

Integration of the Essential Use Concept into REACH – Key Considerations Pertaining to the Manufacture of Pharmaceuticals

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Chemicals are essential in the development and delivery of innovative and high-quality pharmaceuticals. In the recent EU Industrial Strategy¹, pharmaceutical manufacturing is highlighted as a priority sector in the context of the open strategic autonomy. The Pharmaceutical sector will continue with innovative efforts to de-carbonise and reduce the environmental footprint of manufacturing processes in the context of the Green Deal and the EU industrial strategy.

As a key stakeholder, EFPIA welcomes the opportunity to engage with the Commission on the introduction of the Essential Use concept as proposed in the chemical sustainability strategy. The implementation of the Essential Use concept into REACH must take into account the features of the pharmaceutical industry in order to secure legal certainty, global competitiveness and production of medicines in Europe. This will require multi-agency (ECHA, EMA, DG SANTE etc.) engagement by the Commission to ensure that the adaptation of the Essential Use concept does not have any adverse impact on the reliability and robustness of medicinal product supply chains.

When considering the Essential Use concept in the context of the REACH Authorisation and Restriction process, a distinction is made between the industrial use of chemicals in the manufacture of pharmaceuticals and the subsequent use of these pharmaceuticals by patients (see *Figure 1*).

Industrial Use of Chemicals in the Manufacture of Pharmaceuticals

Some chemicals or specified raw materials used in the manufacture of pharmaceuticals are or will be designated as SVHCs (substance of very high concern). There will be occasions when there are no feasible alternatives to a SVHC, and it will be necessary to file an Authorisation Application to ensure continued supply of medicines to patients. EFPIA welcomes the Commission proposal in the Competent Authorities for REACH and CLP (CARACAL) paper (CA/61/2020) illustrating how the Essential Use Concept could make the evaluation of authorisation applications more efficient. However, the terms and conditions of a medicinal products authorisation need due consideration when defining any essentiality criteria for this purpose.

A point of legality – the terms and conditions of medicinal products marketing authorisation

A Marketing Authorisation holder cannot place a medicinal product on the market unless specified raw materials are used as per the conditions outlined in the license granted by the EMA (or national health authority). Therefore, the use of these specified raw materials in a pharmaceutical manufacturing process are essential to the continued supply of medicinal product to patients. Use is considered

¹ <https://ec.europa.eu/info/sites/default/files/communication-new-industrial-strategy.pdf>

essential up until the EMA (or National Health Authority) approves any Type II variation of the existing marketing authorisation, supporting a process change to replace any of these specified raw materials. The timescale for transitioning to alternatives is significant. Key considerations are the time taken to generate the required data to support the process change and then obtain regulatory approval from the EMA. The pharmaceutical sector also supplies medicinal products to global markets outside the EU. Post approval changes by some global health authorities outside the EU can take longer.

Figure 1: Applicability of REACH Title VII (Authorisation) and Title VIII (Restriction) to Pharmaceuticals

	REACH Title VII - Authorisation	REACH Title VIII - Restriction
1. Industrial Use of Chemicals in Manufacture of Pharmaceuticals: <ul style="list-style-type: none"> Raw material used in the manufacture of a medicinal product¹ Transported intermediate² used in manufacture of an active substance³ of a medicinal product On-site intermediate used in manufacture of an active substance of a medicinal product Active substance and excipients used in manufacture of a medicinal product 	<p>In scope</p> <p>Exempt</p> <p>Exempt⁴</p> <p>Exempt⁶</p>	<p>In scope unless a derogation in place</p> <p>In scope unless a derogation in place</p> <p>Exempt⁵</p> <p>In scope unless a derogation in place</p>
2. Use of Medicinal Products by Patients	Exempt	Exempt

The proposed Essential Use Concept goes beyond REACH – Impact on other regulatory fora e.g. medicinal products needs due consideration by the Commission

Explanatory Notes:

- Medicinal product as defined in Directive 2001/83/EC - Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.
- In this context, an intermediate as defined in Article 3(15) of REACH, may include a raw material, starting material or pharmaceutical ingredient which are further defined in ICH guidelines.
- An active substance or API (Active pharmaceutical ingredient), is intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. [ICH Guideline Q7]
- Article 2(8)(b) of REACH - intermediates, as defined in Article 3(15), are exempt from Authorisation
- Article 68(1) of REACH - restrictions in general do not apply to on-site intermediates
- Article 2(5)(a) of REACH – Active substances and excipients used in the manufacture medicinal products are exempt from Authorisation

The REACH Authorisation application process must function in a more agile and efficient way

The re-evaluation of the Authorisation process must be expanded beyond the 2018 REACH Review, which considers a form of simplified applications for low volume use and legacy spare parts.

There is a need for a more flexible and agile authorisation procedure, particularly if it is necessary to file a submission after the latest application date has expired. This necessity could arise during accelerated process development of innovative and promising therapies. The present authorisation application process has the potential to hinder the accelerated development of a pharmaceutical manufacturing process which can take place in a 6-18 month timeframe. ECHA opinion and granting

of Authorisation by the Commission takes a minimum of 24 months. The generic exemption for scientific research and development, is currently capped at 1000kg / year. Faced with accelerated drug development timelines, rather than deprive patients of innovative therapies it will be necessary to locate the manufacturing process in a facility outside the EU.

Unlike Article 55(1) of the Biocidal Product Regulations, there is no derogation in REACH to facilitate the use of a SVHC in situations where there is a danger to public health. One of the major learnings from the COVID-19 pandemic, is that a legal text change is required to enable the use of a SVHC past the latest application date to facilitate the supply of medicines for the protection of public health.

Use of Medicinal Products by Patients

Essential use and essential medicines are not the same thing

The terms essential use and essential medicines should not be used interchangeably. “Essential Use” has not yet been defined in REACH, either in regulation or associated guidance. Whilst the WHO defines essential medicines as those that satisfy the priority health care needs of the population and are selected with regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, as well as comparative costs and cost-effectiveness².

Discussions at CARACAL highlight the complexity of the Essential Use Concept³. Some member states appear to endorse a proposed categorisation criteria⁴, which implies that a pharmaceutical must have life-saving function in order to be deemed “essential”. To link the concept of “Essential Use” to therapeutic area of medicinal product is concerning and could have unintended consequences. Medicines intended for treatment of debilitating, life-changing conditions e.g. neurodegeneration, chronic pain etc. could be deemed to be “non-essential”.

Essentiality criteria must be defined by policy makers with input from all stakeholder groups

We agree with the Commission that essentiality criteria cannot be defined by industry alone, since each sector will be heavily biased⁵. Decision making in the regulatory arena to determine what medicines are essential falls to WHO, governments, health care providers, EMA and national health authorities etc.

The pharmaceutical sector is a key stakeholder in the delivery of reliable and robust supply chains of medicines⁶. EFPIA will help policy makers better understand the vulnerabilities in chemicals management legislation which could hinder the utilisation of EU manufacturing capacities to adapt and support the production of medicines.

Ultimately, the Commission through multi-agency engagement (ECHA, EMA, DG SANTE etc.) must ensure that the chemical sustainability strategy does not have any adverse impact on the reliability and robustness of medicinal product supply chains.

² Serafini M *et al* (2020) *Essential Medicinal Chemistry of Essential Medicines* J. Med. Chem. 2020, 63, 10170-10187

³ Commission Document CS/14/2021 (38th Meeting of Competent Authorities for REACH and CLP) – Essential Uses – Summary of and Response to Comments to CA-61-2020

⁴ Cousins, Ian T., et al. “The concept of essential use for determining when uses of PFASs can be phased out.” *Environmental Science: Processes & Impacts* 21.11 (2019): 1803-1815

⁵ Commission Document CS/14/2021 (38th Meeting of Competent Authorities for REACH and CLP) – Essential Uses – Summary of and Response to Comments to CA-61-2020

⁶ https://ec.europa.eu/health/sites/default/files/human-use/docs/pharma-strategy_report_en.pdf