containing drug and excipients for pulmonary delivery [18]. Propellant selection is generally drug- or formulation-specific. The selected propellant also influences the choice of container-closure system (CCS) components with respect to compatibility of the material of construction (MOC).

Due to their distinctly different chemical attributes (Figure 4), the MDI transition from CFCs to HFAs necessitated changes in drug substance, formulation

and device. Substitution with HFAs resulted in drug products with delivery attributes different from those of the precursor CFC MDIs. The change affected APSD [19], lung deposition [20, 21], PK [22-24] and pharmacodynamics (PD) [25].

However, substitution of HFAs with LGWP propellants in the currently approved MDIs may be less burdensome than the CFC-HFA switch due to relatively fewer differences in the relevant chemical attributes of HFA and LGWP propellants (Figure 4). Nevertheless, due to the unique role of the propellant in drug release from MDIs, its effects on APSD and plume characteristics, and its interaction with drug substance(s) and CCS components, introduction of new propellants warrants consideration of a variety of formulation and device attributes relevant to drug product safety and efficacy (Table 1). Both formulation and device contribute to the desired performance of MDIs in terms of delivered dose uniformity (DDU), content uniformity, APSD of the delivered aerosol, chemical and physical stability of the drug over product shelf-life and the extent of leachables from device components. Propellant change might affect one or more constituents of formulation and device (Table 1). In addition, substitution with new propellants may warrant changes in manufacturing equipment and processes [26-29].

For regulatory submissions, drug delivery attributes for MDIs generally include dose delivered from the actuator mouthpiece and APSD based on inertial impaction studies. These are reported in terms of impactor-sized mass (ISM, Stage 1–Filter), fine particle mass/dose (FPM/FPD) or fine particle fraction/mass/dose (FPF/FPM/FPD) expressed as percent of DD, mass median aerodynamic diameter (MMAD) and associated geometric standard deviation (GSD). The required data also includes plume characteristics such as spray pattern (area and ovality of the plume cross-sections, generally at 3 and 6 cm distances from the orifice) and plume width at the selected longer distance (6 cm). All these drug delivery attributes have been found relevant to pulmonary delivery. Therefore, changes in one or more of the relevant parameters can potentially influence *in vitro* determination of drug delivery as well as pulmonary delivery *in vivo.*

Preparation for the anticipated switch to LGWP propellants has triggered a number of studies characterizing drug delivery from MDIs with new propellants. Investigators have reported acceptable material com-

Table 1

Probable changes in pMDIs for accommodation of LGWP propellants

Constituents	Component	Process/Ingredient/Property	Change
Formulation	**Drug Substance**	Particle Engineering/PSD	Yes
		Morphic Form	Yes/No
		Residual Substances/Impurities	Yes
		Surface Properties	Yes/No
	Propellant	Drug Compatibility	Yes
		Vapor Pressure	Yes
		Material Compatibility	Yes
		Flammability	Yes
	Inactive(s)	Co-Solvents	Yes/No
		Surfactants	Yes/No
Device	**Valve**	Volume	Yes/No
		Design	Yes
		Elastomer	Yes
		Leachables	Yes
		Priming	Yes/No
	Actuator	Nozzle Diameter	Yes/No
		Jet Length	Yes/No
		Mouthpiece Shape and Length	Yes/No
	Canister	Internal Coating	Yes/No

patibility [30], acceptable drug substance impurities [31] and leachables [32, 33]. However, as expected, drug delivery attributes would be affected by device and cosolvents. Antiga, et al. [34] reported increase in delivered dose of salbutamol from a suspension with increase in actuator orifice and ethanol content, but with a decrease in FPF. Also, solution formulations in the two LGWP propellants may respond differently to changes in the size of the mouth throat (MT) used in cascade impaction studies [35].

Differences in physicochemical properties of the HFA, HFC and HFO propellants may affect factors relevant to plume formation and dissipation, thereby resulting in different APSDs. However, such differences might be mitigated by the addition of excipients such as ethanol [36]. The FPDs/FPFs from solution formulations of beclomethasone dipropionate (BDP) in LGWP propellants have been shown to yield different MT depositions with expected directional differences in FPD/FPF and spray pattern. However, observed differences between the products were mitigated by incorporation of ethanol [37].

HFA-152a and HFO-1234ze(E) have lower saturated vapor pressures (SVP) than HFA-134a, which may contribute to larger droplet size in the LGWP propellant plumes [37]. Both LGWP propellants exhibit larger droplet sizes relative to HFA-134a, likely due to differences in SVP and wider plume for HFA-152a due to differences in SVP and lower plume velocity for HFO-1234ze(E). However, both propellants allow adjustment of co-solvent ratios to mitigate the observed differences in performance [38].

The drug substance physical attributes may have little or no effect on the performance of solution formulations. However, in suspension formulations, active pharmaceutical ingredient (API) properties may affect spray morphology [39], influencing spreading rate and aerosol size. This effect is expected to be lower for formulations using the LGWP propellants, due to reduced impact of suspended particles on the flash evaporation rate [40]. Exploration of changes in formulation and device are ongoing and more work may be necessary to achieve equivalence in the *in vitro* performance of MDIs between the currently approved HFA-134a or HFA-227 products and their follow-on versions based on the LGWP propellants [41-45].

The above discussion is indicative of differences in *in vitro* drug delivery between current HFA-based MDIs and their reformulated versions using LGWP propellants. However, as stated above, the observed differences may be reduced by adjustments in cosolvents and device attributes to achieve *in vitro* equivalence between current HFA MDIs and LGWP products. Recently Lachacz, et al. [46]. reported achievement of equivalence for all relevant *in vitro* performance attributes between AstraZeneca's (AZ's) approved HFA-134a-based, fixed-dose, triple combination pMDI (Breztri Aerosphere®) and its revised version using HFO-1234ze(E). It is relevant to note that the AZ MDI products use co-suspension technology wherein drug particles co-suspended with spray-dried phospholipid particles [47] may be more accommodative of propellant substitution. The AZ HFO-1234ze(E)-based triple combination MDI is also pharmacokinetically bioequivalent to its current version [48].

Impact of propellants on dissolution of aerosolized drug

Equivalence of *in vitro* drug delivery parameters enhances the likelihood of equivalence in pulmonary delivery and regional distribution, particularly if the *in vitro* determinations of DDU and APSD are based on methodology that imparts clinical relevance. In addition, dissolution of the aerosolized drug contributes to its availability for local action (relevant to efficacy) and systemic bioavailability (relevant to safety). Dissolution may be influenced by propellants. The impact of propellants on the dissolution rate of aerosolized BDP particles has been reported to be in the order of HFA-134a > HFO-1234ze(E) > HFA-152a [49-51] The observed differences in dissolution may be partly attributed to the morphologies of the aerosolized drug particles.

Discussions about dissolution characteristics of drugs formulated for inhalation have led to the formation of a relevant inhaled biopharmaceutical classification system (iBCS) [52]. However, this data set does not include BDP, due to its extensive metabolism in the lung. The FDA product-specific guidance (PSG) includes dissolution testing for BDP [53] to be conducted using discriminatory analytical methods [54]. In our opinion, it is also important to determine the clinical relevance of *in vitro* testing, which may vary with a drug. For BDP, discriminatory dissolution testing is based on methods that do not yield more than 50% of the drug, even in 60 minutes. Consequently, such testing has very little or no relevance to *in vivo* dissolution of inhaled BDP with the highest systemic concentration (C_{max}) occurring < 5 minutes after drug administration [55]. Therefore, the likelihood of *in vitro/in vivo* correlation for dissolution of BDP is low, limiting its value for inhalation product development because it is the degree of correlation between the drug dissolved *in vitro* and the predicted *in vivo* dissolution that imparts clinical relevance to dissolution testing. Dissolution testing may be relevant to the efficacy of inhaled drugs like budesonide and fluticasone which, compared with BDP, exhibit slower absorption and are not as extensively metabolized in the lung [56, 57]. Clinically relevant *in vitro/in vivo* correlations for dissolution testing of solid oral products are based on predicted *in vivo* dissolution generally determined by *in silico* deconvolution of PK data followed by the development of correlation between the fraction of drug absorbed and the

fraction of drug dissolved. Determination of the *in vivo* dissolution of aerosolized drug in this manner may be complicated and the extent of complexity may vary case-by-case.

Clinical development to support propellant substitution

An outline of classic clinical development of drug products typically entails Phase 1 studies (first in man) to explore tolerability and pharmacokinetics, Phase 2 studies for determination of clinically effective doses along with (where applicable) proof-of-concept for efficacy, and replicated Phase 3 trial determinants of safety and efficacy of the drug in the target population(s) [58]. The study design and populations vary with the study objectives and treatment indication(s). However, the basic outline stated above is applicable to drugs across the board, with the exception of abbreviated testing to support FDA 505(B)(2) New Drug Application (NDA) approvals where BE may be deemed sufficient to demonstrate the safety and efficacy of drugs delivered through systemic circulation.

To support the CFC to HFA transition, clinical development programs included Phase 1, Phase 2 and Phase 3 studies [59-61]. Furthermore, a major change in device of an approved HFA-based MDI was supported by a similar clinical program in a new application, even though its *in vitro* drug delivery and PK characteristics were similar to that of the original product [55]. For further discussion below, the use of a full clinical development program exercised hitherto for approval of the 505(B)(2) versions of approved MDIs is referred to as the "Status Quo" approach.

Most likely, the study designs to support the current propellant substitution may remain the same as those required to support approval of predicate products, despite greater sensitivity of bioanalytical methods and enhanced efficiency of clinical studies available today. Therefore, the clinical development to support approval of the LGWP-propellant-based MDIs may continue to be both expansive and expensive. Should this be the case, given the notably relevant advances in all applicable scientific fields, as well as regulatory science(s), that have taken place since the CFC-HFA switch? In our opinion, streamlined clinical development programs may be adopted to support transition to LGWP propellants, in view of scientific advancements and regulatory considerations that have created greater understanding of the critical attributes of drug substance, devices and propellants relevant to sustained safety and efficacy of MDIs.

Currently, for determination of particle size distribution of aerosols, the FDA recommends the use of realistic (clinically relevant) *in vitro* testing with greater *in vivo* relevance than compendial testing. The latter may not provide information on regional distribution, which is likely related to efficacy [62]. Instead, realistic APSD testing, which draws its clinical relevance from use of inhalation profiles of patients and anatomically relevant MTs, is of greater relevance to pulmonary drug delivery and is a superior predictor of lung deposition. Furthermore, *in silico* methods are now available for computation of regional distribution from realistic *in vitro* data, which may correlate with *in vivo* pulmonary deposition and regional distribution [63, 64].

PK studies are universally accepted for determination of therapeutic equivalence of drugs that are delivered to the site(s) of action through the systemic circulation. However, these studies have also demonstrated sensitivity to differences, even between locally acting inhalation drug products that were deemed sim-

Table 2

In vitro and _in vivo_ studies in the approaches to support propellant substitution

Study	Development Approach	
	Status Quo	**Scientific Rationalization**
In Vitro	Compendial testing for delivered dose, APSD, spray pattern, plume geometry, priming/repriming	Realistic (clinically relevant) determination of delivered dose, spray pattern, plume geometry, priming/repriming
In Vivo - Phase 1	PK determination of comparative systemic exposure in healthy volunteers	PK determination of comparative systemic exposure and pulmonary deposition without and with charcoal blockade of GI absorption, respectively
In Vivo - Phase 2	Dose-ranging studies based on relevant clinical endpoints	Comparative *in silico* determination of lung deposition and regional distribution determination based on realistic APSD data
In Vivo - Phase 3	Replicated placebo and comparator controlled clinical trials determinant of comparative safety and efficacy	Need for single Phase 3 study determinant of safety may be assessed case-by-case

ilar based on *in vitro* testing and clinical end point (CEP) studies [65-67]. The FDA has not accepted *in vivo* BE based solely on PK data, as the drug in circulation may result from both pulmonary and gastrointestinal (GI) absorption.

However, scientific advancements since the CFC-HFA switch have also imparted greater credence to PK studies in determination of lung deposition. In Europe, PK studies serve as surrogates for therapeutic equivalence of inhaled products [68]. Similar to the use of PK data by the FDA, the European agencies utilize PK data for determination of total exposure—a surrogate for safety. Additionally, they allow demonstration of lung deposition based on systemic PK data upon exclusion of GI absorption by application of activated charcoal before administration of the inhalation aerosol [69-71]. It is noteworthy, however, that the FDA now incorporates charcoal-blockade PK studies as an element of its "Alternative" approach for determination of *in vivo* BE in lieu of CEP [54].

During the two decades since the CFC-HFA switch, advancements in understanding of inhalation delivery and refinements in techniques to measure pulmonary drug delivery and regional distribution have been achieved. Therefore, we believe that such advancements should be key considerations in possibly abbreviating clinical programs using the SRA with justifiable departure from the Status Quo.

Table 2 describes our suggestions for application of the SRA as a replacement for the resource-intensive "Status Quo". It includes and acknowledges improvisations in *in vitro* testing and application of *in silico* methods to impart clinical relevance to *in vitro* data. In addition, it utilizes PK as a determinant of both total exposure and lung deposition, with the possibility of deducing regional distribution from *in silico* analyses of realistic *in vitro* testing data. The proposed approach might obviate dose-ranging studies since the delivered dose (based on realistic testing combined with PK studies with and without charcoal blockade of GI absorption) should furnish a fair determination of *in vivo* dose, which yields lung dose(s) that have been proven safe and effective, based on extensive clinical programs that supported approval of currently existing HFA MDIs.

Regulatory pathways

The proposed rationalization will not change the regulatory pathway for product approval. Therefore, a new application with an LGWP propellant remains a 505(B)(2) NDA that may utilize certain safety and efficacy information presented in the regulatory dossier of a corresponding reference MDI. However, it can help make a clinical development program more resource-efficient. Furthermore, though the suggested approach would be applicable in supporting expected revisions of reference MDIs for accommodation of LGWP propellants, it may be inappropriate to support conversion of currently approved generic MDIs in the absence of LGWP propellant-based reference listed drugs (RLDs).

Recently, however, a Prior Approval Supplement (PAS) pathway has been proposed to support substitution of LGWP propellants in both originator products and their approved generic versions [72, 73]. It may be somewhat similar to the pathways being used in Europe [74]. For the US, it is a novel approach and, if found acceptable by the FDA, should have significant impact on the way the FDA determines the safety and efficacy of inhalation products with major and multifaceted changes in formulation and/or device. Its acceptance and implementation by the FDA would be of little help for companies that have already completed, or are in the final stages of, clinical evaluations of their MDIs that have been reformulated with LGWP propellants. However, it may help those who have not yet initiated programs or are at very early stages of product development, provided: 1) they can detain their clinical development beyond Phase 1 PK studies until the proposed PAS pathway is deemed acceptable by the FDA, and 2) the FDA precisely articulates its requirements to support approval of such PAS submissions in a timely manner.

A fundamental premise of the PAS pathway is its dependence upon equivalence between the current HFA-based MDIs and the corresponding LGWP-propellant-based MDIs under development. Based on the brief discussion above, the possibility of achieving equivalence for all parameters determinant of drug delivery and the relevant plume attributes (e.g., spray pattern) is not unequivocal. The degree of departure from equivalence will determine the necessity for clinical determinations beyond the conventional therapeutic equivalence assessment.

A comparison of the established regulatory pathway and the proposed PAS supplement pathway is shown in Table 3. The established pathway provides distinctly different road maps for the development of innovator and generic products. Based on this approach, the modified reference product would be a new application supported by new clinical investigations. It may be entitled to exclusivity and/or protection from genericization if new patents were introduced for the new product. In the absence of exclusivity and patent protection, generic manufacturers would be able to develop and file Abbreviated New Drug Applications (ANDAs) without delay. The requirements for development of generics would be the same as currently enforced by the FDA, with all elements of the "Weight of Evidence" approach to support therapeutic equivalence. The FDA's alternative approach, in lieu of CEPs, may not be applicable because of potentially major formulation change(s) to support propellant substitution [75].

Development of generic MDIs via the PAS pathways may face few regulatory complexities. The suggested roadmap may be conceivable if the FDA allows the approved HFA RLD to be used as a reference in bioequivalence studies and the RLD remains available for a variety of studies essential to support generic MDI development programs. The approved first generic MDI could then become an RLD, if the existing RLD gets withdrawn from the market for reasons other than safety and efficacy [76]. However, that would not be the case if the RLD was not officially discontinued.

If the RLD were discontinued for reasons other than safety and efficacy [77] and if the FDA were to allow its approved first generic version to be used as its own RLD, the development program for the LGWP-propellant-based generics would entail all studies currently required to meet the recommendations of the "Weight of Evidence" approach. Furthermore, given the magnitude of the change, the FDA may enforce requirements beyond those traditionally recommended for generic MDIs with Q1/Q2 sameness of formulations and similarity in devices. Based on available information, the likelihood of a generic product satisfying *in vitro* equivalence is limited, with the exception of special formulations that may be resistant to propellant change [46, 47].

While this manuscript was under review, the Center for Research on Complex Generics held a workshop on "Navigating the Transition to Low Global Warming Potential Propellants," with participation of relevant experts from the US FDA, certain European authorities, industry and academia [78]. At this meeting, several presentations discussed possible applica-

Table 3

Product development and regulatory considerations in pursuit of the established regulatory pathway and the proposed prior approval supplement (PAS) pathway

Established Regulatory Pathway		
Application type	**New Drug Application - 505(B)(2)**	**ANDA - 505(J)**
Application number	New	New
Indication	Original	Same as RLD
Formulation	New (Q1/Q2 different)	Expected to be similar to the new RLD
Device	Possibly different	Expected to be similar to the new RLD
Drug delivery attribute	Same or different	Required to be equivalent to the new RLD
Safety and efficacy	New studies (Pharmacokinetics and clinical)	Meet recommendations for Weight of Evidence approach
Exclusivity	Possible	ANDA to comply with applicable exclusivity
IP protection	Possibility for new formulation patents	Potential for rendering generic approvals "Tentative" until patent expiry
AB rating	Not applicable	AB Rated to the new RLD
Proposed Prior Approval Supplement (PAS) Pathway		
Application type	**Supplemental New Drug Application**	**Supplemental ANDA**
Application number	Original	Original
Indication	Same as original	Same as original
Formulation	New (Q1/Q2 different)	New. May also be Q1/Q2 different from the new RLD
Device	Possibly different	May be same to itself, but different from the new RLD
Drug delivery attribute	Similar or different	Expected to be similar to the new RLD
Safety and efficacy	Based on pharmacokinetic studies	Based on pharmacokinetic studies
Exclusivity	Possible	To be determined
IP protection	Possible	To be determined
AB rating	Same as original	To be determined by the agency

tion of the above-described PAS pathway for approval of the LGWP substitution in both brand and generic MDIs [79, 80] envisaging possible application of the European "Stepwise" approach [81]. The FDA maintained its recommendation for the established 505(B)2 pathway and the traditional clinical development program to demonstrate safety and efficacy, but also discussed the possibility of a "streamlined" version [82] of the traditional resource-intensive clinical development based on comparative quality attributes, equivalence of *in vitro* drug delivery and pharmacokinetic characteristics between the approved reference product and its modified version with an LGWP propellant [83, 84]. The streamlined program would still carry a recommendation for dose-ranging studies which, in our opinion, could possibly be obviated by documentation of comparative pulmonary delivery using charcoal-blockade PK studies and determination of lung dose and regional distribution using realistic APSD testing combined with the stated *in silico* analyses. The industry presentation [79] on the PAS Pathway proposed by IPAC-RS [85] essentially recommends the European Stepwise approach for demonstration of equivalence between MDIs pre- and post-LGWP propellant substitution, based on *in vitro* testing for DDU and APSD and *in vivo* PK studies. At this time, this proposal is not supported either by the US FDA or European authorities. Presentations from the FDA [82-84, 86] European [87], and British [88] regulators also highlighted the need for long-term safety studies on LGWP MDIs, until safety of the new propellant(s) has been established. The British authorities expressed reservations, even for approving the modified MDIs based only on comparative *in vitro* performance data, an allowance generally applicable across Europe for approval of generic (Hybrid) applications and post-approval changes/variations in approved inhalation aerosols.

The proposed SRA has certain parallels to the FDA's streamlining of programs [82, 86] for evaluation of the LGWP versions of the currently marketed HFA MDIs. These programs do embrace certain outcomes of the meritorious scientific advances in OGD that have established in-depth understanding of a multitude of scientific complexities in its relentless pursuit to relieve the generic manufacturers of nasal and inhalation products from the resource-intensive CEPs. The PD study for albuterol MDIs and the 4-week efficacy study suggested for the ICS/LABA are essentially similar to those included on the OGD product-specific guidances for such MDIs. However, for albuterol and certain ICS products with qualitative (Q1) and quantitative (Q2) sameness of formulations, OGD now also includes options for Alternative BE approaches in lieu of the CEPs. The proposed SRA also takes into consideration the Alternative approaches outlined in PSGs developed by OGD, which can possibly be relevant to LGWP MDIs that are Q1/Q2 same as their HFA-based inhalers [46]. It is hoped that the OGD recommended Alternative approaches might also be considered for documentation of efficacy of the LGWP MDIs without the resource-intensive CEPs.

Conclusion

MDIs are complex drug-device combination products. Both device and drug formulation contribute to safety and efficacy of approved inhalation aerosols. The MDI formulations may consist of drug suspended in propellant, or mixtures of drug and propellant and other excipients. The propellants used in MDIs constitute the principal inactive ingredient, based on weight and volume. They are the sole source of the force that effects emission and aerosolization of the formulation to a form suitable for inhalation. In addition, the propellants, based on their physicochemical properties, may interact with formulation and device components, and the outcome of such interactions may also affect product quality attributes determinant of safety and efficacy. Propellant changes in MDIs to address environmental concerns may require re-engineering of these combination products. Consequently, MDIs with new propellants may differ from their currently approved forms with respect to drug product constituents as well as drug delivery attributes relevant to safety and efficacy.

The US FDA approval for the CFC-HFA propellant change required full clinical programs, which were expensive and time-consuming. The same "Status Quo" approach may be recommended by the FDA to support the ongoing transition to LGWP-propellant-based MDIs marketed in the US. However, there have been notable scientific advances in the regulatory arena, as well as in quality considerations for product development since the CFC-HFA change. These developments provide opportunities to develop Scientifically Rationalized Approaches for both cost-effective and efficient transition to MDIs with LGWP propellants. Clinical programs to evaluate MDIs with LGWP propellants can be abbreviated in view of advances in clinically relevant *in vitro* and PK studies. The US FDA has utilized the stated advancements in development of its Alternative approach, in lieu of its resource-intensive clinical end point studies required to support approval of generic MDIs. Cost-effectiveness of the propellant substitution also should be an important consideration for continued availability of inhalation aerosols, which constitute the most-used products for inhalation therapy and provide the sole source of rescue medications utilized across patient populations.

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