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

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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.

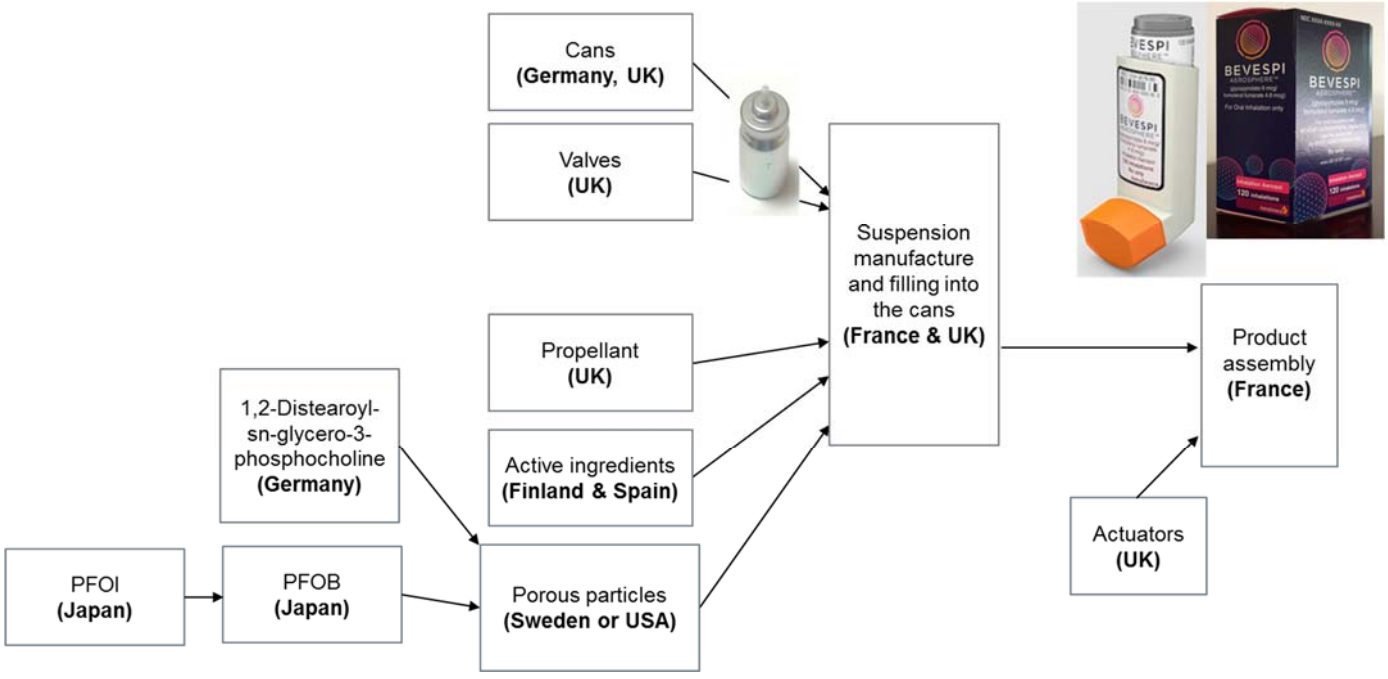
AstraZeneca anticipates making regulatory submissions in Japan and China in the second half of 2018, followed by submissions in the US and Europe.

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.