By mail and e-mail

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Brussels, 26 July 2018

Dear Mr D'Acunto and dear Dr Rys,

Subject: Article 117 of Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices, as it amends Directive 2001/83/EC on the Community code relating to medicinal products for human use

Several leading combination products industry groups have collaborated in the development of this letter. Collectively, this letter reflects the position of the following groups:

- European Federation of Pharmaceutical Industries and Associates (EFPIA)
- European Biopharmaceutical Enterprises (EBE)
- MedTech Europe
- International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)
- Medtech & Pharma Platform (MPP)
- Combination Products Coalition (CPC)
- Medicines for Europe
- Association of the European Self-Medication Industry (AESGP)
- European Association for Bioindustries (EuropaBio)

More information on each of these industry groups is available in the appendix.

We are considering the potential impact of Article 117 (subparagraph 2) of the Medical Devices Regulation (MDR), Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices, regarding Notified Body (NB) opinion on a non CE-marked device constituent of a single integral medicinal product[1] . More than one year into the transition period for the new MDR, it is not clear how this legal

[1] Note on terminology: This letter refers specifically to single integral products, as described in the second paragraph of Article 1 (9) of the Medical Devices Regulation (EU) 2017/745 and European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure, Section 3.3.11.1. The more general term 'Drug-Device Combination' (DDC) products is also used, as per EMA Concept paper on

requirement will be implemented and there remains much uncertainty across industry (medical devices and pharmaceuticals). We would like to highlight the important areas which we believe should be addressed as a priority and request that the Commission brings all concerned stakeholders together, e.g. medicines and medical device regulators, NBs, and industry, to progress towards a rapid, workable solution for all parties involved.

There are increasing numbers of drug-device combination products (DDC), regulated as medicinal products, in development and on the market, including established products such as inhaled and nasal products, injectable products and other drug delivery systems. Biological products (e.g. monoclonal antibodies) represent a significant number of these DDC products. These DDC products offer the advantages of reduced dosing frequency, greater patient convenience and reduced hospital resource, by enabling home treatment; with this come emerging technologies including further utilisation of digital health connectivity.

Due to the nature of DDC products and, in some instances, (for example inhaled and nasal products) due to a change in classification based on new rules within the MDR, it is understood that most of these products will now require a NB opinion for new medicinal products marketing authorisation applications (MAA) from May 2020 onwards, per Article 117, for non-CE marked devices.

Whilst the current regulatory pathway and review approach have allowed review and approval of safe and effective established DDC products in the context of MAA and variations (including line extensions), there is a concern that the new legislation may add complexity, especially for more advanced technology products, which may cause delays for patient access to DDC products and, more broadly, slow down innovation.

With less than two years remaining for the transition period for the new MDR, the expectations, procedures, timings and products in scope of Article 117 are still unclear. As these products will be regulated under the amended Medicinal Products Directive 2001/83/EC, industry would welcome clarification on how the Commission, EMA and national CAs, and NBs will work together to implement the legislation.

The following sections outline the industry questions for which we seek answers, propose cooperation between industry and regulators and request a multi-stakeholder meeting.

In support of our requests, several key reference documents are provided as attachments for your consideration. We look forward to further engagement on this important topic for our industry.

Industry questions

Companies preparing for MAA filings in 2020 have been advised by CAs to contact NBs as soon as possible. However, it is uncertain how many NBs will be accredited and designated to offer this service, which NB codes will be applicable and whether sufficient NB resources will be available to manage an expected high number of applications. Additionally, information has not been published yet on how CAs (national and EMA) will co-ordinate with NBs to define requirements for regulatory submissions and review them.

This uncertainty raises several key questions within the industry:

- Will the NB review include information and data from the full DDC product, the device constituent with some aspects of the drug-device interactions or the device constituent only? There is a risk of significant overlap and a need for transparency in CA and NB review remit. Therefore, unambiguously defining their respective remits must be a priority.

developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product and EBE Reflection paper. 'Combination products are mentioned in recital 10 of the MDR: 'Products which combine a medicinal product or substance and a medical device are regulated either under this Regulation or under Directive 2001/83/EC of the European Parliament and of the Council. (3) The two legislative acts should ensure appropriate interaction in terms of consultations during pre-market assessment, and of exchange of information in the context of vigilance activities involving such combination products. For medicinal products that integrate a medical device part, compliance with the general safety and performance requirements laid down in this Regulation for the device part should be adequately assessed in the context of the marketing authorisation for such medicinal products. Directive 2001/83/EC should therefore be amended'. In this letter "constituent" will be interchangeable with "part" as used in Art 1(8) and Art 1 (9).

- Is the requirement restricted to demonstrating compliance with relevant parts of Annex I of the MDR?
- Will there be flexibility for the final NB opinion to be provided during MAA review (for example by Day 120 for MAA reviewed through the centralised procedure)?
- How will currently authorised and marketed products in any way be affected by the new requirement?
- Would a risk-based NB review be possible for well-established drug delivery technologies used in DDC products?
- Will line extensions for new indication or type II variations involving a new or modified DDC product be in scope for the NB review?
- Will there be enough appropriately designated NBs to accommodate the added workload of reviewing DDC products?

Most of these key questions were discussed at the Biologics Working Party Interested Parties meeting held on 20 June 2018 at the EMA in London (see EBE slide deck provided as attachment 1); the meeting minutes are awaited. Whereas the EMA gave some preliminary feedback, it was also mentioned those questions would formally be addressed at the Commission level.

A more comprehensive list of questions, challenges and opportunities related to Article 117 implementation are outlined in two recent EBE-EFPIA reflection papers. The issues and solutions suggested in those reflection papers are also outlined and further discussed in the attached TOPRA (The Organisation for Professionals in Regulatory Affairs) Regulatory Rapporteur articles. Those articles additionally address further potential issues around Article 117. The EBE-EFPIA reflection papers and the Regulatory Rapporteur articles are provided as attachments 2 to 5.

Regulators and industry co-operation

The Competent Authorities Medical Device (CAMD) implementation roadmap has designated combination products implementation activities as low or medium priorities:

- Section 2.5: 'Guidance for combination products and companion diagnostics (CDx) around appropriate level of interaction with relevant authorities' is a LOW priority only, with a number of different parties involved including EMA, Notified Body Operations Group (NBOG), Classification and Borderline working group (WG) and European Directorate for the Quality of Medicines (EDQM).
- Section 3.4: 'Guidance on different routes for conformity assessment, including communication channels between Notified Bodies (NBs) and Competent Authorities (CAs) on Companion Diagnostics (CDx) and other consultations', led by NBOG, NB Med and In-Vitro Diagnostics Working Group (IVDWG) is a MEDIUM priority only.

The low to medium priority is raising concerns, given the number of challenges that industry highlighted above. However, it is noted in section 8.2 of the roadmap that new stakeholders and a mechanism for engagement with them are to be identified. Industry would welcome clarification of how to participate in this engagement as a stakeholder.

Industry has extensive experience with DDC product development and global regulatory requirements. In this regard, EFPIA and EBE have developed a pragmatic proposal for an optional parallel NB/CA review process, consistent with the scope of Article 117. This proposed parallel review process was inspired by EMA procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of NBs in accordance with Article 9 of Regulation (EC) No 1394/2007. This proposal is described in the EBE-EFPIA reflection paper on Article 117, included as attachment 2 and could be a discussion point at a multi stakeholder meeting (see below).

In addition, it is appreciated that the EMA CHMP Quality and Biologics Working Parties (QWP/BWP) are developing a guideline on 'Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product'. As an industry, we understand that the draft is due for publication in Q4 2018 and we look forward to reviewing and commenting on this draft guideline.

Proposal for a multi-stakeholder meeting

As a cross-industry group with significant experience and expertise in combination products development and licensure, we are interested to work with all key stakeholders – the Commission, CAMD, EMA and NBs to clarify key aspects related to the implementation of Article 117 that are critical for our business.

We suggest that a multi-stakeholder meeting or workshop would be very helpful. In view of such a meeting, we would be willing to prepare a Briefing Book providing a comprehensive list of questions with positions and constructive proposals to serve as basis for interactions.

We thank you for your consideration and we look forward to hearing from you on planned next steps. Please be so kind as to reply to Barbara Freischem (barbara@ebe-biopharma.org) who will ensure dissemination to the represented industry groups.

Yours sincerely,

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Appendix: Industry group descriptions

European Federation of Pharmaceutical Industries and Associates (EFPIA) – www.efpia.eu
The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 40 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients, new medicines that will improve health and the quality of life around the world.

European Biopharmaceutical Enterprises (EBE) – www.ebe-biopharma.eu
The European Biopharmaceutical Enterprises (EBE) represents the voice of biopharmaceutical companies of all sizes in Europe and is a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA). Established in 2000, EBE is recognised as the leading biopharmaceutical association in Europe.

MedTech Europe – www.medtecheurope.org
MedTech Europe is the European trade association representing the medical technology industries, from diagnosis to cure. We represent Diagnostics and Medical Devices manufacturers operating in Europe. MedTech Europe's mission is to make innovative medical technology available to more people, while helping healthcare systems move towards a sustainable path. MedTech Europe encourages policies that help the medical technology industry meet Europe's growing healthcare needs and expectations. It also promotes medical technology's value for Europe focusing on innovation and stakeholder relations, using economic research and data, communications, industry events and training sessions.

International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) – https://ipacrs.org/
IPAC-RS is an international association that seeks to advance the science, and especially the regulatory science, of orally inhaled and nasal drug products (OINDP) by collecting and analyzing data and conducting joint research and development projects. Our members include innovator and generic companies that develop, manufacture or market orally inhaled and nasal drug products for local and systemic treatment of a variety of debilitating diseases such as asthma, chronic obstructive pulmonary disease and diabetes. We aim to build consensus and contribute to effective regulations and standards by sharing the results of our research through conferences, technical journals, and discussions with regulatory bodies.

Medtech & Pharma Platform – www.medtech-pharma.com
The Medtech & Pharma Platform is an industry association with the aim of using the synergies between medtech and pharmaceutical industries by establishing a forum to exchange knowledge and collaborate in technology and regulatory areas, as well as to promote product development and innovation. Beyond the international annual conference that had its inaugural meeting in 2014, the association aims to further strengthen advocacy work for companies to reduce time to market for drugs, devices and combinations thereof, improve access to innovative products, better match patients' needs and expand business opportunities for both industries.

Combination Products Coalition (CPC) – http://combinationproducts.com/
The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues.

Medicines for Europe – www.medicinesforeurope.com
Medicines for Europe began over 20 years ago as the European Generics Medicines Association (EGA) with the goal of representing the emerging generic industry, and later growing to include biosimilar medicines to its portfolio. As the pharmaceutical industry and the healthcare environment within which it operates have evolved, so has our Association. Our members provide the essential medicines that European patients, healthcare professionals and healthcare systems rely on to treat the most acute and chronic diseases ailments covering a wide range of diseases from cardiovascular, to diabetes and cancer. Better access to the most effective therapies means millions more patients are getting better and living longer, while healthcare inequalities are being reduced.

AESGP - www.aesgp.eu
AESGP, the Association of the European Self-Medication Industry, is the representation of manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe. It is composed of national associations and the main multinational companies manufacturing self-care products. AESGP is the voice of more than 2000 companies operating in the consumer healthcare sector in Europe, affiliated with AESGP directly or indirectly through the national associations.

EuropaBio - www.europabio.org
EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a bio-based and zero-waste economy. Our members are involved in research, development, testing, manufacturing and commercialisation of biotechnology products and processes and have a wide range of activities: human and animal health care, diagnostics, bio-informatics, chemicals, crop protection, agriculture, food and environmental products and services. EuropaBio represents 80 corporate and associate members and bioregions, and 17 national biotechnology associations in turn representing over 1800 biotech SMEs.

Attachments

Attachment 1: EBE presentation at EMA Biologics Working Party Interested Parties meeting, June 20, 2018, London

Attachment 2: EBE Reflection Paper on "Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment", Jan 15, 2018

https://www.ebe-biopharma.eu/wp-content/uploads/2018/01/EBE-Reflection-Paper-Integrated-Drug-Device-Products-Final-15-January-2018.pdf

Attachment 3: EBE-EFPIA Reflection Paper on "An Industry Perspective on Article 117 of the EU Medical Devices Regulation and the Impact on how Medicines are Assessed" of 12 July 2018, published on 23 July.

https://www.ebe-biopharma.eu/wp-content/uploads/2018/07/EBE-EFPIA_-Reflection-paper_-Industry-Perspective-on-Art-117-of-MDR_Final_2018.07.12.pdf

Attachment 4: Article 117 of the Medical Device Regulation – An urgent need for further guidance
TOPRA Regulatory Rapporteur, May 2018

Attachment 5: Article 117 of the Medical Device Regulation – An urgent need for further guidance: Part 2
TOPRA Regulatory Rapporteur, June 2018