Exemption request for the import and use of PFOB for the production of pharmaceutical products for the treatment of respiratory diseases in the EU

22 February 2019

AstraZeneca

About AstraZeneca

- AstraZeneca is a global biopharmaceutical business delivering medicines to patients through innovative science and excellence in development and commercialisation

- The main therapy areas are
  - Oncology
  - Cardiovascular & Metabolic Disease
  - Respiratory

Background and purpose

- AstraZeneca developed a new generation of inhalation products based on porous particles technology. Medicines are intended for severe respiratory diseases such as COPD and asthma.
- Porous particles produced in AstraZeneca's site in Sweden with PFOB.
- PFOB is produced by Daikin in Japan from PFOI, a PFOA-related substance.
- Exemption request under the REACH PFOA Restriction due to PFOI impurity in PFOB higher than the authorized threshold
- ECHA recommends a time unlimited exemption for REACH
- Exemption also required under the Stockholm Convention for the use of PFOI in the production of PFOB, currently recommended until 2036
- **The critical need of AstraZeneca is a time unlimited exemption as recommended by ECHA to secure pending and long-term investments in the EU**

Overview of past and pending investments

- AstraZeneca's site in Södertälje, Sweden, chosen in 2014 to be the commercial production site for porous particles.
- Medicines are further processed in AstraZeneca's site in Dunkerque and most of the supply chain is in the EU
- Total investment exceeding €160 million in Europe, creating numerous high skill employment opportunities.

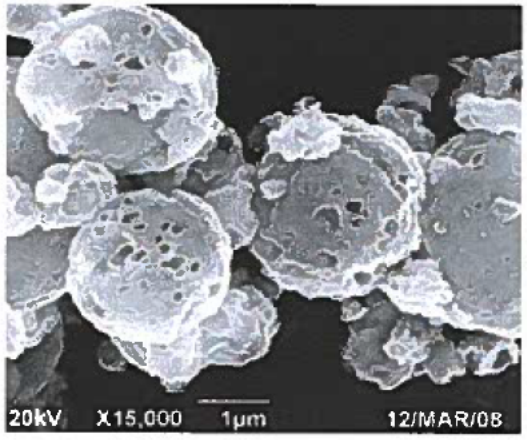
- **Next investment phase in order to secure supply for future demand still pending**
  - Sweden: Currently there are 20 manufacturing roles in Sweden for an 8 hour manufacturing operation in a single facility. This is expected to expand to a 24 hour operation across two facilities, so potentially up to a 6 fold increase, i.e. >100 new employment opportunities.
  - France: The investments are expected to triple the output of the Dunkerque manufacturing site from approx. 20 million to 60 million inhalers per year. The Dunkerque site currently employs approx. 450 people and this number will change as product volumes increase.

Overview of medicines relying on PFOB/porous particles

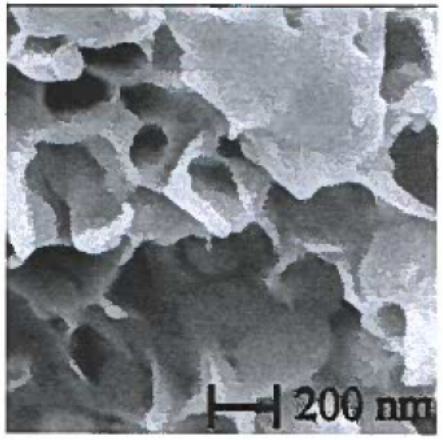
- Bevespi Aerosphere (dual therapy for COPD) was first approved in the USA in 2016 and is also approved in the EU, Canada, Australia, Turkey and Taiwan. Marketing applications are still ongoing in many other markets including, China and Japan.
- PT010 (triple therapy for COPD) has been submitted in China and Japan with approvals and launches likely to start late in 2019 or early 2020. Other marketing applications are ongoing, including in the EU.
- [redacted]
- [redacted]

Quality and Patients Benefits

- The novel porous particles technology prevents settling of the product.
- It enables consistent delivery of one or more different medicines from a single inhaler
- Combined ingredients mean patients use only one device/product (instead of two or three).
- Use of a single device enables better patient adherence and better control of symptoms



Aerodynamically Light Construction



Solid Foam Nanostructure

AstraZeneca

Absence of suitable alternatives

- Despite extensive efforts, suitable alternatives to PFOB have not been identified.
- Inhaled products are very sensitive to changes in particle shape and texture of the powder components.
- Effort to substitute would be equal to developing a new product which will require repeat clinical trials and could be prohibitively expensive with no guarantee of success
- Pharmaceutical products undergo rigorous safety and efficacy studies that can last in excess of ten years from the date a potential new medicine is discovered

The porous particles have very specific properties:

- Particle size controlled to specification
- Low density controlled to specification
- Porous – low aerodynamic diameter with large geometric diameter

Risk assessment

- PFOB is not harmful to humans. It has been approved as a pharmaceutical product.
- We expect to handle approximately 10T per annum PFOB in Sweden by 2025.
- Typically, between 100 and 250 ppm is the concentration of PFOI in the PFOB used, which is above the EU restricted level (1ppm).
- Not more than 2 ppb PFOI in the final pharmaceutical product

Environmental Safety

- 99.8% gaseous waste capture demonstrated from spray drying.
- **The amount of PFOI released to the environment from the Sweden facility is expected to be <4g per annum in 2025 (gaseous waste).**

- Worker Safety
- Protection equipment
- Limitation of exposure at various stages of production

Why might patients want to keep the medicines after 2036

- COPD is a leading cause of morbidity and mortality worldwide that induces and economic and social burden that is both substantial and increasing. Cardiovascular disease, hypertension, anxiety and depression are common with COPD (Global Initiative for Chronic Obstructive Lung Disease 2018 Report)

- It affects an estimated 384 million people worldwide and is predicted to be the third leading cause of death by 2020

- Patients will not typically want to switch to a different medicine if their respiratory condition is already stabilized by their current medication

- More choice of therapies creates a higher likelihood that a patient can identify an optimal treatment that manages its symptoms and increases the probability of a near normal lifestyle

REACH PFOA Restriction

REACH PFOA Restriction

- Reason for exemption:
  - PFOB contains an **impurity of PFOI** (<250ppm) above the threshold set in the REACH PFOA Restriction (1ppm)

- Amendment of REACH PFOA Restriction necessary prior to its entry into effect (4 July 2020)

- Positive opinion of RAC and SEAC for an exemption **without a time limit due to very low emissions and suitable risk control**

- ECHA's recommendation:

  « Import and use of perfluorooctane bromide (PFOB) containing perfluorooctane iodide (PFOI) in concentration lower than 250 ppm for the purpose of producing pMDI (pressurised metered dose inhaler) products for the treatment of respiratory diseases. »

REACH PFOA Restriction

A time unlimited exemption, as recommended by ECHA, is critical to secure AstraZeneca's long-term investments in Sweden

- An expiry date would incentivise investment outside of the EU
- Absence of level playing field with the US represents a threat to investments in the EU
- Finished pharmaceuticals product could continue to be imported in the EU due to <2ppb PFOI content (below the 1ppm threshold)

REACH PFOA Restriction

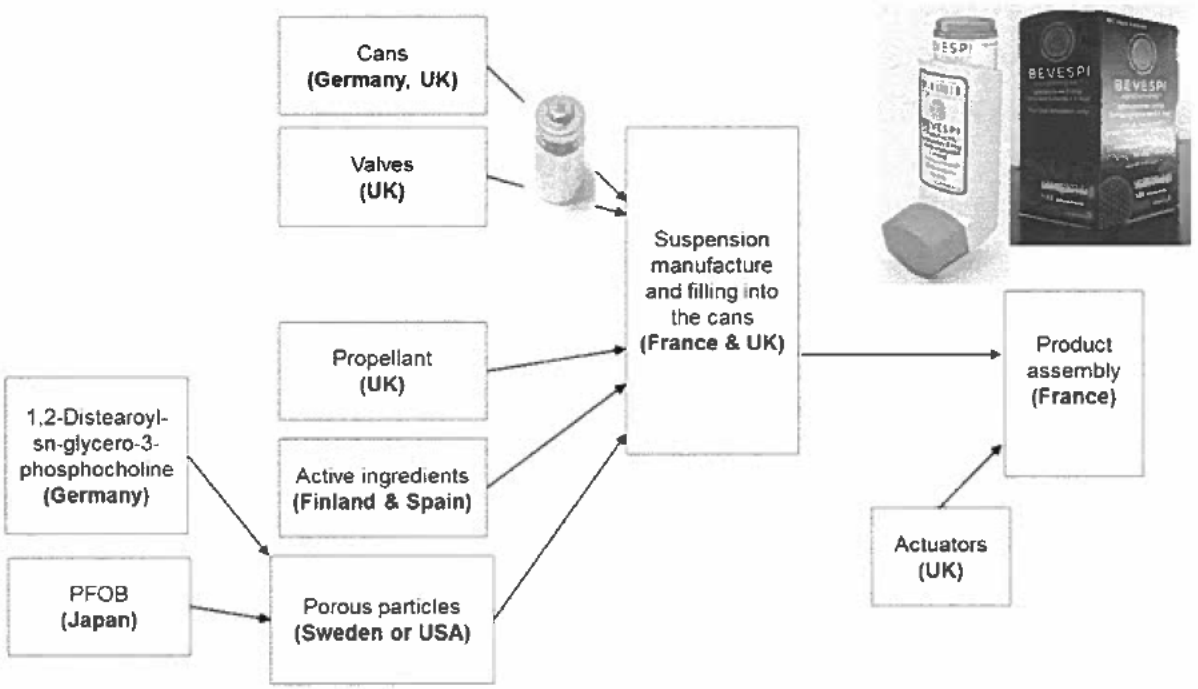
- **No expiry date in the REACH PFOA Restriction is compatible with the Stockholm Convention**

  - Not same scope:
    - Scope REACH Restriction: Use of PFOB due to EU impurity thresholds on PFOI
    - Scope Stockholm Convention: Use of PFOI as transported intermediate.
    - On-site closed system intermediates benefit from a general exemption under the Convention

      → Change in PFOI production and use conditions (e.g. to on-site intermediate, switch to US supplier) may remove need for exemption under the Stockholm Convention

Thank you

Supply chain overview



	Beginning	Supply Chain	End	
Manufacturing step:	1	2	3	4
Article	PFOI	PFOB	Porous particles	pMDI (final medical product - cans)
PFOI Levels	1,000,000 ppm	250 ppm	0.4 ppm	0.002 ppm
How is the article made?	By-product from C6 telomer process	Bromination of PFOI by-product	Spray dried from a mixture of PFOB and water	Mixture of porous particles, active ingredients and propellant
Location manufactured	Japan	Japan	Sweden or USA (dual sourced)	France or UK (dual sourced)

Analysis of Alternatives

Development Stages

Stage 1

Identification of alternative agent and proving

- Process concept proposed with scientific foundation.
- Applicability and validity of concept described and vetted, or demonstrated.
- Experimental proof of concept completed.
- Process validated.

Stage 2
(Phase 1)

Safety Assessment

- Demonstration that the alternative agent is safe.

Stage 3
(Phase 2 & 3)

Dose ranging and clinical assessment

- Assuming that the alternative agent has an impact on the properties of the porous particles, it is assumed that clinical trials will be needed to verify that the correct dose is being used.
- It is likely that clinical trials would be required to demonstrate therapeutic benefit.

Stage 4

Marketing Approvals

- Marketing approvals will be required globally, this would involve significant effort to gain approvals in every market.

Approval times can exceed 3 years in some markets.

Production process

By-product from C-6 telomerization

Transportation to PFOB production site

PFOI

10 ton/yr

Direct bromination

Most efficient reaction

+ Br2

>99.9% converted

PFOI level in PFOB 100-250ppm

PFOB

Closed system

Residuals & waste incinerated

<1kg/yr PFOI

>99.5% trapped in carbon beds and incinerated

PFOI level in finished pharmaceutical products: <2ppb (equivalent to 0,4g/y based on expected sales)

Pharmaceutical products

PFOI emissions during production <4 g/yr

Indicative Timeline