IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

# IPAC-RS Workshop on the Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers

11 October 2023

This workshop will discuss the regulatory and technical aspects of the ongoing transition to low global warming potential (GWP) propellants in metered dose inhalers (MDIs).

# Who we Are

- The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) is an international association that seeks to advance the science, and especially the regulatory science, of orally inhaled and nasal drug products (OINDPs) by collecting and analyzing data, and conducting joint research and development projects.
- Representing the OINDP industry since 2000, IPAC-RS aims to build consensus and contribute to effective regulations and standards by sharing the results of its research through conferences, technical journals, and discussions with regulatory bodies.

# Our Members

- **Members** - corporations that develop, manufacture or contract to manufacture OINDPs

AstraZeneca
Boehringer Ingelheim
Catalent
Chiesi
Genentech
GSK
Kindeva Drug Delivery
Lonza
Lupin Pharmaceuticals, Inc.
Merck & Co., Inc.
Novartis
Recipharm
Teva
TranspireBio
Vectura
Viatris

- **Associate Members** – corporations that (1) develop or manufacture components and/or devices for OINDPs or (2) provide scientific or technical services relating to development and manufacture of OINDPs or (3) are eligible for full membership but have annual revenues of less than seventy-five million US dollars.

Aptar Pharma
Copley Scientific
H&T Presspart
Nemera
PPD
Impel Pharmaceuticals Inc.
Proveris Scientific Corporation
RxPack
Softhale

# Top 5 Reasons to Join IPAC-RS

1. Stay ahead of emerging international regulatory and scientific challenges facing the OINDP industry.
2. Participate in joint industry discussions with and guidance commenting to regulators in North America, Europe, Asia, and South America.
3. Join industry leaders in providing feedback to standard-setting bodies and international pharmacopoeia.
4. Share knowledge, information and experiences with other industry leaders.
5. Stay abreast of pertinent development and also shape national and international trends and requirements.

# Background to Workshop

- Metered dose inhalers have been a mainstay of therapy for many years
- Transition from first CFC to HFA MDIs was initiated due to Montreal Protocol of 1987
- Transition today is due to Kigali Amendment to the Montreal Protocol and related climate legislation
- Industry is responding to be prepared and continue availability of MDIs
- Transition from CFC to HFA was accompanied by issuance of guidances from health authorities
- Purpose of this workshop is to discuss considerations regarding the current transition to lower GWP propellants to enable an understanding of the requirements for all stakeholders

# Agenda

| |
|---|
| **Welcome, Introduction**<br>*Ann Purrington, Kindeva* |
| **MDI Propellant Switch in the 2020s Compared and Contrasted to the Previous Propellant Switch of the 1990s: Don't Panic!**<br>*Rik Lostritto, Lostritto Consulting LLC* |
| **Readout from the IPAC-RS/IPAC Surveys on Alternative Propellants**<br>*Sue Holmes, GSK* |
| **Metered Dose Inhalers (MDIs)/Inhalation Aerosols with Lower Global Warming Potential (LGWP) Propellants – New Drug Quality Perspective**<br>*Craig Bertha, FDA* |
| **Data Requirements When Switching to LGWP Propellants – the EU perspective**<br>*Karolina Törneke (MPA/EMA)* |
| **Materials Aspects of the Transition to Alternative Propellants – an IPAC-RS Working Group Perspective**<br>*Dan Dohmeier, Kindeva* |
| ***Break*** |
| **Panel Discussion with All the Speakers** |
| **Closing Remarks**<br>*Atish Sen, AstraZeneca* |

# Housekeeping

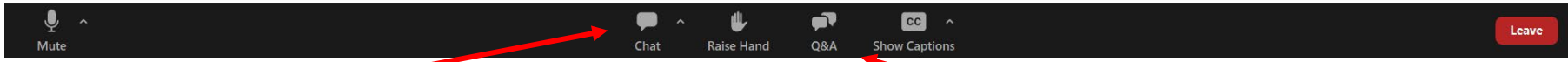
IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

## IPAC-RS Workshop on the Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers

11 October 2023

- All Attendees are on mute.
- The Workshop is being recorded.

This workshop will discuss the regulatory and technical aspects of the ongoing transition to low global warming potential (GWP) propellants in metered dose inhalers (MDIs).




• The Chat function has been disabled for Attendees. Type your question in the Q&A box.

# MDI PROPELLANT SWITCH IN THE 2020'S COMPARED TO PROPELLANT SWITCH OF THE 1990'S: *DON'T PANIC*

Richard (Rik) Lostritto, Ph.D., Independent Consultant

Presented at the IPAC-RS Workshop on Alternate Propellants

October 11, 2023

**DISCLAIMER:** THIS PRESENTATION REPRESENTS MY OWN VIEWS AS AN INDEPENDENT CONSULTANT. I DO NOT REPRESENT ANY ORGANIZATION, COMPANY, OR HEALTH AUTHORITY.

LOSTRITTO CONSULTING, LLC

Science in Quality

# OUTLINE

LOSTRITTO CONSULTING, LLC
Science in Quality

- Background
- Propellant switch scenarios
- Comparisons between switch scenarios: CFC to HFA
- Comparisons between switch scenarios: current HFA to future propellants
- The bottom line
- FDA guidance considerations and implications
- Elephants (hiding) in the room: Human Factors and Labeling
- Summary

# BACKGROUND: LEVELING TERMINOLOGY

LOSTRITTO CONSULTING, LLC
Science in Quality

- Today we're considering MDI switch programs to new propellants either in development or to post approval (A)NDAs
- MDI = metered dose inhaler
- HFA = hydrofluoroalkane (e.g., HFA-134a and HFA-227) currently used
- **HFX = next generation MDI propellants**
  - **HFA-152a**
  - **HFO-1234EZ(E)**

# BACKGROUND: SOME TERMINOLOGY

LOSTRITTO CONSULTING, LLC
Science in Quality

DDU = delivered dose uniformity

APSD = aerodynamic particle size distribution

RLD = reference listed drug

PSG = product specific guidance

PE = pharmaceutical equivalence (*in vitro*)

BE = bioequivalence (*in vivo*)

BA = bioavailability

PD = pharmacodynamic

PAS – prior approval supplement (applies to approved NDAs, BLAs, and ANDAs)

*QE = quality equivalence (in vitro)… a new term?*

CP = citizen petitions

# BACKGROUND: THEN

LOSTRITTO CONSULTING, LLC
Science in Quality

- **Milestone dates**

  1956, 1987 (adopted), 1996

- **The near-ideal nature of CFC's for**

  formulation

  manufacture

  use

- **The 1989 Montreal Protocol driving forces**

  ozone depletion and global warming

# BACKGROUND: NOW

LOSTRITTO CONSULTING, LLC
Science in Quality

- **Current driving forces**
  - global warming and “forever” chemicals (PFAS)
- **The current situation “rhymes” with the 1990’s**
  - Current and previous situations are not entirely independent
  - Yet they are independent in some important ways
    - The next generation of propellants are a less dramatic shift
    - better grasp today of fundamental MDI function, materials, etc.
    - that means more meaningful *in vitro* regulatory expectations
    - generic MDIs exist today: new challenges

# PROPELLANT SWITCH SCENARIOS

LOSTRITTO CONSULTING, LLC
Science in Quality

**Doing nothing is a non-sustainable option that hastens negative outcomes**

- Derogation / allowance for HFA-134a and HFA-227 is a gamble
- Stockpiling current propellants (e.g., 2-5 years) leads to
  - potential quality concerns on storage (seen in the 1990's),
  - potential supply limitations with possible mandated allocations and/or potential drug shortages (also seen in the 1990's)

**Out of scope for today**

- Switch to another dosage form such as DPI, etc.
- Switch to other propellants other than HFA-152A and HFO-1234EZ(E)

# PROPELLANT SWITCH SCENARIOS

LOSTRITTO CONSULTING, LLC
Science in Quality

**- Here are some of the possible cases..**

**The cases of concern for the propellant switch to HFX for MDIs include**

1. NDA in development (bridging pre-NDA submission)
2. Approved NDA; post approval switch
3. ANDA in development (bridging pre- ANDA submission)
    - Switching ahead of RLD (i.e., RLD's switch not yet approved [if any])
    - Following RLD's current propellant if HFA-134a or HFA-227
        - RLD gets their switch approved while ANDA in development

# PROPELLANT SWITCH SCENARIOS

LOSTRITTO CONSULTING, LLC
Science in Quality

4. Approved ANDA

post approval switch ahead of RLD (i.e., RLD's switch not yet approved

post approval switch to HFX after the RLD's approval

**- Adding to the scenarios are overlapping (A)NDA issues**

For generics, in some cases it is unclear what the RLD is /will be

CPs

Patents

Label claims

# INTERIM NOTES

LOSTRITTO CONSULTING, LLC
Science in Quality

A balance of science and regulation must be found that is both reasonable and feasible for the RLD and generic industries to adopt new MDI propellants to avoid negative outcomes such as:

- drug shortages of essential (A)NDA MDI medicines
- exorbitant development costs associated with the switch dramatically increasing the cost to the patient
- supply chain vulnerability (i.e., single source for MOC, propellant, etc.)
- gray practices that manipulate/exploit/obfuscate a facile propellant switch unfairly (e.g., baseless CPs) leading to the aforementioned

# COMPARISONS BETWEEN SWITCH SCENARIOS
## CFC TO HFA

LOSTRITTO CONSULTING, LLC
Science in Quality

**Physicochemcial properties of CFCs (1990's) are very different from HFAs**

- HFAs (and HFX) have multiple C-H bonds. CFCs lack C-H bonds. This impacts solubility and other behavior dramatically favoring CFCs.

- A total rethinking was necessary in the 1990's; this was more than a *switch*

Complete reformulation effort required

Essentially all MOCs no longer compatible

CFC manufacturing methodology not sustainably transferable

In vitro testing methods and specs become non-applicable

# COMPARISONS BETWEEN SWITCH SCENARIOS
## CFC TO HFA

LOSTRITTO CONSULTING, LLC
Science in Quality

- **Complete reformulation was necessary**
  - Lost solubility of then used excipients precluded their use with HFAs
  - Solution MDIs: new solubilizing excipients (e.g., ethanol) created new problems
  - Suspension MDIs: suspension stability issues
- **MOCs failed with HFA formulations** requiring all new (and cleaner)
  - valves (plastics, elastomers, and metals)
  - canister alloys and coating (if any)
  - actuator plastic and stem/nozzle geometry failures.

# COMPARISONS BETWEEN SWITCH SCENARIOS
## CFC TO HFA

LOSTRITTO CONSULTING, LLC
Science in Quality

- **Manufacturing method**
  - No room temp liquid CFC equivalent
  - Pressure filling required new filling lines and equipment
  - Cold filling at -50C required updated process design and development
  - Higher manufacturing pressures pose worker safety risk

# COMPARISONS BETWEEN SWITCH SCENARIOS
## CFC TO HFA

LOSTRITTO CONSULTING, LLC
Science in Quality

**- Testing and performance**

**Existing CFC quality control methods were already relatively aged**

Essentially every in vitro performance test method and specification had to be re-designed and validated for the switch.

Incoming material change controls were not sufficiently effective

New impurities in HFAs were of an entirely new classes

The switch from CFC to HFA triggered heightened awareness and action to purity control, contaminants, change control, and quality specification (methods and acceptance criteria) development

# COMPARISONS BETWEEN SWITCH SCENARIOS
## HFA TO HFX

LOSTRITTO CONSULTING, LLC
Science in Quality

- As far as is known, the physicochemical issues associated with the current HFA to **HFX** change should be less substantive than the 1990's CFC to HFA change. Why?

**- Based on what is known, HFXs** and their properties are more similar to currently used HFAs. This greater similarity is expected to show in terms of solubility, swelling properties, working pressures, and MDI manufacturing considerations.

- Formulation strategy , MOC choices, manufacturing, testing and performance are much less likely to be affected.

**- Quantitative confirmation of the above as they apply to MDIs deserves deep data-based consideration before regulatory pathways, technical requirements and any clinical requirements are decided.**

# COMPARISONS BETWEEN SWITCH SCENARIOS THE TIMES HAVE CHANGED

LOSTRITTO CONSULTING, LLC
Science in Quality

**- In the 1990's**

- Heightened leachable concerns emerged with the propellant switch fueled by nitrosamines found in RBBN and other issues
- New propellant impurities completely unrelated to CFCs
- Aged and non-transferable methods and metrics for DDU, APSD, leak rate, spray pattern, plume geometry, priming, cleaning clogging
- CFC stockpiling and allotments

**Many things were changing simultaneously**

# COMPARISONS BETWEEN SWITCH SCENARIOS THE TIMES HAVE CHANGED

LOSTRITTO CONSULTING, LLC
Science in Quality

- **Since the 1990's through today**
- The availability of generic MDIs
- Cleaner, better understood, and better controlled MOCs
- HFA MDI manufacturing is now routine and better controlled
- Continuous improvement in quality testing methods and metrics that better correlate with safety, efficacy, and BE
- Leachable and extractables are better understood and controlled
- supply chain integrity problems, drug shortages, and cost to patients continue to increase

# THE BOTTOM LINE

LOSTRITTO CONSULTING, LLC
Science in Quality

- **Going from the CFC era to HFAs was a radical and sweeping change** affecting multiple MDI related industries. This was occurring simultaneously with a shifting scientific and regulatory climate.

- Although more data are needed, going from HFA to **HFX** appears to be much less of a change from the chemical, physical, compatibility, manufacturing, testing, and performance perspectives

- A data package supporting a successful HFA to **HFX** switch will be substantial and much work remains to be done

# THE BOTTOM LINE

LOSTRITTO CONSULTING, LLC
Science in Quality

- What type(s) of (abbreviated) human studies studies (if any) are needed to support a propellant switch to **HFX** if adequate in vitro comparability (quality equivalence, TBD) is  achieved for the following cases?
    - An approved NDA
    - An approved ANDA
    - IND in development by phase (phase tiered bridging requirements)
    - pre-ANDA for generic in development (bridging studies)

# 2004 FDA GUIDANCE: *SUBMITTING SEPARATE MARKETING APPLICATIONS… USER FEES* STATES

LOSTRITTO CONSULTING, LLC
Science in Quality

**B**. NDA and BLA Supplements (**note ANDAs are not mentioned so what is meant by "bioequivalence" is open to some interpretation and flexibility**).

**2**. Other **Changes to Approved Products**

A change to an approved product based on chemistry, manufacturing, or controls data and **bioequivalence**, or other studies (e.g., safety and immunogenicity), that changes (1) the strength or concentration; (2) the manufacturing process, equipment, or facility; or (3) the formulation (e.g., different excipients) **can be submitted as a supplement to an approved application**. Such a change would not ordinarily warrant a new original application unless it changes the dosage form or route of administration.

**https://www.fda.gov/media/72397/download**

# 2004 FDA GUIDANCE: *SUBMITTING SEPARATE MARKETING APPLICATIONS… USER FEES* STATES

LOSTRITTO CONSULTING, LLC
Science in Quality

**Reasonable interpretations and practical questions**

- A robust CMC/Quality package would accompany any PAS. If APSD, DDU, Spray pattern, etc. are adequately aligned (quality equivalent) what would human testing beyond BE (or similar) be expected to confirm?

- Regarding human testing, is there a **focused approach** to BE, BA, PD, or some surrogate end point (i.e., "***or other studies***") as an alternative to full clinical testing as was required during the 1990's CFC to HFA switch?

# 2004 FDA GUIDANCE: *SUBMITTING SEPARATE MARKETING APPLICATIONS… USER FEES* STATES

LOSTRITTO CONSULTING, LLC
Science in Quality

- Can the BE approach normally attributed to ANDAs be extended to include supporting the human testing requirements of an NDA's own propellant switch program?

The guidance seems to indicate that is a yes by plain read.

- Can this thinking be applied to approved ANDAs seeking to switch propellants?

Again, the reasonable person answer appears to be yes. That is, if BE applies to an NDA here it should apply to an ANDA in a similarly situated situation.

# ELEPHANTS (HIDING) IN THE ROOM

LOSTRITTO CONSULTING, LLC
Science in Quality

**Human factors**

- Force to fire and Feel / sound/ ergonomics of use
- Altered dose counter error profile in switched products
  over or under counting from different mechanics such as
  valve friction, stroke length, formulation back pressure, lubricity
- Cleaning / priming changes
- Handling / disposal changes

# ELEPHANTS (HIDING) IN THE ROOM

LOSTRITTO CONSULTING, LLC
Science in Quality

**Labeling issues with propellant change**

-What will be the best equivalent of labeled strength?

If it is mass of API delivered from the actuator (delivered dose) then…

the volume of actuation (from the valve) will be different

# SUMMARY

LOSTRITTO CONSULTING, LLC
Science in Quality

- Although more data are needed, the current propellant change from HFA to HFX is very likely to be much less severe than the CFC to HFA propellant change was in the 1990's

- Understanding of the technology associated with MDIs has progressed a great deal in terms of MOC, formulation, manufacture, testing, and controls. Modern capability to produce MDIs with consistent performance is better than in the 1990's. This should reflect a more consistent relationship to *in vivo* performance.

- Bridging studies for (A)NDA MDIs in development needs to be addressed as part of the technical and regulatory schema.

# SUMMARY

LOSTRITTO CONSULTING, LLC
Science in Quality

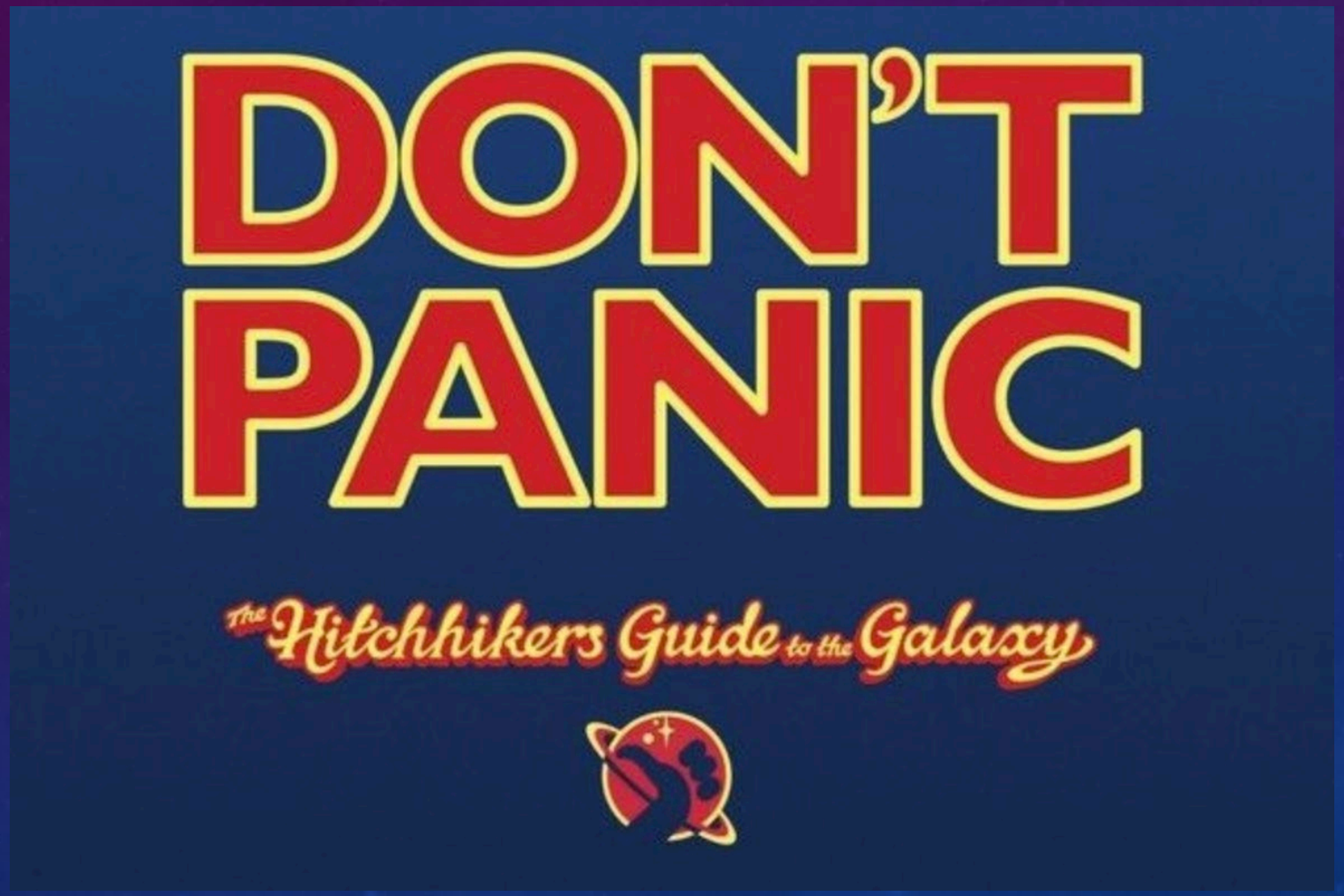
- The CMC/Quality data package to support a propellant switch for an approved MDI product will be data driven and substantial.

- A reasonable interpretation of applicable FDA guidance suggests that human data to support a propellant change for MDIs may be submitted as a PAS to an approved NDA (e.g., as TBD "*bioequivalence*" data); and by reasonable extension to an approved ANDA in the same situation.

- The impact on a propellant switch program has unique (and in some instances overlapping) implications for NDAs and ANDAs that are approved or in development. Regulatory requirements need to consider NDAs and ANDAs holistically and together. To neglect either is to neglect both.

# THANK YOU, AND REMEMBER …

LOSTRITTO CONSULTING, LLC
Science in Quality



# TWO BACKUP / REFERENCE SLIDES FOLLOW WHICH ARE FROM THE FEDERAL REGISTER NOTICE (FRN)FOR THE GUIDANCE CITED IN THE MAIN PRESENTATION

https://www.federalregister.gov/documents/2005/01/03/04-28654/guidance-for-industry-on-submitting-separate-marketing-applications-and-clinical-data-for-purposes

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees.” The guidance describes the agency's current policy on what should be contained in separate marketing applications and what should be combined into one application for purposes of assessing user fees and a definition of “clinical data” for user fee purposes.

**Background:** FDA is announcing the availability of a guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees.” The guidance document describes FDA's thinking on what will be considered separate marketing applications and what will constitute clinical data for purposes of assessing user fees under sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379g and 379h).

This guidance was issued in draft on February 22, 2001 (66 FR 11175) with comments due by March 26, 2001. No comments were received. In the meantime, Congress considered reauthorization of the user fee program. As a result, FDA delayed issuance of the guidance. Now that the program has been reauthorized without change to the relevant language, FDA is issuing the guidance. Other than minor editorial changes, only two changes of note have been made to the guidance. We have reevaluated our policy on pharmacy bulk packages and products for prescription compounding and determined that a separate application is no longer needed for these products unless otherwise noted in the guidance document. Therefore, the subsection entitled “Pharmacy Bulk Packages and Products for Prescription Compounding” has been removed. In addition, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108–173) may require a new application to be submitted because of a change to the reference listed drug. Therefore, a new subsection was added to clarify the user fee liability.

The guidance represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

# Readout from the IPAC-RS/IPAC Surveys on Alternative Propellants

Presented by: Sue Holmes, GSK

# Outline

- Background
- Survey on Alternate Propellants
- Consensus Industry Challenges and Concerns

# Background

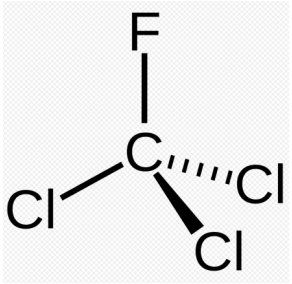
CFC - Chlorofluorocarbon
HFC - Hydrofluorocarbon

# Drivers for Change

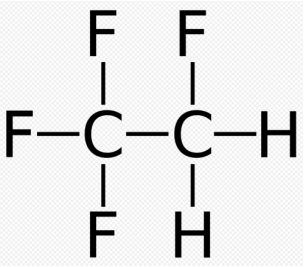
**Montreal Protocol** on Substances that Deplete the Ozone Layer regulates the production & consumption of ozone depleting substances

- First adopted in 1987 and led to a transition from CFC to HFC propellants in early 1990s
- The Protocol was amended in 2016 (in Kigali, Rwanda) and introduced a phase-down schedule for HFCs with a high global warming potential

CFC: e.g., Propellant 11 (trichlorofluoromethane)
Environmental Impact: Ozone depleting




HFC Propellant e.g., HFC 134a (tetrafluoroethane)
Environmental Impact: Non-ozone depleting;
high global warming potential



F-gas – fluorinated greenhouse gas
HFO - Hydrofluoroolefin

# Drivers for Change

**EU F-gas Regulation controls consumption and emissions of fluorinated gases; has been in effect for many years**

The propellants used currently in pMDIs (HFC 134a and 227) are F-gases and are currently exempted from regulation; however:

- Regulation is currently under revision and exemption is proposed to be removed and MDIs subject to the phase-down/quota system
- Clinicians, patients and industry have engaged in EU public consultations to ensure that phase down protects access to essential medicines, avoids unintended consequences, and allows sufficient time to transition to next generation lower global warming potential propellants (HFC-152a and HFO-1234ze)
- Current status: The co-legislators in the EU Parliament and the Council recently reached provisional agreement and the revised regulation should be finalized soon

# Drivers for Change

ECHA – European Chemical Agency
PFAS – Per and Polyfluoroalkyl Substances
REACH – Registration, Evaluation, Authorization and Restriction of Chemicals

**ECHA/REACH PFAS Proposal** (Feb 2023) seeks to restrict use of PFAS in a broad range of sectors, including MDI propellants

***The proposal seeks to ban some medical propellants in near term:***

- The propellants currently used in pMDIs (HFC 134a and 227) and one of the next generation propellants (HFO-1234ze(E)) are categorized as PFAS
- Industry, clinicians and patients are urging that additional time be provided for existing propellants and potentially permanent derogation for HFO-1234ze(E)
- Comments submitted during public consultation:
  - IPAC-RS/IPAC Comments: https://www.ipacrs.org/lgwppropellants
  - European Federation of Allergy and Airways Diseases Patients' Associations Comments: https://www.efanet.org/news/news/4265-efa-submits-respiratory-patients-considerations-to-echa-draft-restriction-on-pfas
  - ..and many others

# Historical Changes

CFC - Chlorofluorocarbon
HFC - Hydrofluorocarbon
CMC – Chemistry, Manufacturing and Controls

- In 1990s CFCs were replaced with HFC 134a and HFC 227 due to the ozone depleting nature of CFCs (under first version of the Montreal Protocol)
- Development was more complex and longer than expected with costly and time-consuming clinical studies and new CMC programs being required
- Manufacturers had to submit New Drug Applications/Marketing Applications
- Industry wants to learn from the prior transition and with substantial improvements in scientific understanding of inhaled products believe that this transition could/should be easier
  - Led to a survey to understand the situation

# Alternate Propellant Survey

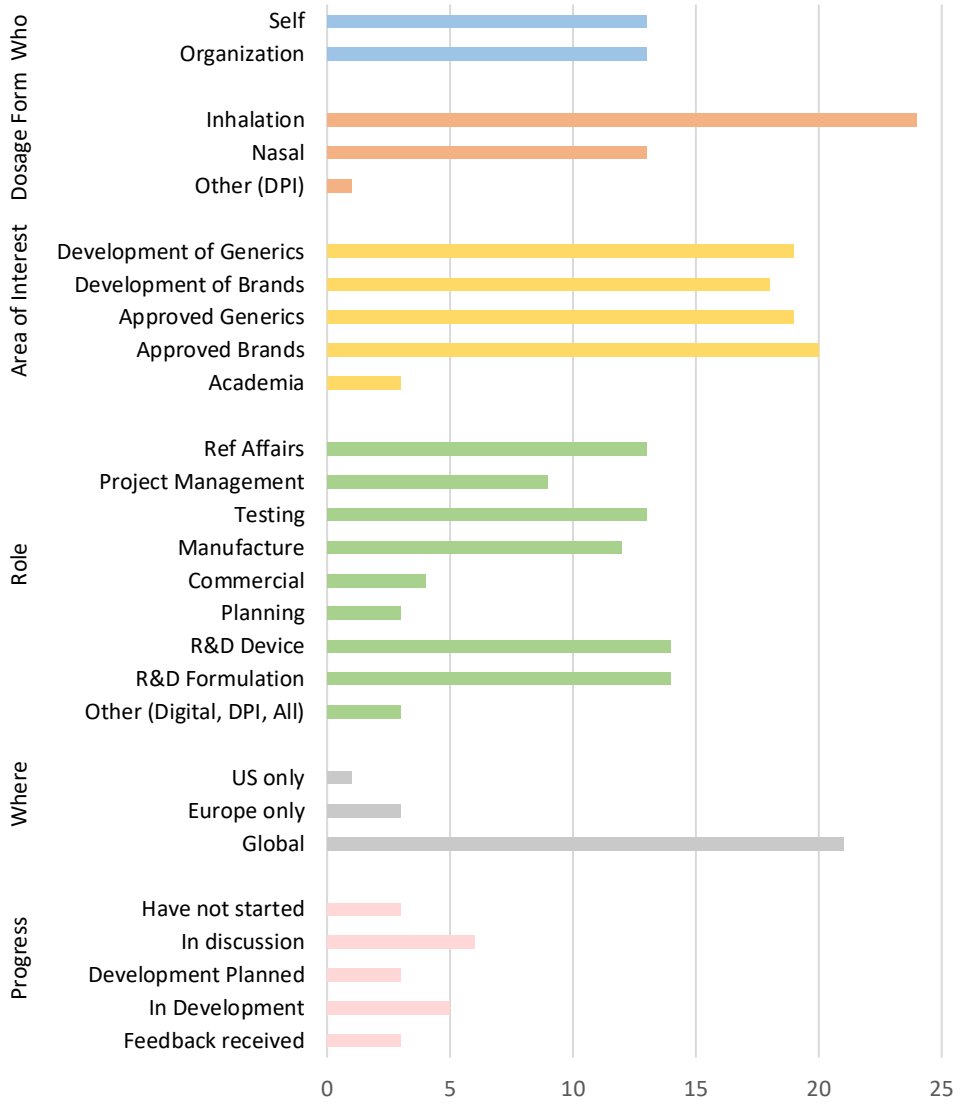
# Alternate Propellant Survey

**Benchmarking Survey**

- Survey was conducted from April 18 to June 13, 2023
- Goals were to understand general industry/regulators concerns and challenges of the forthcoming switch to new propellants
- All interested stakeholders were invited to participate
- There were no responses from Reg Agencies (although there were specific agency questions)

**Demographics**

- 26 participants
- 50% representing their organization
- majority orally inhaled interest
- branded and generic
- spectrum of industry (formulation to regulatory)
- majority have global interest
- companies are at different stages in the process

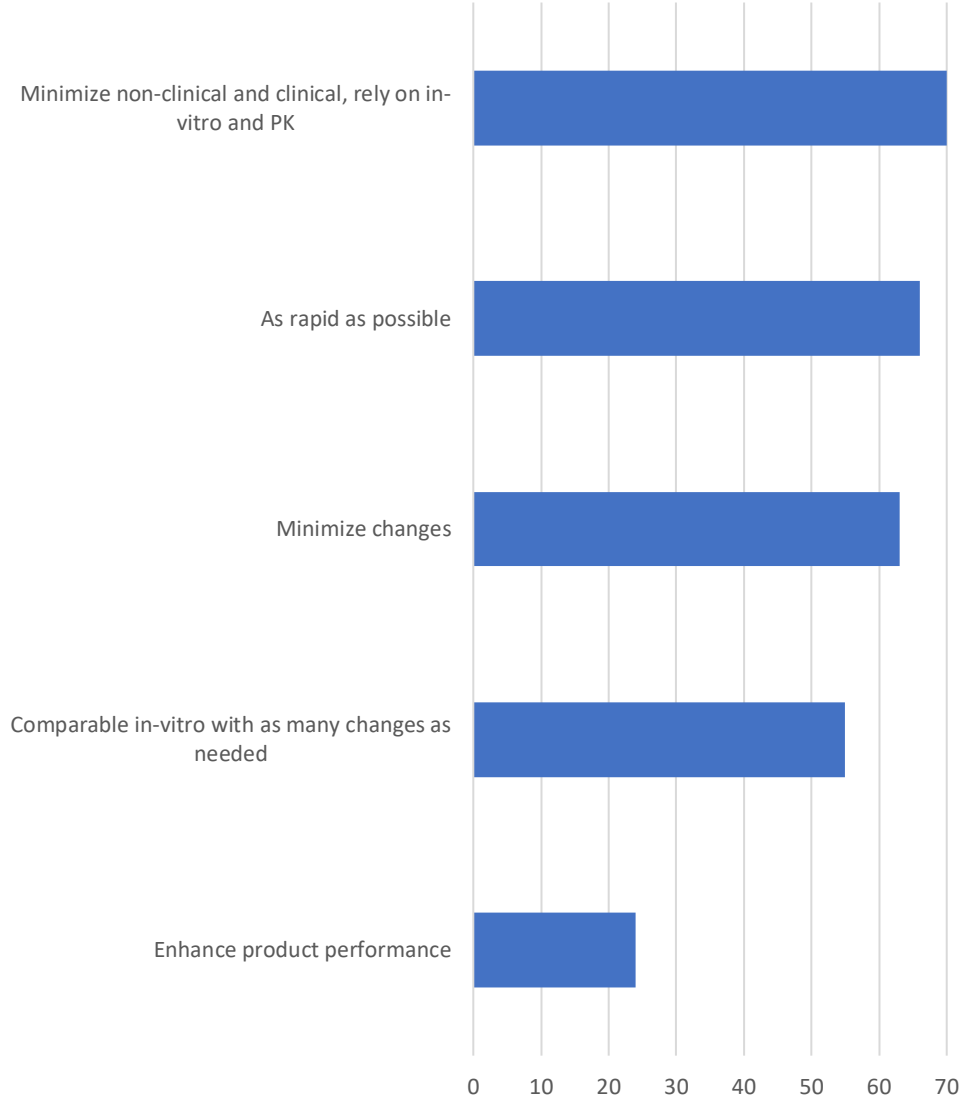


# Priorities

**#1 Priority**: Minimize the requirement for non-clinical and clinical studies

Priorities 2/3: A more rapid switch may only be possible is changes are minimized

It was noted that enhanced product performance will require additional clinical work



# Challenges/Concerns

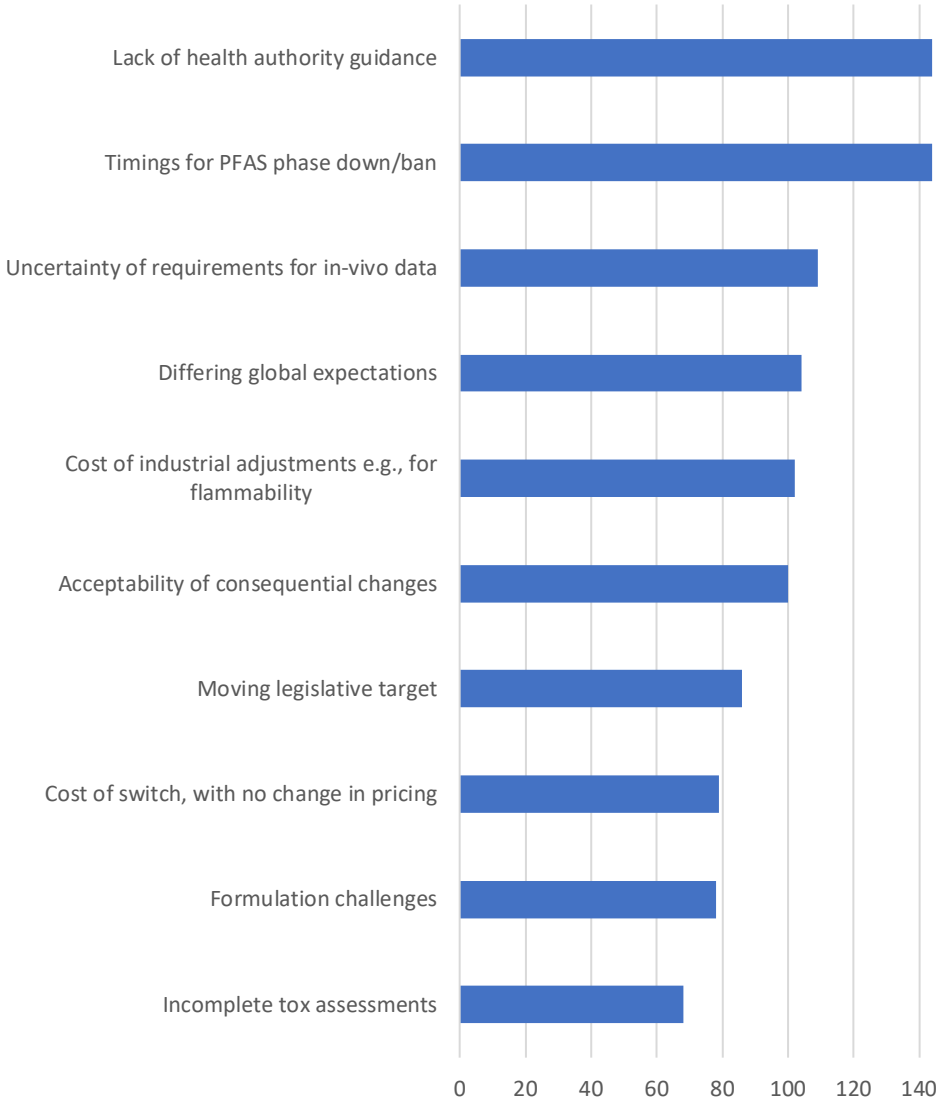
**#1 Challenge/Concern**: Timings for phase down/ban of PFAS **and** Lack of health authority guidance

Uncertainty of requirements is of high concern (for in-vivo data, global expectations & consequential Changes) along with industrialization costs

Moving legislation encompasses looming changes such as EU Can coating ban

Formulation challenges were lower than expected, but may reflect the current early stages of development

Propellant suppliers have clearly provided reassurance on the ongoing tox assessments



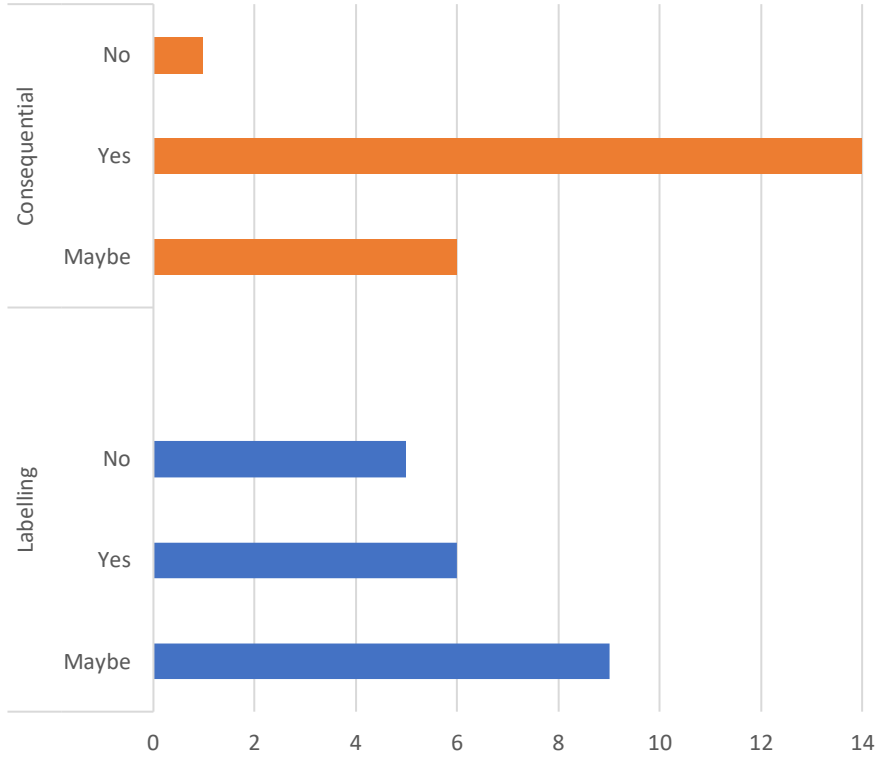
# Changes

**Consequential Changes**

- The majority agreed that changes to components such as valve seal materials to ensure chemical compatibility will be required
- Uncertainty exists in what changes are acceptable to allow the product to be considered “the same/similar enough”

**Labelling Changes**

- Labelling changes beyond the basic changes (eg propellant name) are less clear, and rely on the outcome of the development/clinical studies



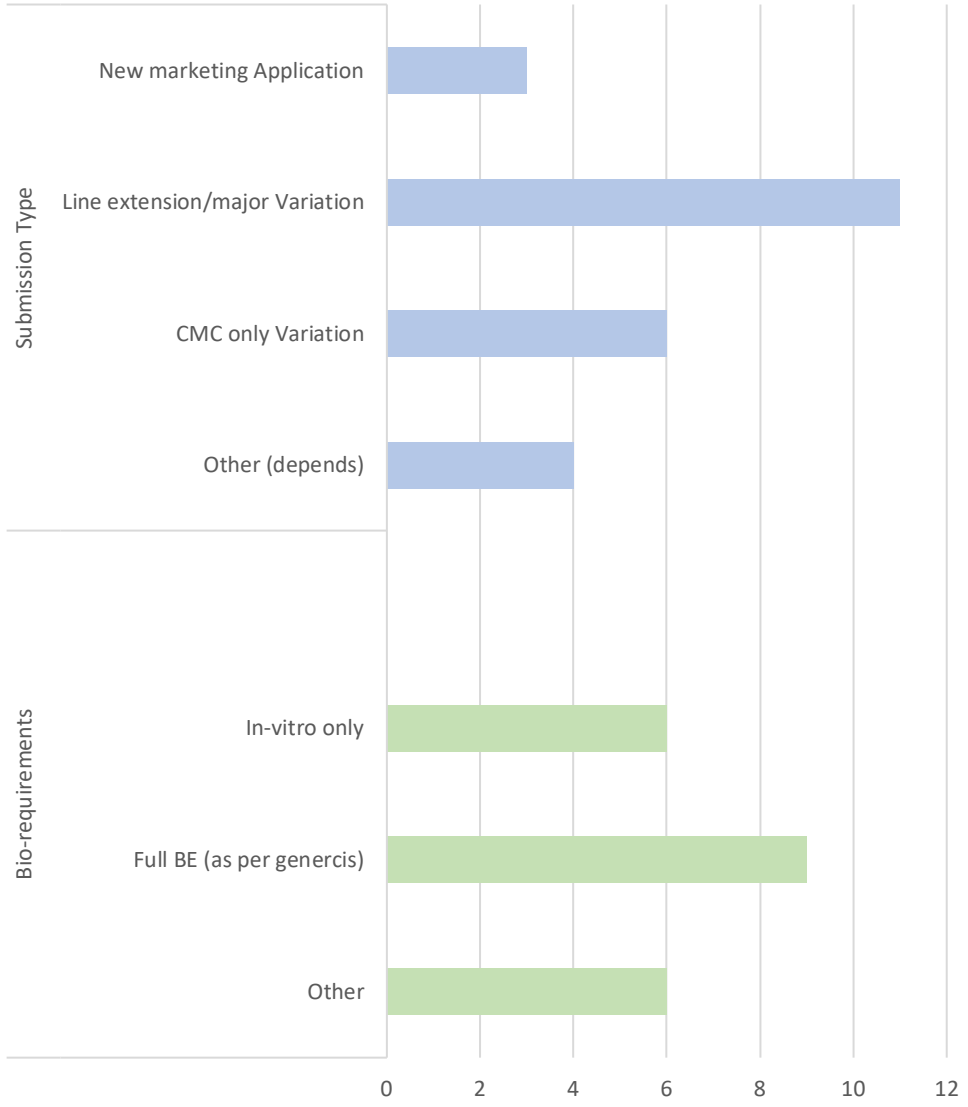
# Expected General Requirements

**Submission Type**

- Over 70% expected this to be considered a “variation” - maybe influenced by the recently issued EMA Q&A

**Bio-Requirements**

- Split of responses reflecting uncertainty and possible influence of EMA Q&A with 26% proposing something like the EU step-wise approach



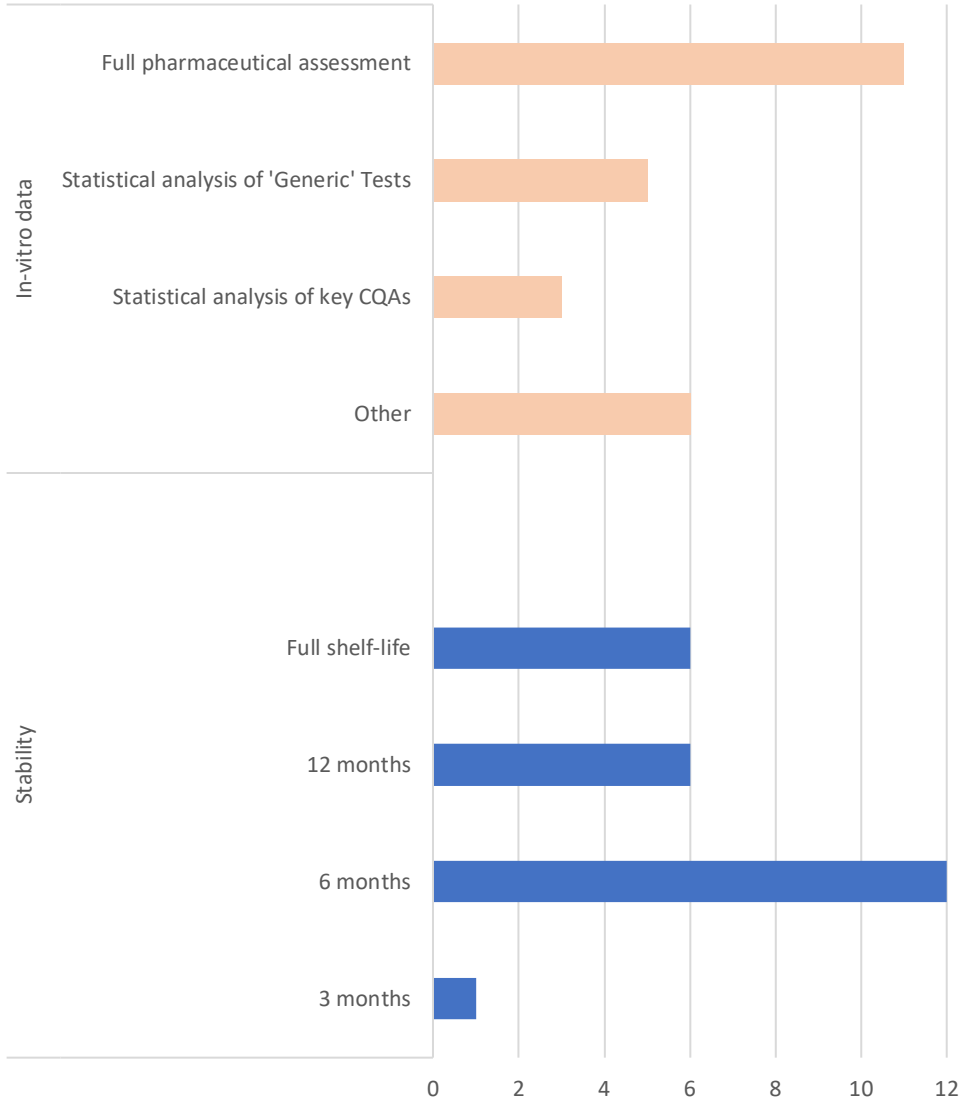
# Expected CMC Requirements

**In-Vitro Data**

- 44% expected a full in-vitro pharmaceutical assessment to be required
- If statistical analysis is used and shows equivalence; is there any flexibility to reduce in-vivo work?

**Stability**

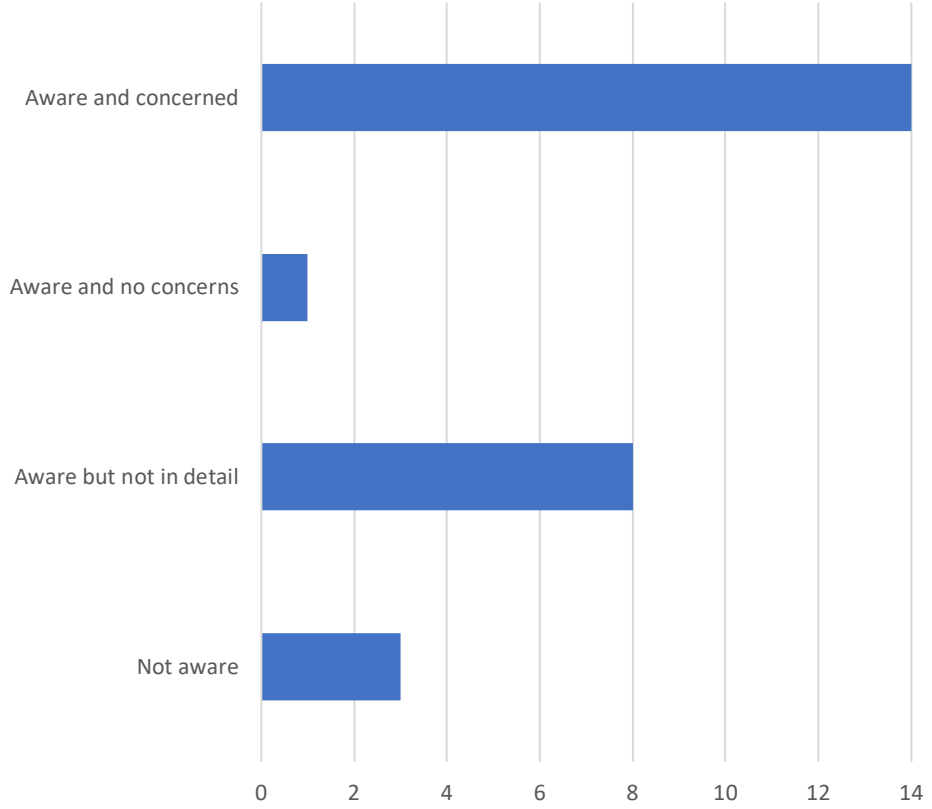
- 48% expected 6 months of data to be adequate (although region specific) reflecting a variation vs a new submission



# Knowledge of ECHA PFAS Proposal

**Primary Concerns with Proposal**

- Timings are too aggressive
- May lead to lack of choice of propellants
- Lack of alternatives for patients



# Industry Challenges and Concerns

# Metered Dose Inhalers (MDIs)/Inhalation Aerosols with Lower Global Warming Potential (LGWP) Propellants – New Drug Quality Perspective

Craig M. Bertha, Chemist, CMC Reviewer

Office of Pharmaceutical Quality

Office of New Drug Products


**FDA Disclaimer:** The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

# Propellants for MDIs

Provide the bulk of an MDI's formulation

Dissolve or disperse the drug in the formulation

Physicochemical properties (e.g., vapor pressure, viscosity) are a major determinant of the properties of the delivered aerosol

Rapid expansion/evaporation of the liquified propellant upon release from the valve:

- Propels the metered drug formulation through the valve stem and actuator to the patient
- Ideally produces an aerosol of drug particles/droplets in a size range suitable for inhalation into the lungs

# Propellant History for MDIs

**1st Generation**

- Chlorofluorocarbons (CFCs):
- Deplete Ozone layer
- 1987 Montreal Protocol to phase out CFCs

**2nd Generation**

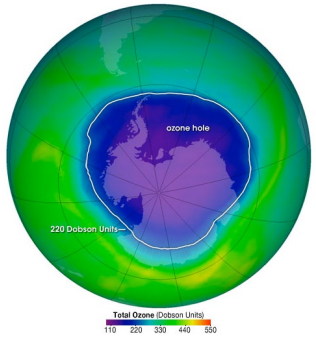
- Hydrofluoroalkanes (HFAs), e.g., HFA 134a and HFC-227ea
- High Global Warming Potential (GWP)
- Used in all current approved MDIs

**3rd Generation**

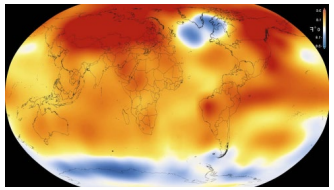
Phase out 2nd Gen HFAs by 80-85% by 2047 (the Kigali Amendment by UN in 2016 to the Montreal Protocol)

- Potential supply shortages of HFAs and cost increases
- Requires manufacturers to seek alternative propellants for MDIs

*




**



***


CFC-11 CFC-12 CFC-114 HFC-227ea HFA-134a HFA-152a HFO-1234ze

Current lower global warming potential (LGWP) candidate propellants:

- 1,1-Difluoroethane (HFA-152a)
- 1,3,3,3-Tetrafluoropropene (HFO-1234ze(E))

*Nasa Ozone Watch
**Scientific Visualization Studio/ Goddard Space Flight Center
***Nasa's Earth Observatory

# Propellant Properties[1]

## Global Warming Potential (GWP)

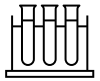
- Second generation MDI propellants:
  - HFA-134a (1,1,1,2-tetrafluoroethane) GWP 1300-fold $CO_2$
  - HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane) GWP 3350-fold $CO_2$
- Third generation MDI propellants:
  - HFC-152a GWP 138-fold $CO_2$
  - HFO-1234ze GWP < 1-fold $CO_2$

## Physicochemical properties

- HFA-152a similar to HFA-134a in terms of BP, viscosity, dipole moment (polarity), and solubility of water, but has lower density
- HFA-152a propellant is flammable
- HFO-1234ze similar to HFC-227ea in terms of BP, density, dipole moment and solubility of water, but has lower viscosity and is more similar to HFA-134a for that parameter
- All four propellants are miscible with common co-solvent, ethanol
- Vapor pressures of LGWP propellants at 20°C (bar)[2] fall between that of the previous propellants:
  - HFA-134a 4.72
  - HFO-1234ze 4.27
  - HFA-152a 4.16
  - HFC-227ea 3.89

[1]J.N. Pritchard *Drug Design, Development and Therapy* (**2020**), vol. 14, pp. 3043-3055; [2]HFA-134a and HFA-152a (Chemours); HFC-227ea (DuPont); HFO-1234ze (Honeywell)

# Formulation/Device Considerations



## Drug solubility in propellant

- Suspension or solution formulations
- Co-solvent (solutions)
- Use of surfactants (suspensions)
- Coated canisters (suspensions)

## Propellant/drug densities (suspensions)

- Density differences between propellants and suspended APIs may impact suspension stability

## Propellant compatibility with valve components (e.g., elastomers, plastic)

- Leak rate
- Moisture ingress
- Leachables

## Propellant physicochemical properties, final formulation, and device configuration dictates aerosol performance and usability

- **Delivered Dose Uniformity (DDU)**
- **Aerodynamic particle size distribution (APSD)**
- Aerosol velocity
- Evaporation rate
- Taste, speed of aerosol plume

## Aerosol performance and product/patient interface will determine the characteristics of the drug deposition in patient airways

- Patient coordination of actuation and inhalation (non-breath-actuated)
- Adherence to cleaning instructions
- Adherence to storage instructions

# Quality Tests for MDI Aerosol Performance

Delivered Dose Uniformity (DDU) & Aerodynamic Particle Size Distribution (APSD) - Key *in vitro* measures used to assess quality of the dose delivery performance of MDI products

- **DDU**
  - Doses are collected from multiple units
  - Assessment
    - intra-unit (B to E)
    - inter-unit for a batch
    - inter-batch
    - over time (stability studies)
    - product characterization studies
  - For quality assessment, results are compared to LC and standard acceptance criteria can be applied (counting test, PTIT)
- **APSD**
  - Typically, multiple actuations collected from multiple units (method sensitivity)
  - Common cascade impactors are the ACI and NGI (see USP <601>)
  - As for DDU, APSD results can be a tool to assess the quality
    - intra-unit (B to E)
    - inter-unit for a batch
    - inter-batch;
    - over time (stability studies)
    - product characterization studies
  - Data are initially presented on a stage-by-stage basis and acceptance criteria can be set based on data for groupings of stages representing coarse, fine, and extra fine drug particles

# DDU/APSD & Quality Assessment

DDU/APSD - Key stability indicating parameters used to assess the products ability to provide consistent *in vitro* dose delivery performance over its shelf life

DDU/APSD – Parameters used to assess product characteristics to inform patient labeling and establish device robustness, e.g.,

- Priming/repriming
- In-use period (w/protective packaging)
- Cleaning requirements
- Tail-off profiling supporting overfill

Agency draft Quality guidance (2018) for MDIs defines "significant change" (similar to Q1A definition) when examining DDU/APSD stability data for these products as:

- For DDU, a change in the mass of the mean dose of 10 percent or more (determined separately on samples taken from the beginning and end of product life
- For APSD, a change in the total mass of fine particles (e.g., particles less than five micrometers) more than 10 percent

These draft criteria were based on the magnitude of changes typically observed on stability for MDI products developed at the time of the drafting of the preceding and withdrawn 1998 guidance

The draft criteria were later used in other situations:

- To gauge the impact of product changes during development or post-approval (e.g., formulation and device component changes), on *in vitro* delivery performance
- To gauge the similarity of *in vitro* delivery performance of monotherapy versus fixed dose combination (FDC) products (21 CFR 300.50(a)

Underlying assumption - the more comparable the *in vitro* DDU/APSD data, the more likely it would be that the *in vivo* lung deposition would be similar

# Quality Data to support new LGWP MDI Products – Drug Substance

## Drug Substance (section S of module 3):

- Applicants may rely on previously submitted drug substance information if used for similar approved products
- If the new product is suspension-based and approved products had solution formulations, additional quality information may be needed:
  - Crystalline form characterization and control
  - Information supporting the micronization process/parameters
  - Amorphous drug characterization and control (from micronization)
  - Application of conditioning and/or waiting period after micronization
  - Characterization and control of particle size distribution
  - Assessment of micronized drug substance stability
  - Updating risk assessments due to application of micronization
    - elemental impurities
    - nitrosamines content

# Quality Data to support new LGWP MDI Products

## Product (section P of module 3):

- P.1: Description of the components and composition of the product formulation
- P.2: Pharmaceutical Development
  - Description all pertinent development aspects leading to the final chosen product configuration
  - Characterization studies for the product with the new propellant to support its robustness and to inform labeling (see IV.C of the 2018 draft MDI/DPI draft guidance, e.g., establishing in-use period, cleaning instructions, priming/repriming).
- P.3: Manufacture
  - Manufactures
  - Batch formula
  - Description of the manufacturing process and associated controls

# Quality Data to support new LGWP MDI Products

## Product (section P of module 3 - continued):

- P.4: Excipients (may reference type IV DMFs)
  - Propellant manufacturer/supplier
  - Characterization studies
  - Specification/certificates of analysis, e.g.:
    - Identity
    - appearance
    - assay
    - moisture content
    - related and unrelated impurities with consideration of:
      - Route of administration
      - Disease/patient population
      - Toxicology (consultation)
  - Analytical test procedures and associated validation information
  - Justification of specification
  - Stability data for the LGWP propellant

# Quality Data to support new LGWP MDI Products

## Product (section P of module 3 - continued):

- P.5: Control of Product
  - Specification
  - Analytical procedures
  - Validation data for the analytical procedures, impurity characterization
  - Batch analysis
  - Justification of the specification
- P.6: Provide information supporting the reference standards used for the analytical procedures for testing the product

# Quality Data to support new LGWP MDI Products – Drug Product

## Product (section P of module 3 - continued):

- P.7: Container Closure System
  - Data supporting the container closure components of the product
    - Canister
    - Valve
    - Actuator
    - Protective packaging
    - Dose counter/indicator)
  - Reference may be made to type III DMFs
- P.8: Stability
- Registration batches
- Supportive batches
- Refer to the 2018 draft guidance for MDIs/DPIs and ICH Q1 guidances.
- P.2 and/or P.8: Include a comprehensive assessment of leachables; refer to USP Chapters <1663>, <1664>, and <1664.1>, and "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products" (PQRI, September 8, 2006) See http://pqri.org/wp-content/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf.

# Final Thoughts – LGWP MDI Products

New LGWPs have differences and similarities in terms of physicochemical properties when compared to second generation propellants

Drugs will likely have different solubility characteristics in the new LGWP propellants, which may require formulation changes

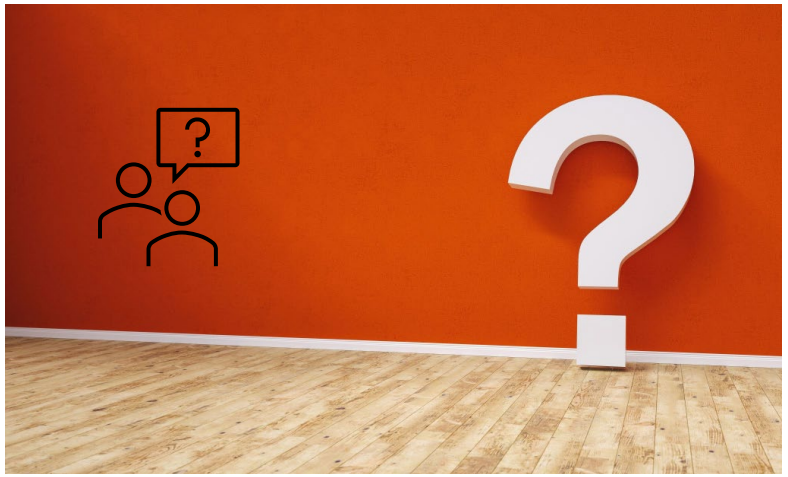
Differences in densities of new propellants and drugs may impact physical stability of suspension formulations

As compared to device components used with second generation propellants, LGWPs may require changes

CONCLUSION - From the quality perspective, submissions for products formulated with LGWP propellants should include all data and information that would be applicable for a new product (ICH M4Q - CTD modules 2 and 3); reference can also be made to pertinent previously submitted information

# Thank you!

Questions?



FDA U.S. FOOD & DRUG ADMINISTRATION

11 November 2023

# Data requirements when switching to LGWP propellants – the EU perspective

**Karolina Törneke**

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Established in 1995
- Responsible for the centralised procedure
- Secretariat coordinating the scientific resources available at the national competent authorities

# Swedish MPA

# Disclaimer

I attend this meeting as an individual expert, and do not formally represent the RIWP. The views expressed here may not be understood or quoted as being made on behalf of the EMA or any of its committees/working groups.

# Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers

- Published for consultation in April 2023
- Revised following comments
- To be finally adopted in October 2023
- Minor revision
- Responses to comments with clarifications will be published

# Follows the same principles as major quality variations

- Could be a type II variation procedure
- The Q&A would apply also to the situation when a company presents a new formulation as an extension to the MMA
- Applies to both originators and ”generics”

- Change of excipient
- Key question: Is it novel or established?
- What can be documented for the propellant as such and what needs to be documented for the product?

# What is being ”novel”?

According to Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006):

**DEFINITIONS**

Novel excipient: A novel excipient is an excipient which is being used for the first time in a drug product, or by a new route of administration (ICH). It may be a new chemical entity or a well established one which has not yet been used for human administration and /or for a particular human administration pathway in the EU and/or outside the EU.

# Data on the propellants as such when classified as novel excipients

- One data set for each propellant
- Quality: Standard data package for excipients
- Non-clinical: Compliance with the ICH M3 (R2)
- Three *in vivo* studies in humans:
  - Ciliary function in healthy volunteers
  - Airway hyperreactivity in asthmatics
  - A 3-month chronic safety study (which may include actives)

# Ciliary function

- Non-smoking healthy volunteers is deemed the most sensitive population
- Thorough justification for the choice of the design needed
- A scintigraphy evaluation would be an acceptable option

# Airway hyperreactivity

- Data on possible airway sensitivity reactions
- Lung function (FEV1 (AUC0-15min) in asthmatic patients
- Cross-over design using a supratherapeutic propellant dose
- Recommended to conduct a pilot study

# A 3-month chronic safety study

- At least one safety study
- Collect adverse events such as bronchoconstriction, hoarseness, and cough
- Ideally a vehicle only version of the final formulation
- The comparator product should be an approved pMDI product supported by a full dossier

# Interlude

- So far requirements for **the propellant as such**
- Guidelines for novel excipients apply
- Any applicable legal base for the variation may be used.
- Same thinking as for any other change of formulation

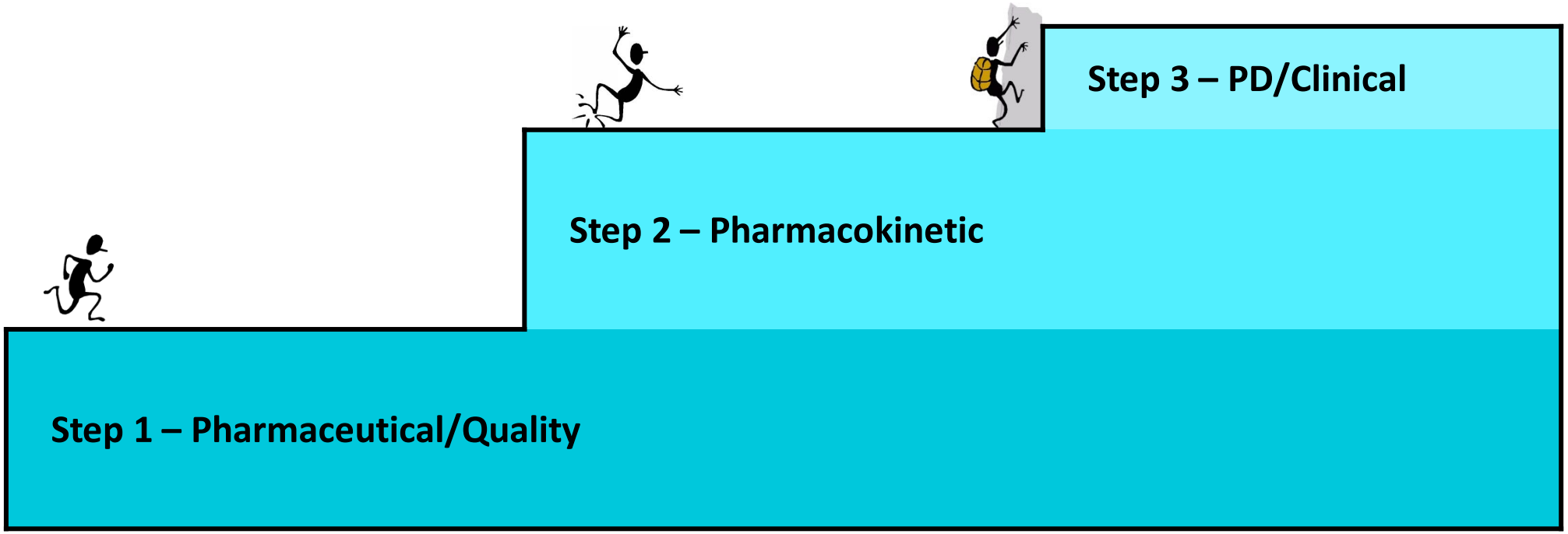
# Data on therapeutic equivalence

What are the data requirements to address possible changes to the exposure to the active substance(s)?

Answer: Same as for (hybrid) generics!

Must be confirmed for each product (strength)

# The step-wise approach



# First step – *in vitro*

- The list of criteria for therapeutic equivalence by means of *in vitro* data principally applies.
- Comparison of the aerodynamic particle size distributions is an important part, acceptance critera clarified.
- Strategy for impactor stage grouping

# Second step – pharmacokinetics

- Kinetic endpoints are pivotal
- Safety – total systemic exposure
- Efficacy – systemic exposure following absorption in the lung

- Currently certain details are missing in the guideline but there are Q&As and a well established practice

# Third step – to be avoided

- According to current practice PD/clinical studies are only used in case there are differences recorded in pivotal PK-studies.
- It is nevertheless difficult to show assay sensitivity/relative potency.
- To be meaningful the study should be able to distinguish the different effect levels when comparing a certain dose level and 1.5 x that dose.

# Children

- Different breathing pattern and size of airways – different exposure at active site?
- Kinetic/clinical studies can’t answer the question due to either ethical restrains or poor assay sensitivity
- Data in children may be waived if adequately justified
- Approved age limits may (likely) be kept

# Handling and experience

- Differences must be documented and presented including aspects such a flammability
- Possibly need for *in vivo* data
- Likely possible to be covered in the PK study

# In the end…

- Don’t reinvent the wheel
- Don’t repeat studies
- Consult guidelines
- Follow practice
- Ask for Sci Adv when in doubt


THANK
YOU!


90

IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

# Materials Aspects of the Transition to Alternative Propellants – an IPAC-RS Working Group Perspective

Presented by: Dan Dohmeier, Kindeva Drug Delivery on behalf of IPAC-RS Materials & Propellants Working Group

# Outline

- Introduction to Materials & Propellants Working Group
- Suitability of HFA 152a and HFO 1234ze(E) as alternative propellants for pMDI
- Importance of materials compatibility for safety & efficacy of pMDI
- Materials considerations & learnings from the CFC → HFC Transition
- Existing data on materials compatibility with alternative propellants
- Summary

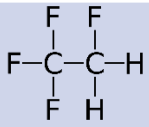
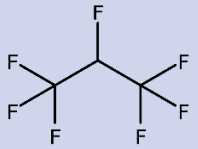
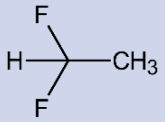
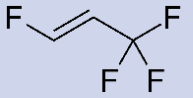
# Introduction to Materials & Propellants Working Group

- pMDI drug product transition to LGWP propellants will require risk review and CMC testing (safety and performance) to manage the change internally and with regulatory bodies.
  - One risk area is the impact of new propellants on leachables profiles and quality of device, packaging, and manufacturing systems in contact with propellant
- WG was formed to create a framework to guide industry and inform both industry and regulatory agencies in navigating this propellant change, focusing on drug product and manufacturing process materials selection and evaluation.  Benefits include:
  - Provide guidance to industry on ways to ensure quality and demonstrate a risk-based approach to propellant change
  - Proactively raise awareness of the transition
- Includes members from pharma companies, CDMOs, CMC component suppliers

# Suitability of HFA 152a and HFO 1234ze for pMDI

- The properties of the propellant play a critical role for performance of pMDIs and delivery to lungs of patients
- Suitable boiling point/vapor pressure results in a balance of liquid / gas phase in the pMDI at ambient temperatures to provide internal working pressures that are:
  - Low enough to be safely delivered to the patient
  - High enough to enable generation of the fine aerosol droplets necessary to deliver medication to the deep lung
  - Maintained at a suitable working pressure during drug product use, ensuring accurate dosing through the life of the pMDI
- Low chemical reactivity with APIs and with pMDI materials of construction (valve, canister) ensures product stability and uniform dosing throughout the life of the pMDI
- Solvating power of the propellant guides formulation design, use of excipients, and solution vs suspension pMDI drug product
- Density of propellant affects settling / creaming rate of suspension formulation

# Key Physicochemical Properties of HFA 152a and HFO 1234ze

| | Current Propellants | | Lower GWP Propellants | |
|---|---|---|---|---|
| **Propellant** | HFA 134a | HFA 227ea | HFA 152a | HFO 1234ze(E) |
| **Formula** | $C_2F_4H_2$ | $C_3F_7H$ | $C_2H_4F_2$ | $C_3H_2F_4$ |
| **Chemical Structure** |  |  |  |  |
| **GWP** | 1430[a] | 3220[a] | 124[b] | <1[c] |
| **Molecular Weight (g/mol)** | 102.0[a] | 170.0[a] | 66.1[b] | 114.0[c] |
| **Density (liquid) at 20°C (g/mL)** | 1.23[a] | 1.41[a] | 0.91[b] | 1.17[c] |
| **Boiling Point (°C)** | -26.3[a] | -16.5[a] | -24.0[b] | -19.0[c] |
| **Vapor Pressure at 20°C (bar)** | 5.72[a] | 3.90[a] | 4.12[b] | 4.28[c] |
| **Water Solubility (ppm)** | 2200[a] | 610[a] | 2200[b] | 225[c] |
| **Dipole Moment (debye)** | 2.06[a] | 0.93[a] | 3.69[b] | 1.44[c] |
| **Log P (octanol/water)** | 1.1[a] | 2.1[a] | 0.75[d] | 1.6[d] |

[a] Daikin, "SOLKANE™ 227 pharma and 134a pharma", Pharma Brochure, 2017. https://www.daikinchem.de/products-and-performance/pharma-propellants
[b] Koura "152a Physical Properties" datasheet, 2020. https://www.zephex.com/zephex-152a/
[c] Honeywell "Solstice® Propellant" Technical Bulletin, 2041 FP SOLA4 | December 2017
[d] Rusch, G.M., "The development of environmentally acceptable fluorocarbons", *Critical Reviews in Toxicology*, Vol. 48(8), pp. 615-665 (2018)

# Safety Information for HFA 152a and HFO 1234ze for pMDI

| Propellant» | Studies | Outcome / Conclusion | Refs |
|---|---|---|---|
| HFA 152a | *In vivo* animal studies:<br>• respiratory sensitization<br>• acute toxicology<br>• sub chronic and chronic toxicology<br>• preliminary rat/rabbit reproductive toxicology studies | "HFA-152a was well tolerated in all conditions evaluated, did not induce respiratory sensitivity under any condition evaluated and, in all species, HFA-152a was rapidly cleared from the blood." | 1 |
| | Phase I clinical trial (n = 8 healthy volunteers) | "… the data showed that following oral inhalation from a pMDI, HFA-152a was well tolerated … and was rapidly cleared from the blood." | |
| HFO 1234ze(E) | *In vivo* testing in mammalian animal species:<br>• genotoxicity<br>• reproductive toxicology<br>• acute and chronic exposure | • genotoxicity findings in the mouse micronucleus test were negative<br>• No signs of maternal or developmental toxicity observed<br>• Considered "practically nontoxic" by the inhalation route of exposure (4-hour inhalation tox)<br>• Overall "favorable" toxicological properties[3] | 2 |
| | Two-year carcinogenicity studies currently underway | Results to be reported in early 2024 | 3 |
| | Phase I clinical trial of HFO-1234ze(E) in a pMDI containing budesonide, glycopyrronium, formoterol fumarate | "… results ... in healthy adults were positive, demonstrating similar safety, tolerability and systemic exposure of the active ingredients when compared to Breztri Aerosphere" | 4 |


1) "Safety, Tolerance and Pharmacokinetics of HFA-152a in Healthy Volunteers", Kuehl et al., RDD 2022
2) Workplace Environmental Exposure Level for 1,3,3,3-Tetrafluoropropylene, AIHA Guideline Foundation , 2011
3) "A Journey to Net Zero Using Solstice Air", Hulse et al., RDD 2022
4) AstraZeneca website: AstraZeneca progresses Ambition Zero Carbon programme with Honeywell partnership to develop next-generation respiratory inhalers

# Importance of Materials Compatibility with Propellant for pMDI

- OINDP critical quality attributes include:
  - Delivered dose
  - Spray pattern
  - Leak rate
  - Moisture content
  - APSD
  - Shot weight
  - Stability (impurities and degradants)
  - Safety (leachables)
- Interaction of the CCS with formulation, including propellant, can significantly impact pMDI CQA
  - Valve can impact – leak rate, shot weight, delivered dose, stability, moisture, safety
  - Canister can impact – delivered dose, stability, safety

# Role of the CCS in pMDI CQA

- pMDI valve components impact leak rate (content over time), moisture ingress (stability, APSD)
  - Elastomer and stem dimensions and swelling in propellant and propellant / co-solvent mixtures are critical physical properties / aspects to evaluate and control
- Materials of construction for valve and canister impact stability, safety
  - Interaction of valve materials and canister with API and formulation can impact stability
  - Leachable compounds from valve materials, canister coating can impact safety
  - Thus valve & canister interactions with formulation (propellant) impact CQA, and materials require characterization and control
- Stability of materials over time is critical, and may be impacted by propellant

# Characterization of CCS Materials Interaction with Formulation (including propellant)

- Screening of valve and canister is a key step in early pMDI development process
- Valve material swelling / shrinkage
  - Target dose is delivered reproducibly through the pMDI lifetime
  - Leak rate is minimized / acceptable
  - Moisture ingress is minimized / acceptable
- Valve & canister materials composition
  - Stability of API (impurities)
  - Stability of formulation (particle growth for suspensions)
  - API deposition on CCS components is minimized
- Changes in material properties over time
  - Leak rate, moisture ingress, API & formulation stability – demonstrate all are acceptable throughout product shelf life
  - Valve and canister leachables are characterized throughout product shelf life
- Choice of valve and canister is data-driven & provides justification for selection of container closure system

# Materials Considerations & Learnings from the CFC → HFC Transition

- Improvements in materials to be compatible with HFCs was a major aspect of previous transition
- Quality and control of materials has been significantly improved in intervening 20+ years
  - Availability of pharma grade elastomers and plastics
  - Include solvent extraction of materials to reduce leachable materials
  - Agreements with materials suppliers and CCS suppliers to control quality upstream, receive notifications of materials changes
  - Use of risk-based approach to qualify materials changes
  - PQRI is industry standard approach for characterization of leachables in pMDI
- Development of pMDI drug products with LGWP propellants will be data-driven, use risk-based approach

# Materials Compatibility with HFA 152a – Overview of (Selected) Available Data

| Material tested | Quality attributes investigated | Refs |
|---|---|---|
| <u>Plastics:</u><br>Polyacetal Polyamide<br>Polyester (two grades) | Change in volume & weight (swelling) | 1, 2 |
| <u>Elastomers:</u><br>EPDM Bromobutyl<br>Nitrile Chlorobutyl | Change in volume & weight (swelling), hardness | |
| Valve with EPDM main seal<br>Valve with Nitrile main seal | Propellant loss / gasket permeability (Ambient and 40°C up to 28 days) | 1, 2 |
| Valve with PBT, polyamide, EPDM, and cyclic olefin copolymer (COC) components | Leak rate, shot weight variability (40°C/75% RH storage up to 6 months) | 3 |


1) Koura website: https://www.zephex.com/wp-content/uploads/2021/04/152a-Material-Compatibility-Sheet.pdf
2) "Compatibility of P152a with Pressurized Metered Dose Inhaler Device Materials", S. Corr and Tim Noakes, RDD 2018
3) "Filling and Dose Performance of pMDIs with New Low Global Warming Potential Propellants", Deraime et al., RDD 2023

# Materials Compatibility with HFO 1234ze – Overview of (Selected) Available Data

| Material tested | Quality attributes investigated | Refs |
|---|---|---|
| <u>Plastics:</u><br>Polyacetal Polyamide<br>Polyester Polyethylene | Change in dimensions & mechanical properties | 1 |
| <u>Elastomers:</u><br>EPDM Butyl<br>Nitrile Chloroprene<br>Thermoplastic polyethylene | Change in dimensions (swelling), hardness, elongation | |
| Aluminum valve components, Stainless steel springs | Corrosion, spring compression | |
| Various plastic and elastomeric materials for industrial application | Change in volume & weight (swelling), hardness | 2 |
| Valve with PBT, polyamide, EPDM, and COC components | Leak rate, shot rate variability (40°C/75% RH storage up to 6 months) | 3 |


1) Honeywell website: https://sustainability.honeywell.com/content/dam/sustainability/en/documents/document-lists/technical/poster-honeywell-propellants.pdf
2) Solstice®ze Refrigerant (HFO-1234ze(E)). The Environmental Alternative to Traditional Refrigerants" 3274 REF A4 EU v7 | October 2018 Technical Bulletin
3) "Filling and Dose Performance of pMDIs with New Low Global Warming Potential Propellants", Deraime et al., RDD 2023

# Materials Compatibility – Overview of (Selected) Available Leachables Data

| Material tested | Propellants Tested | Leachables Testing Details | Refs |
|---|---|---|---|
| Valve with PBT, Polyoxymethylene, EPDM, and cyclic olefin copolymer (COC) components | HFA 134a, HFA 152a | pMDI filled with 100% propellant, or propellant + 15% ethanol, ambient storage for up to 24 months | 1 |
| Valve with PBT, Polyoxymethylene, EPDM, and COC components | HFA 152a, HFO 1234ze | pMDI filled with 100% propellant, ambient storage | |
| Valve with PBT, EPDM, and COC components | HFA 134a, HFA 152a, HFO 1234ze | pMDI filled with 100% propellant, stored at 40°C/75% RH for up to six months (valve down) | 2 |


1) "Investigation of Leachables from pMDIs Containing Propellants HFA 134a, HFA 152a and HFO 1234ze", Le Corre et al., RDD 2022
2) "Leachables Assessment from a New Generation of pMDI Using Low Global Warming Potential Propellants", Faucard et al., RDD 2023

# Materials Compatibility – Overview of (Selected) Available Formulation Compatibility Data

| API(s) | Propellants Tested | Testing Details | Refs |
|---|---|---|---|
| Glycopyrronium / Formoterol / Budesonide | HFA 134a, HFO 1234ze | Comparison of dose delivery, fine particle mass, spray pattern, and plume geometry | 1 |
| Roflumilast / Glycopyrronium / Formoterol / Budesonide | HFA 134a, HFO 1234ze | Aerodynamic particle size distribution assessment | 2 |
| Beclometasone dipropionate | HFA 134a, HFA 227ea, HFA 152a | Dose delivery, APSD comparison | 3 |
| Beclometasone dipropionate | HFA 152a | APSD, dose delivery, and priming/repriming performance | 4 |
| Beclometasone dipropionate, Albuterol sulfate | HFA 152a, HFO 1234ze | Fine particle mass with different anatomical throat sizes | 5 |
| Albuterol sulfate | HFA 152a | APSD, dose delivery, spray pattern, plume geometry, weight loss, and moisture content | 6 |


1) "Comparative Aerosol Performance of an HFA-134a Based Fixed-Dose Triple Combination pMDI to One Made with a Near-Zero Carbon Footprint Propellant", Lachacz et al., RDD 2023
2) "Quadruple Combination in a Pressurized Metered Dose Inhaler with Reduced Environmental Impact for the Treatment of COPD", Lechuga-Ballesteros et al., RDD 2023
3) "HFA152a MDIs: Matching the In-vitro Performance of HFA227ea and HFA134a MDIs", Lewis et al., RDD 2023
4) "A Roadmap for Constructing a Beclomethasone pMDI Solution Using HFA152a", Buttini et al., RDD 2023
5) "An Evaluation of Solution and Suspension pMDIs Containing HFA152a and HFO1234ze Using Clinically Relevant Test Methods", Brittain et al., RDD 2023
6) "Albuterol Sulfate Metered Dose Inhaler Feasibility Using an Environment Friendly Propellant HFA152a and Novel Valves", Mao et al., RDD 2023

# Materials Compatibility – Overview of (Selected) Available Formulation Compatibility Data

| API(s) | Propellants Tested | Testing Details | Refs |
|---|---|---|---|
| Placebo | HFA 134a, HFA 152a | Shot weight, spray pattern and plume geometry | 1 |
| Placebo | HFA 152a | Anti-microbial effects | 2 |
| Placebo | HFA 134a, HFA 227ea, HFA 152a, HFO 1234ze | Content-equivalent droplet diameter as a function of ethanol content and relative humidity | 3 |
| Placebo | HFO 1234ze | Chemical stability of propellant at 200°C in the presence of moisture and metals | 4 |


1) "Comparison of Spray Characteristics of P-134a and Low GWP P-152a pMDIs With and Without Ethanol", Jordan et al., RDD 2023
2) “Anti-Microbial Properties of Low-GWP pMDI Propellant P-152a", Murray at al., RDD 2023
3) "Droplet Characteristics of Low GWP Propellants at Different Ambient Humidities", Wang et al., RDD 2023
4) Honeywell Solstice® propellant technical bulletin

# Summary

- Industry is better-positioned to manage this transition (compared to CFC to HFA transition)
  - Improved materials
  - Improved materials characterization
  - Improved materials control throughout supply chain
  - Risk-based and QbD approaches
- Physicochemical similarities of LGWP with current propellants makes this transition easier with respect to materials compatibility
- Significant amount of information is already available for compatibility of LGWP with common CCS and manufacturing equipment materials
- Industry is already progressing work to demonstrate utility of LGWP propellants

# Materials & Propellants WG Representation

- Aptar
- AstraZeneca
- Chiesi
- GSK
- Impel
- Kindeva
- Presspart
- Proveris
- Recipharm
- RxPack
- Teva
- Vectura

# BREAK

# 12:35 – 1:00 PM ET