Open Letter from EFPIA, AESGP and EGA Addressing the Public Debate Regarding Pharmaceuticals in the Environment, Antimicrobial Resistance and the Manufacturing Aspect

To whom it may concern,

EFPIA, AESGP and EGA, representing the R&D, non-prescription and generic and biosimilar manufacturers in Europe, have actively been engaged in the public debate on pharmaceuticals in the environment (PIE). On 10th December, industry participated in a dialogue at the European Parliament at an event the intention of which was to bring together different stakeholders and find solutions. This letter outlines the action our industries have undertaken to address the manufacturing aspect of this important issue of PIE and the potential for the emergence of antimicrobial resistance that may be derived from it.

The manufacturing supply chain for medicines has become increasingly global. Due to a variety of factors, the sourcing of active ingredients of medicines has shifted from the US and Europe to emerging markets – particularly India and China – over the past 20 years.

Our industries are conscious that environmental and water legislation in non-EU countries may not always be as stringent or enforced as strictly as in the EU. Nevertheless, many companies apply the same high standards at all their manufacturing sites across the globe, and require suppliers and sub-contractors to apply them as well.

Problems may arise where unacceptable levels of active ingredients can be found in wastewater and drinking water due to manufacturing discharges. Manufacturing effluents only account for 2% pharmaceuticals found in the environment in Europe[1], although this may differ globally. In Europe, the other 98% arises mainly from human use (body metabolises the drugs) or when pharmaceuticals are disposed of inappropriately.

The pharmaceutical industry has in place a series of ongoing initiatives aimed at supporting suppliers to operate consistently in line with industry expectations for environmental management: the Pharmaceutical Supply Chain Initiative (PSCI), is one example. The Pharmaceutical Industry Principles for Responsible Supply Chain Management[2] are well known and applied beyond the listed PSCI members.

Moreover, the European industry has developed an Eco-Pharmaco-Stewardship (EPS) framework that applies widely-accepted principles of product stewardship. The EPS initiative is supported by three pillars, which have been identified as the initial key areas of focus for the pharmaceutical industry:

Pillar 1 – IMI iPIE project: the identification of the potential environmental risks of existing and new active pharmaceutical ingredients (API) through intelligent and targeted assessment strategies.

The European pharmaceutical industry has initiated a project under the Innovative Medicines Initiative (IMI) together with the European Commission (EC) and academia. The project will employ all available scientific knowledge to develop tools and assays to prioritise and identify the pivotal areas where more data would

[1] BIO Intelligence Service, 2013
[2] PSCI: http://pscinitiative.org/home

strengthen the understanding of the potential risk from medicinal products in use today, thereby enabling the most efficient and effective use of resources. We anticipate that the output may also be employed to screen new active pharmaceutical ingredients in development and to target environmental testing needs.

Pillar 2 – Manufacturing effluents management: the compilation of best industry practices enabling manufacturers to minimise risks to the environment.
For the most part, the processes used to manufacture medicinal products are largely similar wherever they may be used across the world. It therefore follows that potential losses into the environment from manufacturing facilities should equally be controllable. However, this assumes that both a good understanding of the risk to the environment, and the knowledge required to limit losses, uniformly are available.

In an industry-wide effort, experts from several major manufacturers have shared experiences and developed a "maturity ladder" and associated guidance in order to promote an enhanced understanding of the existing methods and the potential need for specific methodologies relative to the potential environmental risk posed by APIs and/or manufactured medicinal products. Manufacturing companies are encouraged to exchange practices in further developing their level of effluent control systems. A recent publication[3] on a risk-based approach to managing manufacturing effluents illustrates the efforts undertaken in this area.

Pillar 3 – extended ERA: the refinement of the existing environmental risk assessment (ERA) process in the post-approval phase for medicinal products to ensure that they remain up-to-date and relevant.
An important cornerstone of EPS is a refined Environmental Risk Assessment (ERA) process, extending beyond marketing authorisation.

The ERA of a medicinal product is undertaken currently by companies either as part of a new marketing authorisation or when an increase in the environmental exposure of that product is expected, e.g. with the approval of a new indication or the inclusion of a new patient population. ERA must be performed to evaluate potential risks of medicines to the environment and to ensure adequate precautions are taken in cases where specific risks are identified. The extended ERA (eERA) includes provisions to:

(i) Adjust exposure predictions as usage figures become available to better reflect reality, including all products with the same API; and
(ii) Reconsider the effects profile, as relevant and reliable laboratory findings and/or observations in the field linked to an adverse outcome become available.

A further element of the industry work on minimising environmental exposure to medicines is a Europe-wide collaborative project[4] on the **correct disposal of unused and expired medicines,** which is intended to address the potential impact of our products at the disposal phase.

Specifically in relation to antimicrobial resistance, EFPIA, EGA and AESGP support immediate action and global solidarity when it comes to the problem of AMR. Recent recognition of the scale of the problem with regard to public health is very welcome. The

industry has committed itself to promoting the responsible use of antibiotics. For new antibiotics we need to find a model that stimulates innovation without incentivising bigger sales volumes. Industry therefore supports measures to improve stewardship: whatever emerges from our research pipeline needs to be managed responsibly.

Supporting global stocktaking on progress – including on global surveillance, coordination and priority-setting – is therefore of the utmost importance. Given the delays in developing new anti-infectives, we must be conscious from a public health perspective of the need to preserve the currently available anti-infectives on the market, which are essential to provide healthcare professionals with options to treat patients.

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[3] Caldwell et al, 2015:
http://onlinelibrary.wiley.com/store/10.1002/etc.3163/asset/etc3163.pdf?v=1&t=ii0enpri&s=d300459741db37f584ca2a40630ac4a683bdc9b6
[4] www.medsdisposal.eu

In addition, Europe must be more conscious of its over-reliance on foreign manufacturers, bearing in mind that major shortages have narrowly been averted thanks to industry efforts alone. Most importantly, tackling the threat of AMR requires a comprehensive and collaborative response involving key healthcare stakeholders: government; industry; healthcare providers; and patients. Better prescribing habits, more appropriate diagnosis, improved techniques in hospital settings (ie. use of IV catheters) are all immediately necessary to reduce the risk of AMR for patients. Success will only come through a sustained and unwavering commitment from all stakeholders involved.

The pharmaceutical industry is committed to delivering to the highest possible standards. We take seriously any negative environmental impacts that our products and manufacturing might have. We are ready to work with governments, regulators and international organisations to raise standards, while ensuring supplies of life-saving medicines remain available to European patients. The challenge that lies ahead will be to convince all partners to move in the same direction.

Learn more about Eco-Pharmaco-Stewardship and recent activities related to PIE initiated by the European-based pharmaceutical industry associations:

- **Eco-Pharmaco-Stewardship:**
    - AESGP: http://www.aesgp.eu/media/cms_page_media/68/eps-core-V9.compressed.pdf
    - EGA: http://www.egagenerics.com/index.php/publications/environment
    - EFPIA: http://www.efpia.eu/documents/164/61/Eco-Pharmaco-Stewardship-EPS-A-holistic-environmental-risk-management-program
- **Medsdisposal campaign:** http://www.efpia.eu/mediaroom/270/43/Social-Media-Campaign-Launched-to-Raise-Awareness-about-Medicines-Disposal
- **Relevant IMI projects:**
    - Chem21: http://www.imi.europa.eu/content/chem21
    - iPIE: http://www.imi.europa.eu/content/ipie
    - ND4BB: http://www.imi.europa.eu/content/nd4bb
- **Blog**: http://pharmaviews.eu/pharmaceuticals-in-the-environment-lets-face-the-concerns-together/
- **Blog:** http://pharmaviews.eu/finding-solutions-together-efpia-and-health-care-without-harm-meet-to-discuss-pharmaceuticals-in-the-environment/
- **Event report:** http://www.efpia.eu/uploads/Final_EFPIA_-_HCWH_Report_on_joint_Debate_on_Pharmaceuticals_in_the_Environment.pdf