The cumulative impact of developments in the environmental regulation of PFAS and pharmaceutical propellants

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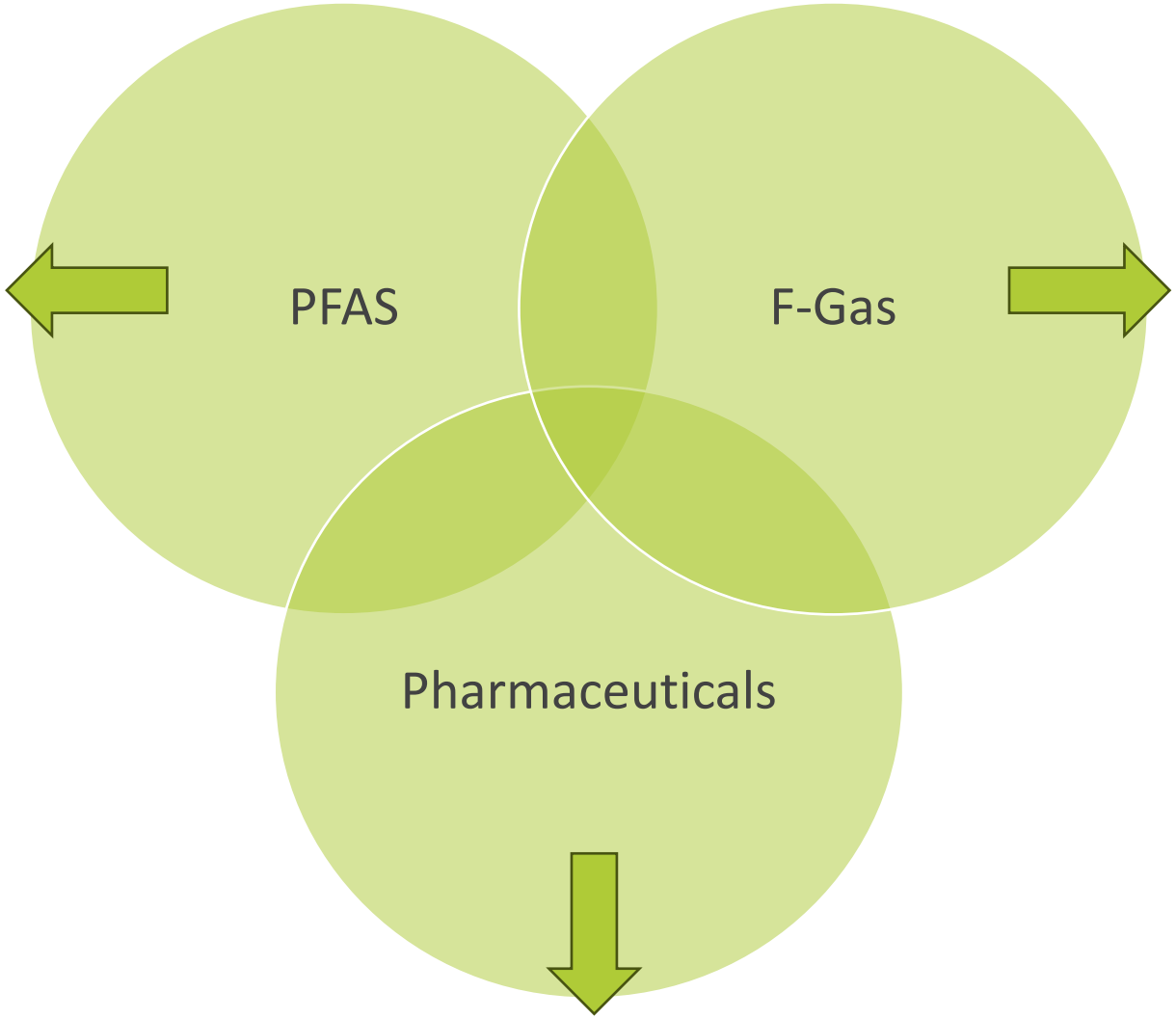
Overview

Environmental Legislation Impact on Pharmaceuticals

- What are PFAS?
- Where are PFAS utilized?
- What is the concern?
- EU situation
- US situation



- Current and proposed propellants
- Importance of the propellant
- What is the concern?
- EU situation
- US situation

- Potential regulatory impact

Per- and polyfluorinated alkyl substances

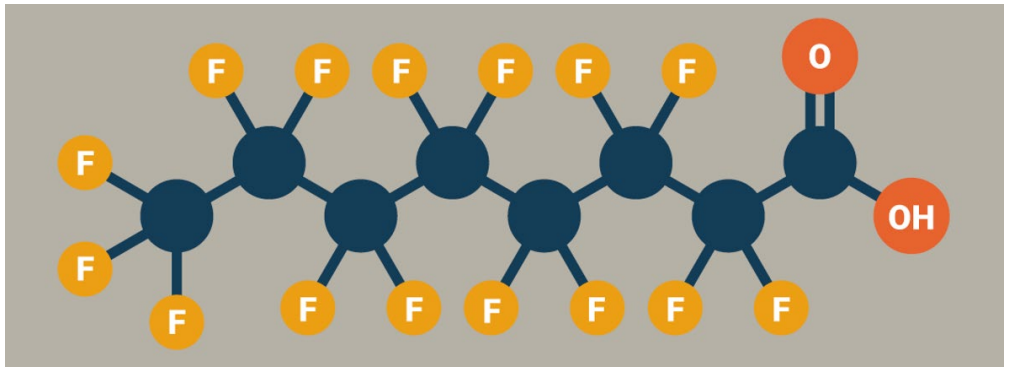
‘Forever Chemicals’

What are PFAS?

- Per- and polyfluoroalkyl substances (PFAS) - man-made organic chemical substances around since the 1940s & 50s
- They contain alkyl groups (-CH_n) on which all or many of the hydrogen atoms have been replaced with fluorine[1]
- Carbon-fluorine bond is one of the strongest, most stable chemical bonds in organic chemistry = "Forever Chemicals"
- Useful properties, such as oil and water repellence, high chemical, physical and temperature resistance and ability to act as surfactants
- Large class of thousands of synthetic chemicals - some more complex compounds can degrade to PFAS

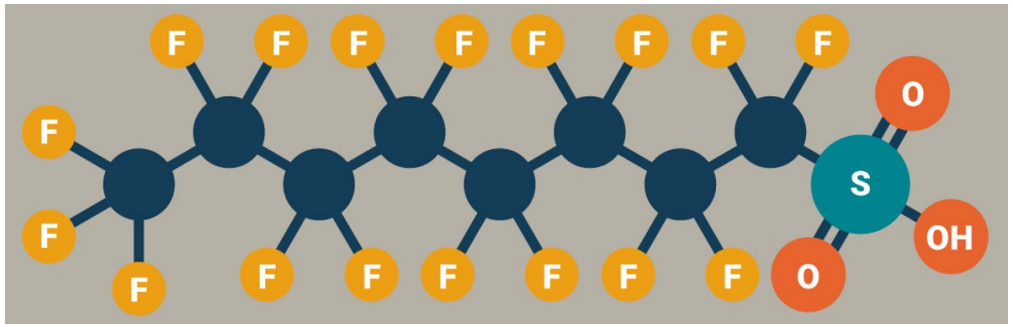
[1]In 2018 the OECD Global PFC Group defined PFAS as chemicals with at least one perfluorocarbon moiety (–CnF2n–).

Perfluorooctanoic acid (PFOA)



PFOA (plus salts/related compounds) banned under the EU's Persistent Organic Pollutants (POPs) Regulation since 4 July 2020.

Perfluorooctanesulfonic acid (PFOS)



PFOS (plus derivatives) restricted in the EU for more than 10 years already, under the POPs Regulation.

US EPA September 2022 proposed rule designated PFOA and PFOS and their salts and structural isomers as hazardous substances.

What are PFAS and Their Concerns?

From the FDA Homepage as of June 2024

Per- and polyfluoroalkyl substances (PFAS) are chemicals that resist grease, oil, water, and heat. They were first used in the 1940's and are now in hundreds of products including stain- and water-resistant fabrics and carpeting, cleaning products, paints, and fire-fighting foams. Certain PFAS are also authorized by the FDA for limited use in cookware, food packaging, and food processing equipment.

Chemically, individual PFAS can be very different. However, all have a carbon-fluorine bond, which is very strong and therefore, they do not degrade easily.

The widespread use of PFAS and their persistence in the environment means that PFAS from past and current uses have resulted in increasing levels of contamination of the air, water, and soil.

Accumulation of certain PFAS has also been shown through blood tests to occur in humans and animals. While the science surrounding potential health effects of bioaccumulation is developing, exposure to some types of PFAS have been associated with serious health effects.

Use this link Per- and Polyfluoroalkyl Substances (PFAS) | FDA

EU: ECHA Draft Legislation

Current
- EU already has restrictions on some PFAS

European Union (EU):

Restricted PFOS, PFOA, C9 to C14 PFCAs (perfluorocarboxylic acids) their salts and related substances and, in near future, PFHxA its salts and related substances

Categorised certain PFAS as substances of very high concern (SVHC)

Future
- EU moving to broader class bans on all PFAS via REACH - ANNEX XV Report
- Restriction proposal from 5 member states
- Bans manufacture, use and placing on market of PFAS
- Two restriction options:

RO1	A full ban with no derogations and a transition period of 18 months after EiF
RO2	A full ban with use-specific time-limited derogations (18 month transition period plus either a 5 or 12 year derogation period) or unlimited (e.g. API) after EiF

ECHA: European Chemicals Agency / REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals; RAC: Risk Assessment Committee / SEAC: Socio-Economic Analysis Committee

US: Developing Legislation

Current

- US EPA already has restrictions on some PFAS
- April 2024, National Primary Drinking Water Regulation legally enforceable MCIs for 6 PFAS in drinking water
- Federal vs State actions have differed – Federal bans on the use of specific products, some independent state action has been class based (US State PFAS)

United States (U.S.) (from 2023):

Banning certain PFAS chemicals and reporting obligations for manufacturers and importers

Future

- EPA PFAS Strategic Roadmap - Review previous decisions on PFAS 'Efforts Ongoing'
- EPA Announces New Framework to Prevent Unsafe New PFAS from Entering the Market
  - Targets new PFAS and new uses of current PFAS
  - Extent of assessment depends on risk (human and environmental exposure)
  - Low risk require basic information submitted to EPA
  - More extensive testing / information required prior to commercialisation for high risk
  - No commercialization until EPA assessment complete
  - Canada: Risk Management Scope for PFAS – document outlining proposed options for consultation

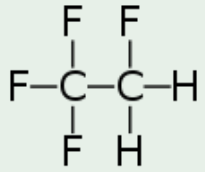
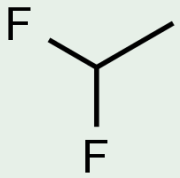
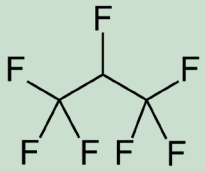
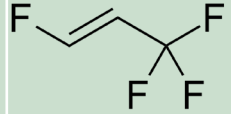
Sept 2023 - Final rule issued for PFAS reporting requirements: manufacturers (including importers) of PFAS and PFAS-containing articles in any year since 2011

EPA: Environmental Protection Agency

Fluorinated Propellants

Pressurized Metered Dose Inhalers

Current and Proposed Propellants

Current Propellants				VS	Proposed Propellants			
Propellant	Structure	GWP (CO_2 = 1)	Atmospheric Lifetime		Propellant	Structure	GWP (CO_2 = 1)	Atmospheric Lifetime
HFA 134a		1,300	14 years		HFC 152a		138	51.45 years
HFA 227a		3,350	31-42 years		HFO 1234ze		<1	18 days

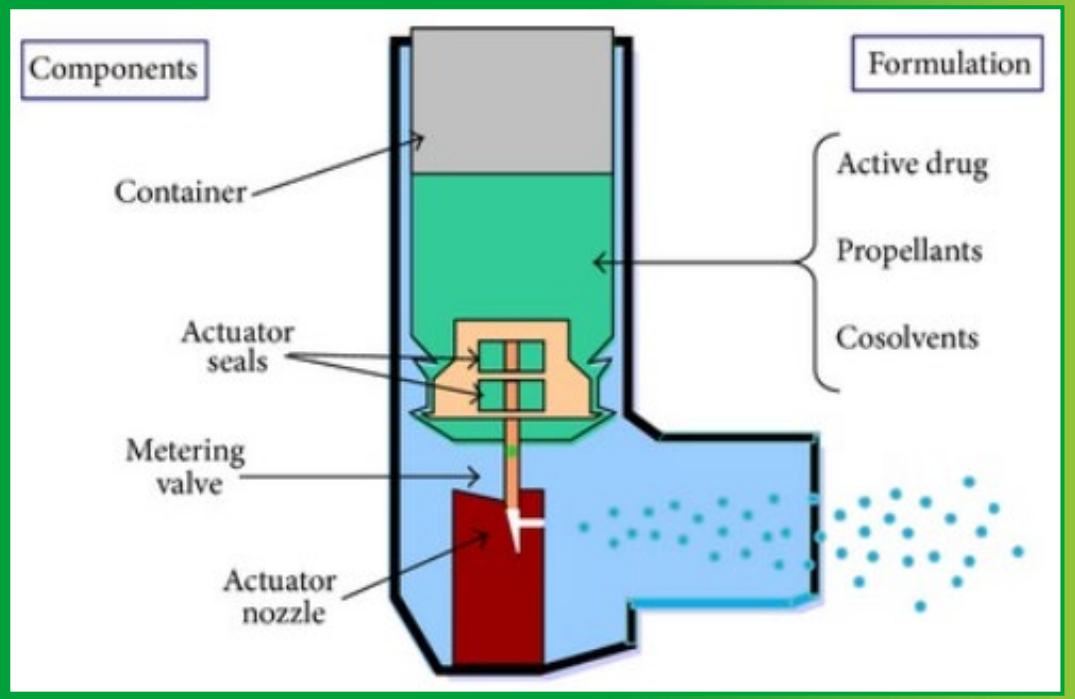
Reference: Parry M, “Considerations when Switching from Current pMDI Propellants to New Lower-GWP Propellants”. ONdrugDelivery, Issue 145

Note: HFA 134a, HFA 227a and HFO 1234ze fall under the definition of PFAS

Importance of the Propellant

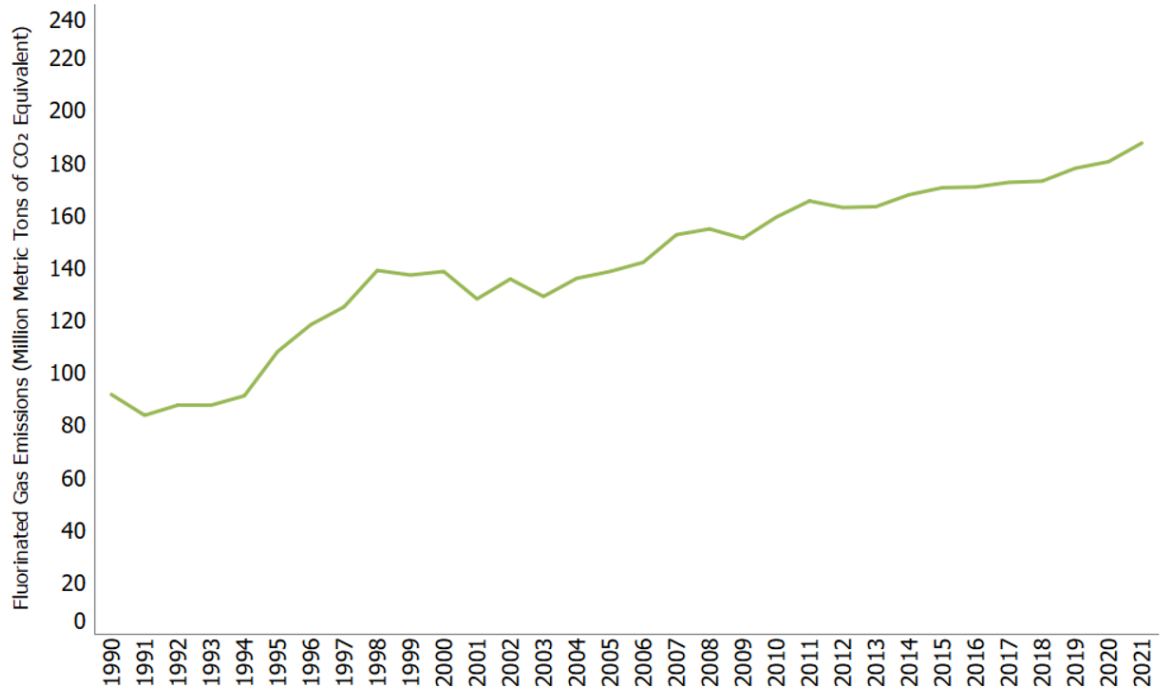
- Provides energy to deliver the formulation to the patient
- Is the solvent for solution pMDI
- Provides media for suspended formulations
- Comprises the significant majority of a pMDI formulation
- Different propellants differ in critical material attributes, for example density
- Interacts with key inhaler components, particularly the valve

- Changing the propellant is a significant re-formulation of the drug product



What is the Concern?

- Current propellants, HFCs do not deplete the ozone layer but are powerful greenhouse gases that contribute to climate change.
- Fluorinated Gas emissions increasing - the US as an example:
  - Seen an increase of 105% in Fluorinated Gas emissions between 1990 and 2021
  - Driven by 349% increase in HFC emissions since 1990
  - HFCs widely used as a substitute for ozone-depleting substances
- US and EU/UK health authorities have not mandated a switch in propellant



U.S. Environmental Protection Agency (2023). Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990–2021

- As older propellants become scarcer and more expensive, newer propellants will be adopted.

Montreal Protocol - Kigali amendment, 2016 details F-gas reduction: implement a global HFC phase-down which will reduce HFC production and consumption by >80 % over the next 30 years

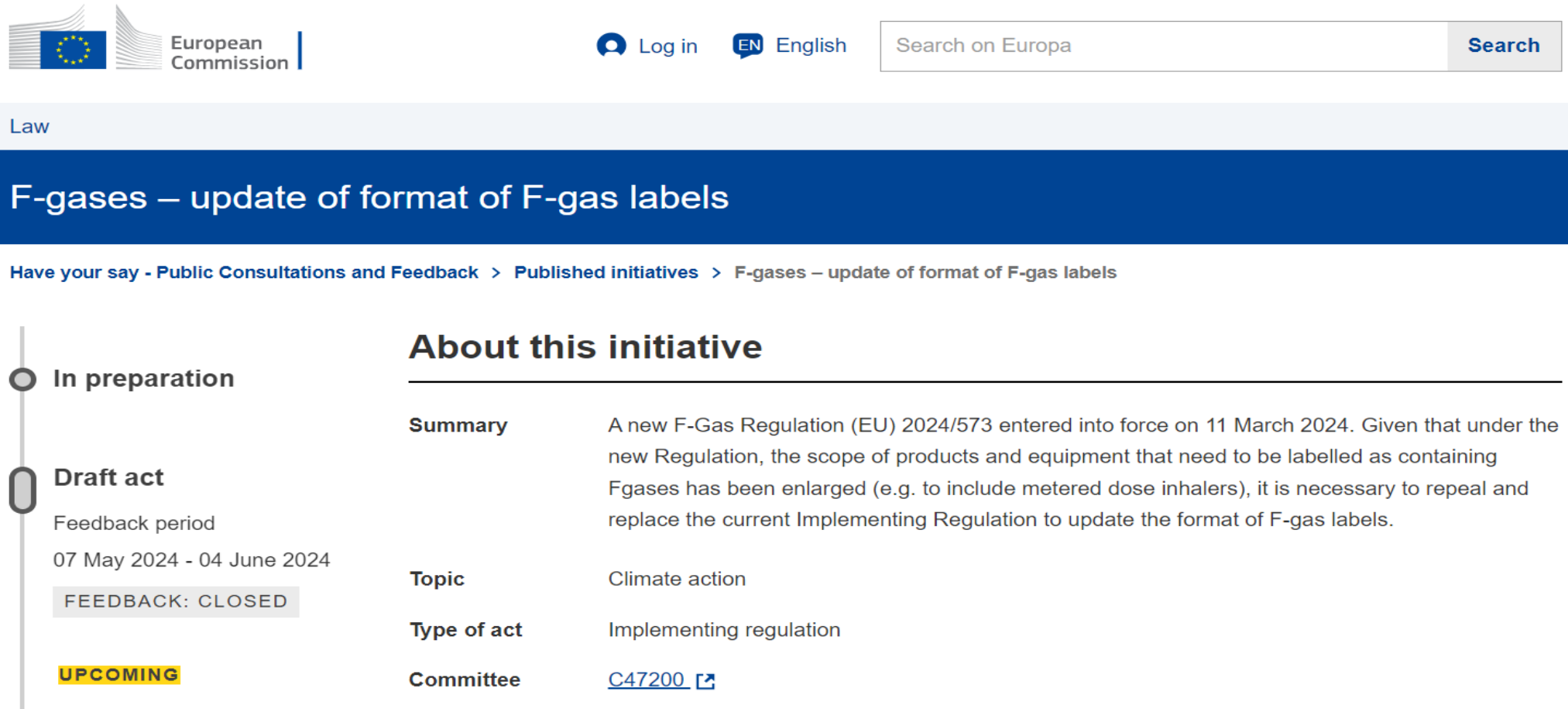
HFCs: Hydrofluorocarbons

EU: F-Gas Regulation

Regulation (EU) 573/2024 on fluorinated greenhouse gases ('the F-gas Regulation')	• Measures to decrease F-Gas emissions • Gradually decrease # of HFC available on market • Require licences to import and export certain substances • Extended operator obligations and training for mobile air-conditioners and refrigerator systems
Established an 'EU HFC phase-down'	• Quota system to implement a gradual reduction in the amount of HFCs that propellant importers / producers may place on the market annually • However, Emission savings envisaged by 2030 would not be fully achieved and Compliance beyond 2030 must be ensured
Revised regulation published 5th April 2022 (comment period closed June 2022)	• Commission proposal for updated regulation being negotiated by the co-legislators in the EU Parliament and the Council • Achieve additional emission reductions to contribute reaching 55% reductions by 2030 and net carbon neutrality by 2050 • Exemption for pharmaceutical inhalers had been removed

EU - IMPACT ON LABELS

Update of Format of F-gas labels



Proposed EU Quotas

- Industry awaits outcome of the EU Commission / Parliament / Council trilogue discussions
- These will determine F-gas consumption in pMDIs plus other aspects (fees for quotas, activation of 'emergency break', safeguards such as revising quotas / fees)
- Implementation date for the F-Gas Regulation: EU Parliament / Council aiming for 1 January 2024 entry into force

EU Commission Proposal (April 2022)	EU Parliament Proposal (March 2023)	EU Council Proposal (April 2023)
2024-26: 100% 2027-29: 42.4%	2024-26: 100% 2027-29: 70%	2024-28: 100% 2029: 50.53%

US: American Innovation and Manufacturing Act

AIM Act of 2020 authorizes EPA to address HFCs with new authorities in three main areas	• Phase down the production and consumption of listed HFCs • Manage these HFCs and their substitutes • Facilitate the transition to next-generation technologies through sector-based restrictions
Phasedown of HFCs	• Established a methodology for allocating HFC production and consumption allowances for years 2024 through 2028 • Similar to methodology used for 2022 and 2023
pMDIs benefit from application specific phase down	• Current exemption for pMDIs runs until end of 2025 (42 USC 7675: American innovation and manufacturing (house.gov)) • However propellant supplies may still be impacted by the general phasedown across other industries

Proposed US Quotas

- US EPA imposing F-gas quotas from 2022
- Target to Reduce US F-gas emissions by 85% by 2036

Year	Consumption & Production Allowance Caps as a Percentage of Baseline
2022-2023	90 percent
2024-2028	60 percent
2029-2033	30 percent
2034-2035	20 percent
2036 & after	15 percent

Regulatory Scenarios

A Generic Perspective

Gx Regulatory Impact

PFAS Scenario

- Impact of EU legislation (primarily) is far reaching for global pharmaceutical supply chains and manufacture.
- HFO 1234ze is currently covered by the proposed PFAS regulation in EU.
- Will potentially impact approved and future products – Rx and Gx equally.
- Legislation is being driven by Environmental, not Pharmaceutical agencies.
- Uncertainty until final EU legislation is published.
- Potential short time frame for implementation of new legislation.
- **Risk of significant regulatory burden updating US and EU applications.**
- How will the US situation develop?

Gx Regulatory Impact

F-Gas Scenario

Generic companies need to respond to stay competitive; companies must prepare to transition to green propellants

Assumption: Innovator companies may launch new 'green' pMDI product ranges via new applications or submit variations/supplements for existing products.

US Gx

- If new application, will likely require new ANDA for Gx.
- Possible need for studies as per PSG or will new FDA guidance with alternative approach made available?
- FDA may require use the same new propellant as the RLD (Q1/Q2 requirements) or alternative approaches.
- Will some F-Gas changes require new devices?

EU Gx

- Line extension submission may be permitted for Gx.
- EMA Q&A - Permits step-wise approach to Bioequivalence.
- Will some F-Gas changes require new devices?

Questions?

Thank you!