REQUEST FOR ADDITIONAL DEROGATION TO ENTRY 68 OF ANNEX XVII OF REACH

Annexes 1 to 3:

Annex 1: Chemical Safety Report

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Chemical Safety Report for the Use of PFOB Containing up to 200 ppm PFOI

Date March 2018

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1. INTRODUCTION

AstraZeneca is seeking an exemption from the REACH Restriction on PFOA and PFOA-related substances[1] that would prohibit the use of PFOB (perfluorooctyl bromide) in the manufacture of pharmaceutical products. This is due to the presence in the PFOB of trace levels of PFOI (perfluorooctyl iodide), which is a PFOA-related substance, in a concentration exceeding the threshold set in the REACH Restriction on PFOA and PFOA-related substances. PFOI presence as an impurity in PFOB is inevitable due to the synthetic route for the manufacture of PFOB. AstraZeneca uses PFOB at a manufacturing site in Snäckviken, Södertälje, Sweden for the production of porous particles, which are a functional component in a new generation of AstraZeneca pressurised metered-dose inhaler (pMDI) medicines. These medicines use a novel Co-Suspension™ Technology that contains low-density phospholipid porous particles.

PFOB is used as a processing aid and is critical to delivering the unique aerodynamic properties of the porous particles, which ensure the efficient delivery of the medicine to the lungs.

PFOB is anticipated to be both chemically and biologically stable and is not considered as a PFOA related substance. It was a key component of IMAGENT® (licensed by Alliance Pharmaceuticals, Inc); an injectable suspension for use in patients with suboptimal echocardiograms, which following demonstration of safety and efficacy was approved as a medicinal product by the US Food and Drug Administration (NDA 21-191) in 2002. The PFOB is produced outside the EU and typically contains up to 200 ppm PFOI, which exceeds the threshold of 1 ppm set in the REACH Restriction. It is not possible to source PFOB which meets the REACH Restriction as all synthetic routes proceed via prohibited substances, hence trace amounts inevitably remain in the PFOB.

The porous particles are designed to provide a uniform suspension inside a pMDI, which is able to deliver an optimal distribution of drug crystals in the lungs for alleviation of lung diseases such as COPD[2]. The porous particles also enable consistent delivery of multiple active ingredients from a single pMDI. The technology is utilised in Bevespi Aerosphere which was approved by the FDA in April 2016 for the treatment of COPD. Bevespi Aerosphere is also under marketing review by the authorities in the European Union. There are also other AstraZeneca projects currently in clinical development, such as the fixed-dose triple combination of LAMA/LABA/Inhaled corticosteroid (PT010)[3].

The scope of the exemption request to the REACH Restriction relates to the use of PFOB containing up to 200 ppm of PFOI in the production of porous particles at the AstraZeneca manufacturing facility in Sweden. All subsequent steps in the supply chain are in compliance with the REACH Restriction.

This report discusses the risks with respect to the PFOI impurity in PFOB. It summarises risk management assessments and demonstrates that PFOB is being used responsibly in the manufacture of medicines for the treatment of respiratory diseases.

1.1 European Union and Global Legislation Affecting Use of PFOB

The European Union issued a new regulation under Annex XVII to Regulation (EC) No 1907/2006, the REACH Restriction on PFOA and PFOA-related substances, which will come into force in July

[1] Commission Regulation (EU) 2017/1000 of 13 June 2017, which will come into force in July 2020.
[2] COPD = chronic obstructive pulmonary disease.
[3] Positive late stage clinical results were announced for PT010 in January 2018. AstraZeneca anticipates making regulatory submissions in Japan and China in the second half of 2018, followed by submissions in the US and Europe.

2020. This would prevent the porous particle manufacture described above at the manufacturing facility in Sweden, with significant knock on effects for onward manufacturing activities in France and the UK.

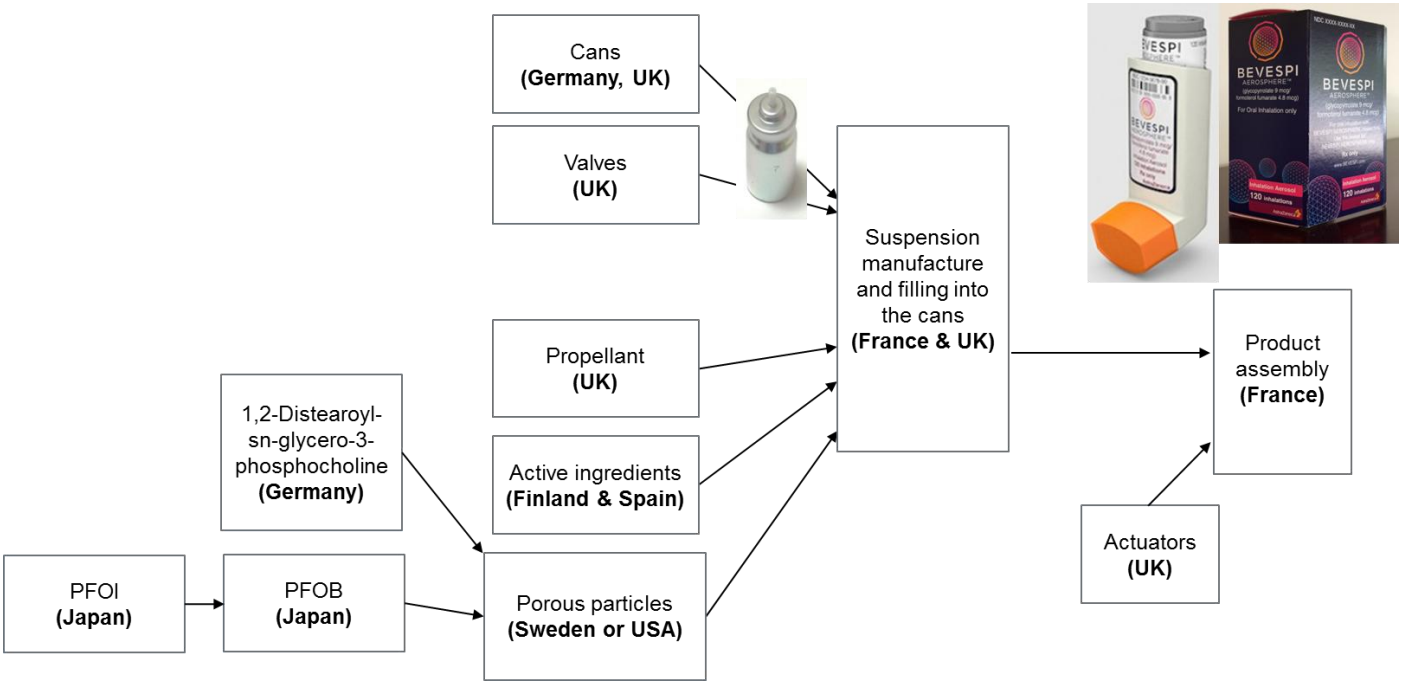
The United Nations Environment Programme (UNEP), under the Stockholm Convention, has also been evaluating pentadecafluorooctanoic acid (CAS No: 335-67-1, PFOA, perfluorooctanoic acid), its salts and PFOA-related compounds. PFOB is exempt from any UNEP proposals, but PFOB is typically synthesised via PFOI which is considered a PFOA related compound. The UNEP Persistent Organic Pollutants Review Committee met in Rome 17th – 20th October 2017 and recommended to adopt the following exemption to ensure medicines are not impacted:

> *"(an exemption) For use of perfluorooctane iodide, production of perfluorooctane bromide for the purpose of producing pharmaceutical products with a review of continued need for exemptions. The specific exemption should expire in any case at the latest in 2036."*

It is anticipated that the exemption described above will be adopted by the European Union eventually, but a time gap is expected between the entry into effect of the REACH PFOA Restriction and the amended global regulation, the length of which cannot be determined at present. Therefore, an exemption is requested to ensure there is not a temporary restriction in place during that time gap, which would force AstraZeneca to move the manufacture outside the European Union, or withdraw the medicines from sale, with potential negative impacts for patients.

1.2 Supply Chain from PFOI through to pMDI Medicines

The Bevespi Aerosphere supply chain has a strong European footprint and is summarised in the flow diagram below:



Note that the PFOB is spray dried away from the porous particle component of the final product, hence there is no significant solvent remaining in the final product, which meets the requirements of the European regulation. The table below shows the levels of PFOI that could be present at each stage in the manufacture of the final product assuming a residual level of PFOI at 200 ppm in PFOB.

Supply Chain Beginning ⟶ **Supply Chain End**

Manufacturing step:	1	2	3	4
Article	PFOI	PFOB	Porous particles	pMDI (final medical product)
PFOI Levels	1,000,000 ppm	200 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)

This exemption request relates to the handling of PFOB during the manufacture of porous particles at the AstraZeneca manufacturing facility in Södertälje, Sweden. The PFOB contains PFOI at levels higher than permitted under Annex XVII to Regulation (EC) No 1907/2006. All subsequent steps in the supply chain are in compliance with the EU regulation.

1.3 Volume Predictions

By 2025, it is anticipated that AstraZeneca will use up to 10 T per annum of PFOB at the Sweden site. The PFOI typically represents up to 200 ppm in the PFOB, hence a maximum of 2 kg PFOI is expected to be handled per annum as a low level impurity in 10T of PFOB. AstraZeneca can manufacture porous particles in the USA but expansion opportunities are limited at the existing facility, so the Sweden site might ultimately manufacture most of the porous particle component of the final pMDI product. AstraZeneca will need to invest in an additional manufacturing suite in 2018 to meet expected supply chain demand and would prefer to make this investment at the Sweden facility.

2. EXPOSURE ASSESSMENT

2.1 General Remarks Regarding the Safety of PFOB

PFOB is not harmful to humans and has been approved by the FDA as a drug product (NDA 020091). PFOB has no known receptor targets and therefore no known biological mode of action. Very little systemic uptake has been observed in mammals following oral administration and bioavailability is considered to be low. In both aquatic and mammalian toxicity studies, PFOB has been shown to be of low toxicity. At environmentally relevant concentrations in the aquatic environment (i.e. up to the limit of solubility) no toxicity to aquatic species is anticipated.

Based on the measured physical-chemical properties and predictive models, PFOB is expected to be biologically and chemically stable and PFOB should be considered as potentially persistent and potentially bioaccumulative.

The handling of PFOB in a controlled environment is therefore of negligible risk to the workforce at the Sweden AstraZeneca facility. The risks from the PFOI impurity are discussed in Section 3. The Sweden AstraZeneca site works closely with local authorities to ensure the site is meeting strict environmental requirements. The site is well established for the manufacture of pharmaceutical products, hence AstraZeneca would like to continue manufacture of the medicinal product at Snäckviken, Sweden, rather than develop the required expertise and manufacturing capability outside the European Union.

2.2 Overview of PFOB use in the Manufacture of Porous Particles

PFOB is used in the preparation of porous particles, which are a functional ingredient in the pMDI products. PFOB typically contains approximately 200 ppm PFOI and the PFOB waste stream therefore contains a proportionately low level (200 ppm) of PFOI.

The porous particles are prepared according to the following stages:

- Preparation of an emulsion (mixture) of $CaCl_2$, water, DSPC and PFOB.
- Homogenisation of the mixture to prepare the feedstock.
- Spray drying of the feedstock to give porous particles.

During the emulsion preparation, DSPC and $CaCl_2$ are dispersed into a vessel containing heated water and PFOB (perfluorooctyl bromide or perflubron) using a high-shear mixer. The coarse emulsion is then further processed with a high-pressure homogenizer before spray-drying using a spraydryer. Gaseous emissions from spray drying are extracted directly from the spray drier and captured through carbon beds in a standalone building. The waste PFOB is removed from the carbon beds for incineration and the carbon bed is re-used.

2.3 Route of Exposure: Workers

Open handling is limited in the manufacturing facility and higher risk activities such as liquid dispensing are managed through use of containment, ventilation/extraction and personal protective equipment, see images below.

Image of extraction unit used during the dispensing/weighing of PFOB.

Image of protective gowns worn by workers during dispensing of PFOB

The most likely route of workers exposure is through inhalation and/or dermal contact. PFOB is not harmful by ingestion, however this is not an anticipated route of exposure in any case. Worker exposure to PFOB is limited by working practices and the risk of exposure to PFOI is further diminished by the high boiling point and very low levels of PFOI present (typically <200 ppm). The risk of PFOI exposure is assessed in Section 3.

2.4 Route of Exposure: Environment

Publicly available data on the environmental fate and effects of PFOB in the aquatic environment is limited. AstraZeneca use of PFOB as a processing chemical is expected to amount to between 1 and 10 tons per annum in the European Union. Therefore, acute aquatic toxicity studies, a ready biodegradation screening assay and determination of the physical-chemical properties of PFOB have been undertaken to support registration under the EU REACH Regulation (No 1907/2006). These studies used PFOB test material from the same source as used in the manufacture of the porous particles, i.e. it contained trace amounts (up to 200 ppm) of PFOI.

Further understanding of the environmental fate and potential for degradation of PFOB has been gained from a quantitative structure–activity relationship (QSAR) model. In this report the environmental assessment and results from the environmental testing, QSAR model and available toxicity data are provided, see Annex: Environmental Fate and Effects Data.

2.4.1 Management of Gaseous Waste

AstraZeneca has installed the best available technology to ensure there is negligible impact on the environment. PFOB is shipped to the Snäckviken site in barrels which are stored in an engine room, then the PFOB is pumped to the manufacturing equipment. The porous particle manufacturing process utilises a mixture of water and PFOB, which are removed from the porous particles during spray drying of the material.

The resulting gaseous PFOB containing PFOI is directed to a dedicated treatment plant where it is passed through dual carbon beds with a total capture rate typically >99.8%. The carbon beds are

equipped with a system that automatically shuts down the manufacturing facility if the emissions exceed the threshold agreed with the local authority. The carbon beds regenerate via in-situ removal of PFOB (containing trace levels of PFOI). As such, no significant releases of PFOI to the environment are expected, particularly as PFOI is present in PFOB at trace levels, typically 200 ppm. 10T of PFOB per annum is expected to be used in Sweden in 2025, this corresponds to <4g per annum PFOI released to the atmosphere as gaseous waste.

To minimise environmental exposure the waste streams containing high concentrations of PFOB and low levels of PFOI are diverted to dedicated tanks before proceeding to off-site incineration at high temperature (at least 1100°C) with 2 seconds residence time for flue gases.

2.4.2 Management of Liquid Waste

Liquid waste from other streams, e.g. dishwashers and laboratories is currently captured for specialised waste treatment by incineration. This liquid waste represents approximately 2% of the total PFOB used, hence the total quantities of PFOI in this waste stream are very low.

This presents a significant amount of incinerated aqueous waste, hence the low concentration waste stream is eventually proposed for treatment at the on-site AZ Waste Water Treatment Facility (WWTF). A Best Available Technique (BAT) is being evaluated with a view to undertake on-site treatment of the low concentration waste stream from the production of porous particles. This would be discussed with the local Sweden authorities.

2.5 Consumer Exposure

The porous particle product is spray dried to remove all PFOB (the control limit is 0.2%). The porous particles represent a small proportion of the final pMDI product, so this controls the levels of PFOI to < 2 ppb in the final pMDI product. This level of PFOI is well within the 1000 ppb limit in the EU regulation and the final products are assessed by medical authorities and have been subjected to extensive trials to demonstrate safety and efficacy of the final product.

Management of potential mutagenic impurities is well established for pharmaceutical products in ICH M7 Guidance[4]. The maximum daily dose for the consumer is approximately 250 mg of the Co-suspension™ product, which at 2 ppb comprises a maximum of 0.0005 micrograms of PFOI in the final product. This provides a 3,000 fold safety factor against the daily threshold of 1.5 micrograms per day in ICH M7 guidance.

2.6 Indirect Exposure of Humans via the Environment

PFOI emissions are calculated to be < 4 g per annum. The low levels of PFOI emitted would be released into a very large air volume and thereby largely diluted because the emission is gradual and gaseous.

Based on total emissions of 16 mg per day, it is extremely unlikely that any single individual, locally and regionally, would be exposed to a hazardous level of PFOI. This is discussed in more detail in Section 3.

[4] ICH Harmonised Tripartite Guideline: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7.

3. RISK ASSESSMENT

3.1 DNELs for Workers and the General Population

This section describes how the DNEL (Derived No Effect Level) and risk factors have been considered for PFOI content in PFOB.

PFOI can be broken down to PFOA in the environment and it is likely that PFOI also will be metabolised to PFOA in living organism. To what extent and at what rate is not easy to assess so a very conservative 100% conversion rate is used in this estimate

The critical study for the PFOA is the reprotox study by Lau et al according to the Committee for Risk Assessment (RAC)

https://echa.europa.eu/documents/10162/2f0dfce0-3dcf-4398-8d6b-2e59c86446be

RAC have identified a NOAEL and used estimated serum levels in their DNEL.

Serum levels are hard to use for the described use of PFOB containing trace levels of PFOI, so the administrated oral dose in the critical study described above is used in this assessment.

Critical study: reprotox study in mice (Lau et al)

NOAEL =1mg/kg/d

Recommended assessment factors

Intraspecies, allometric scaling for mice: 7

Interspecies, remaining differences: 2.5

Intraspecies, workers: 5

Interspecies, general population: 10

Total factor for workers: 87.5

Total factor for general population: 175

(RAC uses a total factor of 12.5 (2.5 x 5) since they use serum levels in their assessment and therefore do not have to use the allometric scaling factor.)

DNEL for workers and the general population can then be calculated.

NOAEL = 1 mg/kg/d

Assessment Factor = 87.5

Body weight = 70kg

Assume that bioavailability is the same for oral and inhalation exposure

$DNEL_{workers}$ = 1mg/kg/d / 87.5 x 70 kg =0.8mg/d

$DNEL_{general\ population}$ = 1mg/kg/d / 175 x 70 kg =0.4mg/d

3.2 Risk Factor Ratio for Workers

This can then be compared with a worst case exposure estimate:

AstraZeneca Occupational Exposure Limit (8h Typical Working Average) for PFOB is 1mg/m^3

Default breathing volume over a full workday = 10m^3

PFOI concentration= 200ppm

1mg/m^3 x 10m^3 x 200e-6 = 0.002mg/d

The ratio between worst case exposure and DNEL is then (risk ratio for PFOI):

0.002mg/d / 0.8mg/d =0.0025

This shows a very favourable risk ratio as the worst case PFOI exposure scenario is well below the derived no effect level. The actual margin is larger since the potential for exposure is limited to a few short steps in the manufacturing process and is not 8 hours, 5 days per week. Like PFOA, it is possible that PFOI has a long half-life and there will be some accumulation over time, which is not accounted for in the critical study or in the exposure assessment and this will reduce the margin of safety. Nevertheless, the margin of safety is expected to remain well within acceptable thresholds.

3.3 Risk Factor Ratio for the General Population

Assuming that the Snäckviken site handles 10 T of PFOB per annum, which typically contains a maximum of 200 ppm PFOI, this would represent a total PFOI quantity of 2 kg. The typical carbon capture efficiency of 99.8% would reduce the actual PFOI emissions to < 4 g per annum, typically <16 mg per working day.

The low levels of PFOI emitted would be released into a very large air volume and thereby largely diluted because the emission is gradual and gaseous. As shown in the DNEL assessment, the derived no effect level for humans is 0.4 mg / day. Based on total emissions of 16 mg per day, it is extremely unlikely that any single individual, locally and regionally, would be exposed to a hazardous level of PFOI from this manufacturing process.

3.4 Risk Characterisation for the Environment

Air monitoring is undertaken at the emissions plant and has been demonstrated to be 99.8% efficient at removing PFOB from gaseous emissions. It is calculated that this equates to a maximum PFOI emission of 4g per year based on expected PFOB volumes handled in 2025. All liquid waste is currently incinerated. As such, the manufacturing process does not emit PFOI at levels that pose a significant risk to the environment.

4. CHEMICAL SAFETY REPORT CONCLUSIONS

This Chemical Safety Report demonstrates that the handling of PFOB represents minimal risk to human health and the wider environment. PFOB is not harmful and the residual PFOI impurity in this substance typically represents only 200 ppm.

Current waste management procedures ensure that less than 4 g PFOI per annum would be emitted to the environment with annual use of 10 T PFOB, which is the anticipated volume in 2025.

ANNEX

1. ANNEX - ENVIRONMENTAL FATE AND EFFECTS DATA

1.1 Ecotoxicology

1.1.1 Acute toxicity to *Daphnia magna*

The acute toxicity of the PFOB to *Daphnia magna*, was assessed in study FK88QS, in accordance with the OECD Guidelines for Testing of Chemicals No 202. The water solubility of PFOB in the test media was < 0.02 mg/L, therefore a limit test was conducted with a control, solvent control and single exposure concentration prepared at 0.02 mg/L to determine the toxicity of PFOB at the limit of solubility. The limit of solubility and mean measured concentration of PFOB was 0.011 mg/L. Exposure of *Daphnia magna* to PFOB gave a 48 hour EC50 value of greater than 0.011 mg/L and an observational No Observed Effect Concentration (NOEC) of 0.011 mg/L. This study showed that there were no toxic effects up to the limit of solubility.

1.1.2 Toxicity to the green alga, Pseudokirchneriella subcapitata

The toxicity of the PFOB to the green alga *Pseudokirchneriella subcapitata* was assessed in study NS67LH, in accordance with the OECD Guidelines for Testing of Chemicals No 201. The water solubility of PFOB in the test media was < 0.02 mg/L, therefore a limit test was conducted with a control, solvent control and single exposure concentration prepared at 0.02 mg/L to determine the toxicity of PFOB at the limit of solubility. The limit of solubility and geometric mean measured concentration of PFOB over the test period was determined to be 0.00061 mg/L. Exposure of *P. subcapitata* to PFOB gave a 72 hour EC50 value of greater than 0.00061 mg/L and a statistical NOEC of 0.00061 mg/L. This study showed that there were no toxic effects up to the limit of solubility.

1.2 Environmental Fate

1.2.1 Ready Biodegradation

The potential for PFOB to be readily biodegraded was assessed in study XY05SR, in accordance with the OECD Guidelines for Testing of Chemicals No 301F. In the OECD 301F Manometric Respirometry test, potential for biodegradation was measured indirectly as change in the pressure within the headspace of the test vessel as evolved carbon dioxide was absorbed in a solution of 50% v/v ethanolamine.

The test results show that PFOB attained 66% biodegradation during the 28 day test period. However, the time taken to pass the 60% biodegradation threshold exceeded the 10-day window and PFOB cannot be considered as readily biodegradable.

Although this study appears reliable and to provide evidence of rapid and extensive biodegradation, information available in the literature suggests that whilst biodegradation of some poly- and per-fluorinated compounds is possible, such biodegradation is expected to be incomplete and is unlikely to result in evolution of carbon dioxide, due to the stability of the C-F bond. Whilst dehalogenation and biodegradation of some halogenated organic compounds has been widely and accurately reported, there are no scientific reports in the peer reviewed literature that provide evidence to support the biodegradation of structurally similar compounds to PFOB or compounds with this level of halogenated substitution. Consequently, we conclude that PFOB is not readily or rapidly biodegradable.

1.2.2 QSAR Predictions

To further the understanding of the environmental fate and potential for degradation of PFOB during wastewater treatment a structural-based biodegradation estimate was conducted using the Estimation Programs Interface (EPI) Suite™ program (US EPA, 2012).

Based on its structural properties, the estimated probability of primary or ultimate degradation of PFOB during waste water treatment was low; PFOB is predicted to be recalcitrant. PFOB is not predicted to be readily biodegradable.

The estimated soil adsorption coefficients (K_{OC}) were 5.0×10^5 L/Kg (Kow method) to 1.6×10^6 L/Kg (Molecular Connectivity Index method). K_{OC} provides an indication of the extent to which a chemical is expected to partition between solid and solution phases in soil, or between water and sludge solids in wastewater treatment. The estimated K_{OC} values indicate that during waste water treatment significant removal of PFOB is anticipated via adsorption to sludge solids.

The EPI suite prediction shows good correlation between the estimated vapour pressure 7.62 mm Hg (equivalent to 1016 Pa) and the experimentally measured vapour pressure.

The 'Removal in wastewater treatment' screening model (a model within the EPI Suite™ program) estimates the fate of a chemical as it becomes subject to removal by evaporation, biodegradation and sorption to sludge. This model predicts the full removal of PFOB from waste water during sewage treatment. After entering a waste water treatment system, approximately 59.5% of PFOB in aqueous solution is predicted to be retained on sludge solids and remain within the sewage treatment plant, a further 40.3% is predicted to be removed via losses to air. Overall, following wastewater treatment, exposure of PFOB to the receiving water course is expected to be minimal (<1%). At present, all waste water is incinerated.

1.3 Summary of toxicity data

No biological receptor targets are known for PFOB. Following oral administration, systemic uptake and bioavailability is low. PFOB is regarded to be chemically and biologically stable and inert. The critical effect, based on the available studies, including is general toxicity both long term studies and reproductive toxicity studies, is non-specific general toxicity which was evident in long term studies after repeated dosing. Overall the toxicity of PFOB in test animals was considered to be low.

2. SUMMARY OF ENVIRONMENTAL RISKS

2.1 Potential for Toxicity

PFOB has no known receptor targets and therefore no known biological mode of action. Very little systemic uptake has been observed in animal species following oral dosing and bioavailability is considered to be low. PFOB is likely to be both chemically and biologically stable.

Aquatic toxicity tests on representative algal and invertebrate species show no toxicity up to the limit of solubility. Therefore, toxicity to aquatic organisms is not anticipated at environmentally relevant concentrations.

Based on the lack of biological target and low levels of observed toxicity; both the short- and long-term toxicity of PFOB to species found in the natural environment is anticipated to be low.

2.2 Potential for Bioaccumulation

Although the bioavailability of PFOB via oral exposure has been shown to be very low, the octanol-water partition coefficient is above the bioaccumulation screening criterion established by ECHA (ECHA 2014). Therefore, it is concluded that PFOB may be potentially bioaccumulative.

2.3 Potential for Persistence

Although the results of ready biodegradability test appear to show extensive degradation of PFOB, it is considered unlikely that these results represent true biodegradation. In line with the scientific rationale presented in Section 1.2.1 and the low predicted likelihood of biodegradation within the QSAR model (Section 1.2.2), and in the absence of other evidence indicating non-persistence, it is concluded that PFOB may be potentially persistent in the environment.

3. CONCLUSIONS (ENVIRONMENTAL FATE & EFFECTS DATA)

At full production the proposed used of PFOB is expected to result in a maximum concentration of 0.03 µg/L of PFOB in the receiving environment. This prediction is based on a worst-case exposure scenario and as described in the QSAR calculations (Section 1.2.2), it is anticipated that following the separation of the high PFOB concentration aqueous waste stream for incineration, any residual PFOB entering the WWTF will largely be removed (via adsorption to sludge solids and volatilisation). Therefore, exposure to the aquatic receiving environment is expected to be minimal.

As the worst case predicted environmental exposure is well below the water solubility value, the environmental risk and potential for toxicity to aquatic species in the receiving environment is considered to be low.

The potential for PFOB to be persistent and/or bioaccumulative cannot be ruled out.

To minimize the PFOB exposure to recipient a best available technique will be used to pre-treat the aqueous waste streams resulting in a PFOB concentration below 10 µg/L, prior to further treatment in the WWTF. The aim of pre-treatment is to remove as much PFOB as possible, but 10 µg/L is chosen given the limit of quantification (LOQ) of analysis using GC-MS as an analytical technique. Whilst an LOQ of 1.9 µg/L has been determined for PFOB, the complexity of environmental matrices necessitates a level of 10 µg/L for reliable results allowing for continued understanding and improved mitigation.

Analysis of Alternatives to PFOB

Date March 2018

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1. INTRODUCTION AND SUMMARY

Perfluorooctyl bromide (PFOB) is used by AstraZeneca as a processing aid in the manufacture of pressurised metered-dose inhaler (pMDI) medicines. This substance is safe to use and is exempt from restrictions, but its supply is threatened by the recently adopted REACH Restriction on PFOA, its salts and PFOA-related compounds[1]. The PFOB typically contains up to 200 ppm of perfluorooctyl iodide (PFOI), which is considered a PFOA-related substance. The PFOB is currently purchased from Daikin who manufacture it in Japan from PFOI by-product derived from a C6 telomer process. Daikin would otherwise incinerate the PFOI by-product.

The PFOB is used as a processing aid in the manufacture of porous particles, which are a functional excipient in pMDI products. The porous particles have very specific properties that would be compromised by using a different processing aid and this would affect the performance of the final drug product.

This document discusses potential alternative scenarios to the current use of PFOB in the manufacture of the pMDI medicines. Even if an alternative agent was identified, this would require significant marketing regulatory activity and re-approvals, plus it is also likely that repeat clinical trials would be required. The baseline position is therefore that substitution will be very difficult to achieve for a pharmaceutical product, even if an alternative agent was readily available.

All medicines must undergo extensive clinical trial programmes before seeking marketing approvals. A process to develop, test and validate alternatives to PFOB would require an extensive programme of work and involve significant research and development costs. As such, the work to identify an alternative is on-going and the viability of this may depend on whether repeat clinical trials are required. For example, any change in product performance (enhanced or otherwise) will require repeat clinical trials, which could cost hundreds of millions of dollars across the product range and delay access to medicines for patients.

The risks with the use of PFOB are well managed by AstraZeneca as summarised in the Chemical Safety Report, hence there is no significant benefit with switching to an alternative substance, which would require repeat clinical trials and development costs. These trials may be totally unviable from an economic perspective with any restrictions simply resulting in the products being withdrawn from patient use. AstraZeneca presents four alternative scenarios in this report, these are:

1. PFOB which is further purified to reduce residual levels of PFOI
2. PFOB that is manufactured via alternative synthetic routes
3. PFOE used instead of PFOB
4. Use of structurally different alternatives to PFOB

Significant work has already been conducted and the following pages illustrate the challenges. The analysis presented includes the following elements:

- Availability and suitability
- Risks to human health and the environment
- Technical and economic feasibility

It is anticipated that the remaining work to develop an alternative would incur significant research and development (R&D) costs and take between 5-10 further years to complete. This is based on

[1] Commission Regulation (EU) 2017/1000 of 13 June 2017, which will come into force in July 2020. This restricts use of any substance, mixture or article that contains greater than 1000 ppb of PFOA-related substances.

typical pharmaceutical development costs and timelines, particularly as it can take up to 3 years to receive product approval authorisation in some global markets.

Some of the information is sensitive and has been presented at a high level only to protect intellectual property interests.

2. ANALYSIS OF SUBSTANCE FUNCTION

2.1 Overview

AstraZeneca uses PFOB as a processing aid in the manufacture of porous particles, which are a functional component in a new generation of AstraZeneca pressurised metered-dose inhaler (pMDI) medicines. These medicines use a novel Co-Suspension™ Technology that contains low-density phospholipid porous particles. These porous particles are designed to provide a uniform suspension inside a pMDI, which is able to deliver an optimal distribution of drug crystals in the lungs for alleviation of lung diseases such as COPD[2].

The Co-suspension™ Technology also enables consistent delivery of multiple active ingredients from a single pMDI. The technology is utilised in Bevespi Aerosphere which was approved by the FDA in April 2016 for the treatment of COPD. Bevespi Aerosphere is also under marketing review by the authorities in the European Union. There are also other AstraZeneca projects currently in clinical development, such as the fixed-dose triple combination of LAMA/LABA/Inhaled corticosteroid (PT010)[3]. Positive late stage clinical results were announced for PT010 in January 2018, hence AstraZeneca anticipates making regulatory submissions in Japan and China in the second half of 2018, followed by submissions in the US and Europe.

The manufacture of the porous particles uses perfluorooctyl bromide (PFOB) as a processing aid, which is critical to delivering the unique aerodynamic properties of the porous particles, which ensure the efficient delivery of the medicine to the lungs. The PFOB is produced in Japan and typically contains up to 200 ppm perfluorooctyl iodide (PFOI), which is a PFOA related substance. It is not possible to source PFOB which meets the EU regulation as all synthetic routes proceed via prohibited substances, hence trace amounts inevitably remain in the PFOB.

3. PROCESS DESCRIPTION

The porous particles are constructed from a binary mixture of calcium chloride and phospholipid. The properties of the porous particles are controlled by spray drying precipitation from an emulsion of PFOB and water. The emulsion properties can affect the macroscopic size (diameter) of the porous particles and can also influence the size of the pores and the density and aerodynamic properties of the material. All of these properties are critical to the final performance of the pMDI product.

[2] COPD = Chronic obstructive pulmonary disease, which is the name for a group of lung diseases that cause breathing difficulties over time. These breathing difficulties tend to worsen over time and affect quality of life.

[3] LAMA/LABA = long-acting muscarinic antagonist/long acting β2 agonist and are the active ingredients in Bevespi Aerosphere. LAMA decreases bronchoconstriction, LABA promotes bronchodilation. PT010 also contains an inhaled corticosteroid that suppresses airway inflammation.

The emulsion properties are controlled by homogenization and intrinsic reagent properties and the spray drying parameters are carefully controlled to ensure product quality.

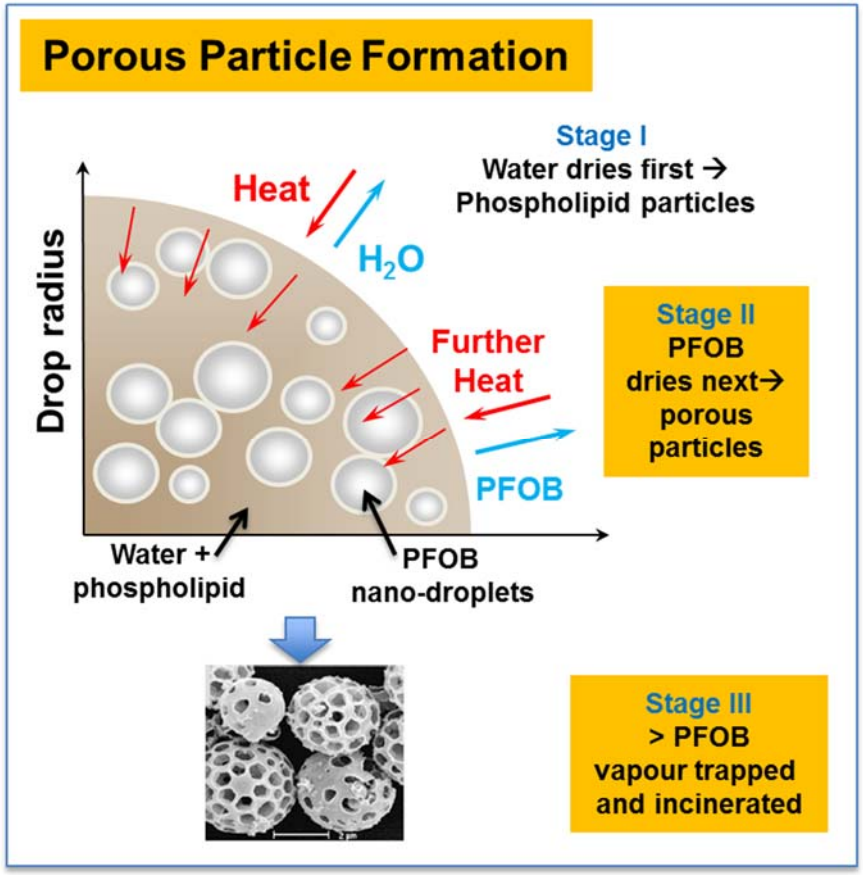
3.1 Tasks Performed by the Substance and Substance Function Data

In analysing the substance function, consideration has been given to the task performed by PFOB. The restricted substance, PFOI, represents a very low proportion (typically <200 ppm) and has no significant impact on the properties of the PFOB.

The PFOB forms a stable emulsion in water with a phospholipid ingredient that is compatible with the lung. The boiling point of PFOB is significantly greater than that of water, such that water can be preferentially spray dried and PFOB subsequently dries away with greater heat to give the well controlled macrostructure and porous properties of the porous particles. Spray drying allows for various levels of control over critical particle features such as particle size and distribution, particle density, surface energy, surface rugosity, porosity and microstructure[4].

[4] Future Med. Chem. (2011) 3 (13).

Functional Aspect	Information
Substance ID and properties	Chemical Name: 1-bromoheptandecafluorooctane / perfluorooctylbromide (PFOB) IUPAC Name: 1-bromo-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane CAS Number: 423-55-2 EC Number: 207-028-4 % (w/w): 100% (typically up to 200 ppm PFOI) Appearance: colourless liquid Classification of the substance (EC 1272/2008, Self classification): Aquatic Chronic Category 4 – H413).

Functional Aspect	Information
Description of function	PFOB is very insoluble in water and able to form an aqueous emulsion that delivers the specific properties of the porous particles that are key to the performance of the Co-suspension™ products. The boiling point of PFOB is significantly greater than water, such that water can be preferentially spray dried and PFOB subsequently dries away with greater heat to give the well controlled structure of the porous particles. The role of PFOB in the emulsion spray drying process is illustrated in the diagram below: 

Functional Aspect	Information
Process and performance constraints	The process and performance constraints are summarised as follows: • Liquid substance (PFOB melting point is 6°C) • Insoluble in water for emulsion formation (PFOB is insoluble in water) • Boiling point higher than water (PFOB boiling point is 142°C) • Boiling point amenable to spray drying away of the substance (PFOB boiling point is 142°C)
What customer requirements affect the use of the substance in this use?	The porous particles are a functional component in the next generation of AstraZeneca pMDI medicines. Aerosol medicines are very sensitive to subtle differences in the particle properties of the ingredients. The pharmaceutical industry is heavily regulated in all markets - detailed product quality attributes and specifications are registered with the authorities. Alternatives to PFOB are expected to prompt repeat clinical trials and would certainly require complex regulatory updates as the manufacturing processes and specifications are registered with the authorities. The AstraZeneca requirements are driven by the desire to maintain quality products on the market for patients and to ensure adherence to strict regulatory requirements. Updates to the registered manufacturing processes and specifications can take up to 3 years to complete in some markets outside the European Union.
Are there particular industry sector requirements or legal requirements for technical acceptability that must be met and that the function must deliver?	The PFOB is used in the manufacture of pharmaceutical products, which are closely regulated worldwide. Details of the manufacturing process are registered with the medicines/health regulators in each territory including specifications for residual PFOB. It will not be possible to substitute PFOB without re-registering the product(s) in the relevant markets. Substitution of PFOB is very likely to require clinical trials in all markets. Any change in final product performance would result in the product not meeting the required specifications.

Functional Aspect	Information
Stages to introduce an alternative substance	For the introduction of alternative substances to PFOB, the potential stages are summarised as: 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 in laboratory using representative development equipment Stage 2: Safety Assessment • Demonstration that the alternative agent is safe. Stage 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.

4. IDENTIFICATION OF POSSIBLE ALTERNATIVES TO PFOB

4.1 List of Possible Alternatives & Factors Affecting Suitability of Alternatives

The identification of possible alternatives examines 4 different scenarios.

The following scenarios are examined in turn:

- PFOB which is further purified to reduce residual levels of PFOI.
- PFOB that is manufactured via alternative synthetic routes
- Use of similar molecules to PFOB.
- Use of structurally different alternatives to PFOB

5. SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

5.1 Option 1: Reduction of PFOI levels in PFOB

5.1.1 Substance ID and Properties

Perfluorooctyl bromide, properties described in Section 3.

5.1.2 Technical Feasibility

Daikin supplies PFOB with typical residual levels of PFOI at 200 ppm. PFOI is an intermediate in the PFOB synthesis, hence trace levels remaining are inevitable. Daikin has already taken steps to optimize the process and reduce the level of PFOI.

The chemical conversion is already 99.9% efficient, which is exceptional and there is little scope to improve this conversion rate. The PFOB is distilled to purify it further, repeated distillations may have marginal impact on purity while creating alternative risks to the environment.

The PFOB currently used is already 99.98% clear of PFOI, which is exceptionally pure.
Efforts will continue to reduce levels of PFOI, but it should be recognized that the process is already very well optimized.

5.1.3 Economic Feasibility

Option 1 will be progressed on an ongoing basis. Economic feasibility does not apply to Option 1 as the limitations are mainly technical. There is a very low probability that PFOB can be manufactured to the purity demanded by the EU regulation regardless of the levels of financial investment made.

5.1.4 Reduction of Overall Risk due to Transition to the Alternative

Not applicable this option will be pursued on an ongoing basis.

5.1.5 Availability

Not applicable.

5.1.6 Conclusion on Suitability of Option 1

This option will be pursued in any case but is very unlikely to provide PFOB that meets the impurity thresholds in the European Union regulation.

5.2 Option 2: Manufacture of PFOB via Alternative Synthetic Routes

5.2.1 Substance ID and Properties

Perfluorooctyl bromide, properties described in Section 3.

5.2.2 Technical Feasibility

PFOB could be manufactured via analogous molecules such as sulfonic equivalents, but this could be considered even less desirable than the current intermediate, PFOI. It is also highlighted that the current route for PFOB uses a by-product that would otherwise need to be incinerated. There is a risk that alternative chemical routes will force the synthesis of undesired chemicals for use as intermediates, whereas the existing process consumes an inevitable by-product that is otherwise incinerated.

From a technical perspective, alternative synthetic routes to make PFOB are possible but these are less desirable than the current synthetic route.

5.2.3 Economic Feasibility

Use of alternative synthetic routes will mean identifying a supplier who is able to supply alternative intermediates that can be converted to PFOB. This will infer uncertain costs which may result in a less desirable situation than now.

5.2.4 Reduction of Overall Risk due to Transition to the Alternative

The alternative synthetic route is unlikely to reduce risks to the environment as it would synthesise PFOB via alternative chemicals that are considered even more harmful to the environment than PFOI. As such, Option 2 results in an 'undesirable alternative' status and is not favoured from a risk management perspective.

5.2.5 Availability

Not evaluated further as the alternative has been discounted on the grounds of technical feasibility.

5.2.6 Conclusion on Suitability and Availability for Alternative 2

This is not considered a candidate for substitution due to the shortfalls in technical suitability and potential risks with the use of less desirable chemical intermediate.

5.3 Option 3: Use of Similar Molecules to PFOB

5.3.1 Substance ID and Properties

Perfluorooctyl ethane. The physical properties, e.g. solubility and boiling point are comparable to PFOB.

5.3.2 Technical Feasibility

PFOB related molecules have been assessed for viability as alternative processing aids. Only the ethane analogue of PFOB (perfluorooctyl ethane) was considered suitable. This material can form stable emulsions, etc, but the following issues were identified:

- PFOE can bioaccumulate and is metabolized in the human body.
- PFOE is less stable than PFOB.
- PFOE is made from PFOI so the switch makes little sense.

5.3.3 Economic Feasibility

Not applicable as PFOE is not considered suitable from a technical perspective.

5.3.4 Reduction of Overall Risk due to Transition to the Alternative

Use of PFOE fails to eliminate any risks with use of PFOB containing trace levels of PFOI, while also introducing new risks.

5.3.5 Availability

Not applicable, this option is not viable.

5.3.6 Conclusion on Suitability and Availability for Alternative Option 3

Use of PFOE fails to address any of the current risks while introducing new risks.

5.4 Option 4: Significantly Different Processing Aids

Option 4 encompasses totally different chemicals that are structurally unrelated to PFOB.

5.4.1 Substance ID and Properties

No suitable substances have been identified to date. The physical properties, e.g. water solubility/miscibility and boiling point should be comparable to PFOB otherwise there would be a significant change to the properties of the porous particles.

Water and PFOB are used to form an emulsion for the current process, hence it is unlikely that a mixture of substances can be used as a direct alternative to PFOB.

5.4.2 Technical Feasibility

The initial development of the porous particle process evaluated a large number of alternative substances. The fluorinated substances were chosen because of the very low solubility in water and a boiling point that is significantly higher than water, but still amenable to removal by spray drying. Switching to similar molecules poses a risk of undesirable alternatives, which must be avoided for pharmaceutical products where the clinical trials are very expensive.

Significantly different molecules are likely to affect the properties of the porous particles, which would make clinical trials necessary. The following summarises the clinical trials that might be necessary:

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 in laboratory using representative development equipment

Stage 2: Safety Assessment

- Demonstration that the alternative substance is safe for human dosing.

Stage 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.
- 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.

5.4.3 Economic Feasibility

Prohibitively expensive with no guarantee of success. This could result in removal of medicines from the market (or reduced access due to supply chain constraints). If new trials were funded, this could be at the expense of clinical trials for completely new medicines.

Pharmaceutical products undergo rigorous safety and efficacy studies that can last in excess of 10 years from the date a potential new medicine is discovered. The remaining process to develop, test and validate genuine alternatives to PFOB is estimated to require at least 5 to 10 years and involve significant research and development costs. In practice, this could remove funding from potential new products or result in Bevespi Aerosphere being removed from the market.

Care must also be taken to prevent use of regrettable alternatives, particularly considering the long timescales and costs of the substitution activities.

For reference on clinical trials, the initial registration of Bevespi Aerosphere was based on two pivotal 24 week trials with a total of 3699 patients. This demonstrated superior improvements in lung function relative to its individual components and placebo.

5.4.4 Reduction of Overall Risk due to Transition to the Alternative

Minimal reduction in risk, considering that the current risk management results in very low (4g per annum) being released to the environment.

5.4.5 Availability

Not known at this stage.

5.4.6 Conclusion on Suitability and Availability for Alternative Option 4

Use of alternative agents is expected to be prohibitively expensive because this would necessitate clinical trials. Given the financial risks associated with clinical trials and the potential to limit funding for new medicines, it is more likely that the supply chain would be constrained until such time that AstraZeneca could manufacture porous particles with current risk mitigations in territories that have not imposed regulations that prevent the handling PFOB.

6. ALTERNATIVES ASSESSMENT MILESTONES

6.1 Description of Efforts Made to Identify Possible Alternatives

6.1.1 Research and Development

Research and Development activities in this area are confidential. Historical efforts and recent research show that porous particle properties will be affected by any substitution, hence confirming that clinical trials would be required to make any substitution of PFOB with alternative agents.

6.1.2 Data Searches

Data searches has been performed for substances with similar properties to PFOB. Closest matches are similar fluorinated molecules that could result in an undesirable substitution situation. While it might be possible to identify alternative chemicals which totally different structures that perform a similar function to PFOB, these do result in different properties of the porous particles.

7. OVERALL CONCLUSIONS ON SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

Alternatives to PFOB are not readily available and even if an alternative was found, any substitution is likely to require repeat clinical trials and regulatory approvals worldwide, which could take many years to complete. AstraZeneca has risk mitigation in place which ensures the use of PFOB is not harmful to the environment with less than 4 g per annum of the prohibited component (PFOI) being released to the environment. An enforced search for alternatives is not well balanced against the low environmental risks given the high cost of substitution, low probability of success, long timelines and strong risk management processes in place for use of PFOB.

In October 2017, the United Nations Environment Programme Persistent Organic Pollutants Review Committee proposed an exemption until 2036 for the use of perfluorooctane iodide in the production of perfluorooctane bromide for the purpose of manufacturing pharmaceutical products. If alternatives to PFOB are not identified, this would mean these medical products are no longer manufactured from 2036, which could result in patients struggling to manage their medical condition.

Socioeconomic Analysis for the Use of PFOB Containing PFOI at Levels up to 200 ppm

Date March 2018

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1. AIMS AND SCOPE OF THE SOCIOECONOMIC ANALYSIS

AstraZeneca is seeking an exemption from the REACH Restriction[1] on PFOA, its salts and PFOA related substances for the continued use of perfluorooctyl bromide (PFOB) at an existing Sweden manufacturing facility. The exemption request is to cover the period between the date of the entry into effect of the Restriction in July 2020 and such date that the European Union transposes a pharmaceutical use exemption from the Stockholm Convention[2]. Any time gap in the ability to manufacture at the existing Sweden facility will force AstraZeneca to transfer the manufacture outside the European Union, which would represent a permanent move of this employment and skillset outside the EU.

Use of perfluorooctyl bromide is permitted under the EU regulation, but PFOB supply and its use are threatened by the strict impurity thresholds in the regulation. PFOB is typically manufactured via the iodide analogue (perfluorooctyl iodide, PFOI) and therefore typically contains up to 200 ppm PFOI. AstraZeneca has strict risk management processes in place to ensure the use of PFOB is not a threat to the environment, which is described in the Chemical Safety Report.

The aim of this Socio-Economic Analysis (SEA) document is to provide further evidence to support the case for the authorisation of ongoing use of PFOB containing PFOI at typical levels of up to 200 ppm in the manufacture of pharmaceutical products.

2. THE USE OF PFOB IN THE MANUFACTURE OF PHARMACEUTICAL PRODUCTS

AstraZeneca has manufacturing capability in Snäckviken, Södertälje, Sweden for the production of porous particles, which are a functional component in a new generation of AstraZeneca pressurised metered-dose inhaler (pMDI) medicines. These medicines use a novel Co-Suspension™ Technology that contains low-density phospholipid porous particles. These porous particles are designed to provide a uniform suspension inside a pMDI, which is able to deliver an optimal distribution of drug crystals in the lungs for alleviation of lung diseases such as COPD[3] and asthma.

The Co-suspension™ Technology also enables consistent delivery of multiple active ingredients from a single pMDI. The technology is utilised in Bevespi Aerosphere which was approved by the FDA in April 2016 for the treatment of COPD. Bevespi Aerosphere is also under marketing review by the authorities in the European Union. There are also other AstraZeneca products currently in clinical development, such as the fixed-dose triple combination of LAMA/LABA/Inhaled corticosteroid (PT010)[4]. Positive late stage clinical results were announced for PT010 in January 2018 and

[1] Commission Regulation (EU) 2017/1000 of 13 June 2017, which will come into force in July 2020. This restricts use of any substance, mixture or article that contains greater than 1000 ppb of PFOA-related substances.

[2] In October 2017, the United Nations Environment Programme Persistent Organic Pollutants Review Committee proposed the following exemption to ensure medicine supplies are not affected by restrictions "(an exemption) For use of perfluorooctane iodide, production of perfluorooctane bromide for the purpose of manufacturing pharmaceutical products with a review for continued need for exemptions. The specific exemption should expire in any case at the latest in 2036."

[3] COPD = chronic obstructive pulmonary disease, which is the name for a group of lung conditions that cause breathingdifficulties. These breathing difficulties tend to worsen over time, which affects quality of life.

[4] LAMA/LABA = long-acting muscarinic antagonist/long acting β2 agonist and are the active ingredients in Bevespi Aerosphere. LAMA decreases bronchoconstriction, LABA promotes bronchodilation. PT010 also contains an inhaled corticosteroid that suppresses airway inflammation.

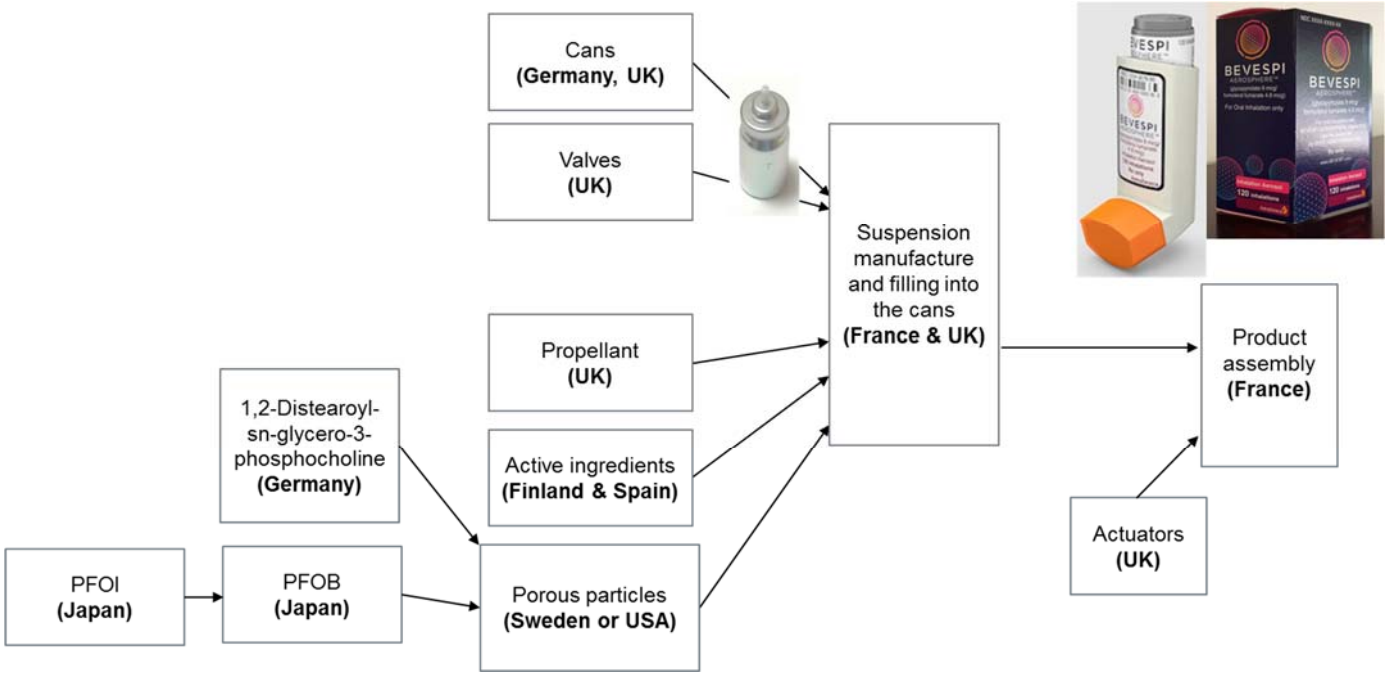
AstraZeneca anticipates making regulatory submissions in Japan and China in the second half of 2018, followed by submissions in the US and Europe.

The manufacture of the porous particles uses PFOB as a processing aid, which is critical to delivering the unique aerodynamic properties of the porous particles, which ensure the efficient delivery of the medicine to the lungs. The porous particle technology was developed in the USA and AstraZeneca maintains capability to manufacture porous particle at a small facility at Redwood City, California. AstraZeneca has also established the capability to manufacture porous particles at a large well established pharmaceuticals manufacturing facility at Snäckviken, Sweden. AstraZeneca would have to transfer activities outside the European Union if an exemption is not granted for the ongoing use of PFOB containing levels of PFOI at up to 200 ppm. Porous particle manufacture already employs approximately 20 full time equivalent staff in Sweden. Investment in a second Sweden manufacturing suite is expected if long term operations can be assured, which would generate additional employment opportunities.

The porous particles are manufactured into final pMDI products at sites in France (Dunkerque, Hauts-de-France) and the UK (Holmes Chapel, Cheshire), which provides substantial employment as described below.

Bevespi Aerosphere pMDI has already been launched as a commercial product and other products using the Co-suspension™ technology are expected to be launched in coming years. These are new products and the commercial volumes are difficult to predict, but AstraZeneca has invested €135 million in new production facilities at a site in Dunkerque, France to meet anticipated demand. The Co-suspension™ products are expected to nearly triple the Dunkerque site manufacturing capability from approx. 20 million units per annum to in excess of 60 million pMDI units per annum. It is difficult to predict the sales of the new Co-suspension™ products, but for comparison, Symbicort pMDI is already manufactured at the same Dunkerque facility and this product family including dry powder inhaled achieved sales of approximately $3 billion in 2016.

The Dunkerque site directly employs more than 450 staff and the new Co-suspension™ products are expected to drive a significant increase in employment opportunities at the site and in the associated supply chain. The overall supply chain for the Co-suspension™ products represents a significant European footprint, the supply chain map for Bevespi Aerosphere is shown below:



The total quantity of PFOB imported to AstraZeneca Sweden is expected to be less than 10 T per annum up to 2025 and the proportion of PFOI is very low (typically <200 ppm). State of the art carbon capture technology is used with proven ability to capture 99.8% of gaseous PFOB (and any low level PFOI therein). This is described in detail in the Chemical Safety Report.

A number of risk management measures (RMMs) are employed by AstraZeneca to protect human health and the environment from the potential risks of using PFOB. Based on the monitoring data presented in the CSR, the risks to human health and releases to the environment are considered to be acceptable based on the RMMs in use and the extremely low risk ratios achieved.

It may not be possible to find a suitable alternative to PFOB and the development would incur significant research and development (R&D) costs and would take 5-10 years to complete, when medicine approval times are considered. A technically viable alternative to PFOB is not available at this time, despite extensive searches for alternatives. Any change to the medicine design or manufacture will require extensive research, testing and regulatory approval, which could cost hundreds of millions of dollars across the range of products.

3. GENERAL COMMENTS ABOUT THE IMPACT OF COPD ON SOCIETY AND THE UNIQUE OFFERING OF THE CO-SUSPENSION™ PRODUCTS

COPD is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing. In the European Union, the direct medical costs for COPD are estimated to account for €38.6 billion annually[5]. COPD exacerbations account for the greatest proportion of the total COPD burden on the healthcare system. Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care, and the cost distribution changes as the disease progresses. For example, hospitalisation and ambulatory oxygen costs soar as COPD severity increases. Any estimate of direct medical expenditure for home-based care under-represents the true cost of home-based care to society, because it ignores the economic value of the care provided by family members to people with COPD.

In developing countries where there is less long term support care service, the indirect costs can be even more significant as it may require two individuals to leave the workplace the affected individual and the family member than stays home to care for their disabled relative[6].

3.1 Unique Offering of the Co-suspension™ Products

The Co-suspension™ technology enables consistent delivery of one or more different medicines from a single pressurised metered-dose inhaler (pMDI). This has already been approved in the USA for the Bevespi Aerosphere LAMA/LABA combination. Patient education can be a challenge with use of devices in respiratory healthcare, hence the combination of multiple medicines in the same product increases the probability that a patient receives the correct dose of

[5] Page 9 of the 2017 Global initiative for chronic Obstructive Lung Disease (GOLD) Report, http://goldcopd.org/

[6] Sin DD, Stafinski T, Ng YC, Bell NR, Jacobs P. The impact of chronic obstructive pulmonary disease on work loss in the United States. *Am J. Respir Crit Care Med* 2002; **165**(5): 704-707.

medicine and is able to manage their symptoms and lead a near-normal lifestyle. Note that the treatment of asthma and COPD is also anticipated with some of these therapies.

The Co-suspension™ technology is being applied to a range of AstraZeneca respiratory inhaled combination therapies currently in clinical development, such as the fixed-dose triple combination of LAMA/LABA/Inhaled corticosteroid (PT010). GOLD[7] recommends a personalized approach to COPD treatment, i.e. more choice of therapies creates a higher likelihood that a patient can identify an optimal treatment that manages their symptoms and increases the probability of a near normal lifestyle. Removing or limiting Bevespi Aerosphere from the market clearly reduces patient choice and it also removes a unique product from the market.

4. SOCIOECONOMIC ANALYSIS SCENARIOS

The 'applied for use' scenario considered by the SEA is that an exemption is granted by the European Commission for continued use of PFOB manufactured via PFOI until such time that the Stockholm exemption is transposed into European legislation or an alternative substance is developed and, validated and approved in all markets globally. Under this scenario it is expected that current R&D activities would require 5 to 10 years to confirm the suitability of a viable alternative and it is likely that any alternative found will require clinical trials.

The 'non-use' scenario considered by the SEA is that if PFOB use is not granted by the European Commission then the specified manufacture will not be possible in the existing facility in Sweden, which would reduce manufacturing activity further down the supply chain in France and the UK. It is noted that manufacture could be relocated outside of the European Union and this is discussed in the results in Section 5.

5. RESULTS OF THE SOCIOECONOMIC ANALYSIS

A combined assessment of the SEA impacts of the 'applied for use' and 'non-use' scenarios is presented below.

Impact	Applied for Use Scenario (exemption granted)	Non-use Scenario	Commentary
Human health (workers)	Adequate risk control measures mean there is no risk to the health of staff involved in the manufacture of porous particles using PFOB. This is described in the Chemical Safety Report.	No significant health benefit for workers as strong risk control measures are established at the Sweden manufacturing site. The risk measures are described in the Chemical Safety Report. It is likely the Sweden employment roles would move to the USA.	There is no health benefit for workers arising from the non-use scenario because there are adequate risk management procedures in place.

[7] GOLD (Global initiative for chronic Obstructive Lung Disease). GOLD was launched in 1997 in collaboration with the World Health Organisation and National Heart, Lung and Blood Institute, National Institutes of Health, USA.

Impact	Applied for Use Scenario (exemption granted)	Non-use Scenario	Commentary
Human health (patients)	Significant health benefit for patients as the supply of Bevespi Aerosphere is able to grow unhindered. Bevespi Aerosphere is a unique product in many markets as the only unique approved LAMA/LABA combination in a pMDI product. Patient choice; the choice of inhaler device has to be individually tailored[8], so a choice of products potentially helps to manage lung disease symptoms so that sufferers can lead a near normal lifestyle.	European Operations are halted and investment is made in the USA or other territories that are immediately aligned with the expected Stockholm Convention exemption, which allows use of PFOB manufactured via PFOI. This transfer of manufacturing capability will limit capacity which could affect the supply of Bevespi Aerosphere or new medicines in clinical trials.	Bevespi Aerosphere is approved in the USA & Canada and marketing approval is pending in numerous other markets including the European Union. Product launches may have to be delayed in some markets if AstraZeneca is forced to close the Sweden manufacturing capability. There is also a risk that clinical trial supplies would be affected if the Sweden facility is closed, thus delaying the development of new medicines for patients.
Environment	Small quantity of PFOI released to the environment (<4g per annum). This is described in more detail in the Chemical Safety Report.	Small quantity of PFOI (<4g per annum) not released to the environment. Significant materials and energy use for relocation of the production to outside of the EU. AstraZeneca has strong controls within the facility at Sweden which it may be difficult to mimic elsewhere.	Environmental impact of relocation of production is likely to be significant and may increase risk from a global perspective. The current operation is of negligible risk to the environment, regulations that force relocation of the manufacturing operations and use of alternatives to PFOB could be counter-productive.

[8] GOLD report 2017 (page 57)

Impact	Applied for Use Scenario (exemption granted)	Non-use Scenario	Commentary
Economic (for AstraZeneca)	Unhindered manufacture of next generation pMDI products in the EU with anticipated sales that reach billions of Euro over the commercial life span of the products[9]. Approximately 20 manufacturing roles are maintained in Sweden with expected new investment and employment in 2018. Expected new employment opportunities grow unhindered in France[10] and elsewhere in Europe with the associated supply chain. The Sweden inhaled manufacturing centre of excellence is fully engaged with the next generation of AstraZeneca products and this creates a Europe based centre of excellence for these products.	Loss of sales in the event that manufacturing capability does not meet commercial demand. This could have long term consequences if product launches are delayed. High equipment relocation costs and significant investment in a new production plant outside Europe would be required or significant R&D costs to develop a process with an alternative to PFOB – this may not be economically viable and would certainly interrupt the supply of medicine to patients.	The economic impacts of non- use of PFOB are very high and could affect competitiveness in the market place. Production leakage to outside of Europe is likely to occur if authorisation is not granted and this is not the intention of REACH when the risks are already adequately controlled. Ultimately this scenario forces AstraZeneca to develop expertise outside Europe in order to maintain the quality of its products – this potentially weakens the unique capability and employment opportunities in Europe.

[9] Projected sales figures are confidential, but for comparison, the Symbicort family of products reached sales of $2,989 million in 2016.

[10] The Dunkerque manufacturing site output is expected to increase from approximately 20 million units to 60 million pMDI units per annum. The site currently employs approximately 450 people directly.

Impact	Applied for Use Scenario (exemption granted)	Non-use Scenario	Commentary
Patient impact	Positive for patients; GOLD recommends a personalized approach to COPD treatment, i.e. more choice of therapies creates a higher likelihood that a patient can identify an optimal treatment that manages their symptoms and increases the probability of a near normal lifestyle. Removing or reducing availability of Bevespi from the market clearly reduces patient choice and it also removes a unique product from the market. Multiple active ingredients in the same product enables better patient compliance as they only need to use a single device to manage their condition.	AstraZeneca may not be able to supply the same volume, resulting in a lack of patient choice as AstraZeneca may have limited capability to keep up with commercial demand of the medicines. This could affect the ability of patients to manage their symptoms. It is impossible to quantify the impact of this but the economic impact runs into many multiples of the headline figure from sales of COPD treatments.	COPD is the fourth leading cause of death worldwide and the numbers are growing. COPD is a leading cause of morbidity and mortality worldwide that induces and economic and social burden that is both substantial and increasing. (page 7 of 2017 GOLD report).

Impact	Applied for Use Scenario (exemption granted)	Non-use Scenario	Commentary
Social	Continued opportunity for high skilled jobs at the manufacturing site in Sweden. Onward manufacture of the final product in France and the UK meets full commercial demand and roles are not reduced by closure of a European facility that manufactures a crucial ingredient in the final products. The products have the opportunity to grow in the market place with continued opportunity for growth for component suppliers (cans, valves, actuators, etc.) A large element of the supply chain remains in Europe.	Loss of high skilled jobs at the Sweden manufacturing site with likely movement of the roles to the USA. Significant loss of employment opportunities in France and the UK, dependent on whether porous particle manufacture can be transferred outside the EU to meet commercial demands. New jobs created outside of Europe and complexity of supply chain created.	Without an exemption, the current Sweden facility will close. There is a need to protect European manufacturing jobs from further decline. The Co-suspension™ technology is AstraZeneca's next generation of pMDI medicines. This provides the opportunity to develop a centre of excellence in Europe, which otherwise might move to the USA in order to simplify the supply chain.
Wider economic	All patients recommended by their physician for use of Bevespi (and follow on Co-suspension™ products) are able to acquire the medicine as AstraZeneca manufacturing facilities will be able to operate at full capacity. Patients are receiving a pharmaceutical product with the capability to stabilize their condition and enable a near normal standard of living.	As a medical treatment, this potentially affects the wider economic output of patients if they cannot find an alternative product that controls their symptoms. This may mean patients are unable to work.	The wider economic impacts of non-use may be significant if patients cannot manage their symptoms.

Impact	Applied for Use Scenario (exemption granted)	Non-use Scenario	Commentary
Overall Comparison	AstraZeneca risk management measures are shown to protect human health and the environment. The negative impacts of the applied for use scenario are considered to be small and manageable.	The negative impacts of the non- use scenario are considered to be high and likely to result in production leakage to non-EU countries with potential employment reductions in Sweden and reduced growth of employment in other parts of the supply chain (France, UK and elsewhere)	The SEA results are provided to support the case for use of PFOB containing 200 ppm PFOI

6. CONCLUSIONS

In the 'applied for' use scenario, AstraZeneca has demonstrated that adequate control of human health and environmental risks is achieved in the manufacturing process which uses PFOB containing up to 200 ppm PFOI. AstraZeneca will continue to apply the risk management measures set out in the Chemical Safety Report to ensure that there are no negative impacts on human health or the environment.

A viable alternative to PFOB is not available at this time. AstraZeneca considers that the negative economic, health and social impacts of the 'non-use' scenario could be significant and would result in no significant environmental benefits. The SEA results are provided to support authorisation for continued used of PFOB.

In October 2017, the United Nations Environment Programme Persistent Organic Pollutants Review Committee proposed an exemption until 2036 for the use of perfluorooctane iodide in the production of perfluorooctane bromide for the purpose of manufacturing pharmaceutical products. If alternatives to PFOB are not identified, this would mean these medical products are no longer manufactured from 2036, which could result in patients struggling to manage their medical condition.