IPEC Europe and IPEC-Americas comment on
ECHA Annex XV Restriction Report "intentionally added microplastics"

IPEC-Americas and IPEC Europe (IPEC) welcome the opportunity to comment on the proposed restriction on intentionally added microplastics. IPEC-Americas and IPEC Europe are non-profit associations representing producers, distributors and users of pharmaceutical excipients offering a forum to exchange good practices and develop harmonised standards for pharmaceutical excipients. Goals include to continuously promote and achieve worldwide acceptance and use of IPEC developed guidelines as a means of improving and ensuring quality, safety, and functionality of pharmaceutical excipients.

Article 1 (1) (a) 3b. Directive 2011/62/EU on falsified medicinal products defines an excipient as any constituent of a medicinal product other than the active substance and the packaging material.

Polymers which may be used as pharmaceutical excipients in medicines to impart a given functionality, for example, to control the release of an active ingredient. IPEC's comments in this document are related to the broad characterization of excipients used in controlled release medicinal products as microplastics which is not accurate. Additionally, as their use is not exclusive to pharmaceutical applications, IPEC monitors activities in related sectors to assess any indirect consequences for their use in medicines. Restrictions in one sector could potentially lead to their extrapolation to the healthcare field with consequent temporary or permanent withdrawal of useful medicinal products from the market while alternatives are developed, if this is possible. Accordingly, IPEC would like to make the comments provided below on this draft Annex.

General Concerns

Proportionality

The amount of intentionally added "microplastics" compared to the amount of "microplastics" resulting from decomposed plastic articles and plastic waste found in the environment is negligible. The impact of a restriction of intentionally added "microplastic" on the overall amount of "microplastics" emitted into the environment is likewise very small, but has significant consequences for certain industries. In particular, pharmaceutical applications represent approximately 2.7% of the total amount of intentionally added "microplastic". The estimated cost of implementing this restriction would amount up to 9.4 billion Euro (three times the cost of the entire registration of all substances under REACH) to tackle an estimated 0.2% of the total contribution of plastic waste. From a risk perspective, this would seem to be disproportionate and IPEC would suggest that a narrower scope focussing on uses that are identified to be of high risk would be more appropriate.

Reporting and Labelling Requirements

Although pharmaceutical applications are derogated from a ban, if the reporting and labelling requirements are implemented for medicinal products, this is likely to raise significant concerns and confusion within the patient population. Where labelling indicates that the medicinal product contains plastic, this would be presumed to present additional risk to the patients and would misrepresent the extensive nonclinical and clinical evaluations undertaken on the medicinal product and its components before a marketing authorisation is granted.

While the responsibility for reporting requirements lies with medicinal product manufacturers, the reporting process would place a significant burden on both medicinal product and excipient manufacturers. Multiple requests for information across the supply chain could result which

also may compromise Intellectual Property protection. In view of the high investment and protracted development costs associated with such excipients and medicinal products, this is a matter of concern. Based on information presented by ECHA, disclosure of confidential information of the following types could include:

a) Identity of polymer used
b) Description of the use of the microplastic
c) Quantity of microplastic used in previous year
d) The quantity of microplastic released to the environment (estimated or measured)

IPEC therefore submits to ECHA that the labelling and reporting should not apply to polymers that do not retain the microplastics characteristics when discharged into the environment. Language in derogation 5b refers to substances or mixtures containing microplastic where the physical properties of the microplastic are permanently modified when the substance or mixture is used, such that the polymers no longer fulfil the meaning of a microplastic. Exemptions in p. 3 apply to polymers that given their characteristics, biodegrade and therefore "cease to exist". As the proposed restriction is focused on the uncontrolled release of microplastic particles into the environment, IPEC would assert that polymers under 5b should qualify for an exemption in paragraph 3, as they effectively cease to exist as a microplastic particle at the point of release into the environment.

In conclusion, polymers that are transformed along the production process or excipients that no longer fit the definition of a microplastic once the medicinal product is excreted into the environment, should be exempt from reporting and labelling obligations.

Definition of "microplastic"

Criteria to classify materials as "microplastics" remain unclear. For instance, the solubility of a material that determines whether a substance retains a particle shape in the environment or not is not adequately addressed.

In 1.2.2.1 Proposal for a regulatory definition of a microplastic under REACH it is stated that "*The Dossier Submitter has not interpreted the term 'microplastic' in a strictly semantic sense, but rather considers that the term is representative of small, typically microscopic, synthetic polymer particles that resist (bio)degradation.*" Many synthetic, non-biodegradable polymers excipients are excreted with the faeces as film particles, or polymer liquid gels that take up water in substantial quantities. These would be consistent with the properties of hydrogels and swollen polymers described in REACH Section B.1.1.9.4 where the gels lose their particulate form. ECHA's assumption that all polymers used as coatings or in control release applications retain their solid state although the physical structure changes are not accurate.

Emission of microplastic from medicinal products

It is assumed that 100% of the ingested microplastics are excreted from the body through the faeces as solids (microplastics) and impact the environment. However, many excipients like carbomers absorb water and transform into a liquid gel composed of >95% water, similar to the superabsorbent polymers (SAP) mentioned in the Annex to the Annex B1.1.9.4: they do not retain shape in any dimension and are not solids. Therefore, IPEC considers the 1,400 tonnes microplastic / year resulting from medicinal use to be an overestimate.

IPEC would support that a better approach to address risks of environmental issues related to medicinal products could be adapted from Article 8c of Directive 2008/105/EC aka Water Framework Directive (amended by Directive 2013/39/EU). Here, the European Commission is obliged to develop a strategic approach to water pollution from pharmaceutical substances. It is also required to follow up, where appropriate, with proposals for measures to be taken at EU and/or national level, to address the possible environmental impact.

Comments on the socio-economic impacts of the proposed restriction on medicinal products

Inclusion of medicinal products in the scope of REACH restriction is not justified as the analysis does not sufficiently address the fact that the benefits to patients can outweigh any perceived risks. The average estimated annual releases from controlled release medicinal product is estimated to be 1,400 tonnes / year which is likely to be an overestimate as explained above. This amounts to an approximate 1% of total releases of microplastics that are not intentionally added and an approximate 5% of the intentionally added microplastics releases based on current ECHA estimates. The contribution from medicinal products is likely to be much lower once a scientific assessment is conducted on the amount of drug ingredients that may fall under the microplastic definition.

The volume share of microplastic in medicinal product (synthetic polymeric excipients) and medical devices is very small compared (according to Figure 10 < 4%) to all other applications. However, such materials are not exclusive to pharmaceutical applications: the manufacturers of polymeric excipients are in many cases the same companies that manufacture coatings and raw materials for all other uses. If these applications are restricted and will be banned in the future, this could impact the availability of polymeric excipients for use in medicinal products for the following reasons:

a) Prices for monomers could increase, because they will no longer be available in such quantities and lose their commodity status.
b) The manufacturers of polymers may have to restructure their business and consider giving up the production of synthetic polymers.

Replacing pharmaceutical excipients that are "microplastics" according the restriction proposal.

Although the intent of replacing synthetic, non-biodegradable polymers by excipients that are fully biodegradable is commendable, it must be noted that the functionality of many pharmaceutical excipients is directly linked to their physicochemical properties, such as their polymeric nature, particle size, particle shape and (in)solubility in aqueous media.

Many of pharmaceutical excipients that are considered microplastics according to the restriction proposal have been developed because there were no natural alternatives that provided the required functionality, such as controlled drug release, enteric coatings, taste masking, compressibility of tabletting mixtures.

Developing new chemical entities (referred to as "Novel Excipients" in the pharmaceutical industry) with the same functionality and delivering the same bioavailability of the active ingredient is challenging, if not impossible.

In addition, it must be considered that the time frame from development of a novel excipients to approval for use in drug formulations by health authorities usually takes approximately 10-15 years. Replacing of all currently used, and approved excipients could take decades. All costs related to research (development, pre-clinical and clinical evaluation of the excipient safety profile, environmental risk assessments etc.) would need to be considered in the socio-economic impact analysis, which at this stage, does not appear to have been studied.

Collectively, therefore such a restriction could lead to the unintended consequence of at worst, product withdrawals or at a minimum, drug shortages while alternatives are developed, if this is possible. There is potential for major price increases for medicinal products formulated with synthetic polymers which could therefore contribute to a major burden to EU health insurance systems.

I recommend a concluding statement. In conclusion, IPEC requests ECHA to review the information presented above and consider exclusion and/or refinement of the restriction

proposal as it applies to medicinal products. IPEC would be happy to provide any additional information or clarification to ECHA.

Initially created in 1992, IPEC Europe is a non-profit European association representing producers, distributors and users of pharmaceutical excipients. IPEC Europe offers a unique forum to exchange good practices and develop harmonised standards for pharmaceutical excipients striving to continuously promote and achieve worldwide acceptance and use of the IPEC developed guidelines as a means of improving and ensuring quality, safety, and functionality of pharmaceutical excipients.

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