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Towards an EU-wide suitable regulatory framework for faecally derived, industrially manufactured medicinal products

Tue Anker Mikkelsen[1], James Roger McIlroy[2], Madeleine Mimiague[3], Alice Rouanet[4] and Luc Sterkman[5]

We read with great interest the editorial by Keller et al.,[1] reporting the need for guidance and legislation at national and European levels for human stool/faeces used for faecal microbiota transplantation (FMT). The authors of this editorial state they 'strongly believe that stool should be considered a transplant product, or be regarded equivalent in status to blood products used for transplantation or transfusion purposes'. We agree that a careful, multidisciplinary and proactive approach to the regulation of this emerging field would help prevent potentially avoidable adverse events and assure consistent efficacy.

In this context, a consortium of European-based biopharmaceutical companies has established the *Intestinal Microbiome-based Medicines European Task Group* (IMM-ETG) as a collaboration focused on creating a proposal with recommendations for a common European regulatory framework for human intestinal microbiome whole ecosystem-based medicinal products. The IMM-ETG operates under the umbrella of the Pharmabiotic Research Institute (PRI), which provides regulatory support to the IMM-ETG. The PRI is a European independent non-profit group with vast experience on the regulatory challenges arising from the drug development of microbiome-based medicinal products.

The European Commission has identified stool as a substance of human origin (SoHO).[2] Stool is composed of a heterogeneous and complex consortium of micro-organisms (bacteria, archaea, viruses, bacteriophages and fungi), human cells, water, mucus, metabolites and undigested food substances. In this sense, stool is a 'combined substance' because it contains human cells in addition to a number of other components.

Previously, the European Commission has explained[3] that the European Union Tissues and Cells Directive[4] (EUTCD) covers combined substances only when the human tissues and cells contained therein are the active components of the substance.[5] In this evaluation, the European Commission concluded the human cells contained within stool, when administered to a recipient through FMT, are not the active component of this substance and therefore are not *'intended for human application'* within the meaning of the EUTCD. In light of this, stool is not considered as falling within the scope of Directive 2004/23/EC (EUTCD) on human tissue and cell legislation. However, in reaching this conclusion, the European Commission noted that Article 168(4)(a) of the Treaty on the Functioning of the EU allows for the adoption of measures, setting high standards of quality and safety for all substances of human origin. At present, the regulation and classification of human stool intended for human application in the EU falls within the remit of each respective national competent authority.[6]

Human stool intended for empirical transplantation as defined previously[7] is currently prepared in hospital pharmacies in accordance with an individual medical prescription for an individual patient (a magistral formula) for specific cases where there is no licensed therapeutic alternative (i.e., neither a drug with a marketing authorisation nor a drug with early access authorisation for the indication).

To enable patient access beyond the small-scale production under the magistral formula/pharmacy exemption and to facilitate academic research, stool banks have been created.[8,1] These stool banks are, for the most part, operating without rigorous oversight from competent authorities and without any Good Manufacturing Practice (GMP) accreditation.

[1]Ferring Pharmaceuticals, International PharmaScience Center, Copenhagen, Denmark
[2]EnteroBiotix, Aberdeen, United Kingdom
[3]MaaT Pharma, Lyon, France
[4]Pharmabiotic Research Institute, Aude, France
[5]Caelus Health, Amsterdam, Netherlands

Corresponding author:
Alice Rouanet, Pharmabiotic Research Institute, 1 Quai vallière Appt 108 Narbonne, Aude 11100, France.
Email: alice@pharmabiotic.org

Stool, intended for therapeutic application, that is not 'manufactured using an industrial process' or 'intended to be placed on the market' (i.e., products administered within the same legal entity) could in theory be regulated under the same regulatory framework as other SoHO (blood, tissues and cells).[9] This would ensure that best practice and standards on quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution are adhered to and that inspections from competent authorities should take place.

However, as soon as stool or any other SoHO is used as a starting material for an 'industrial process', it is only the collection, procurement and testing of the starting material that is covered by the SoHO directive. The processing, preservation, storage and distribution of the stool will in this case be regulated under medicinal product regulation[2] and must comply with GMP.

In other words, the existing drug framework of Directive 2001/83/EC[10] already applies to any product derived from human stool and manufactured on a routine basis using an industrial process. The IMM-ETG is of the view that this also means any proposal to classify stool as human tissue or cells does not alter the medicinal product status if the product is industrially prepared and intended to be placed on the market, be it large-scale preparation through a stool bank or the intestinal microbiome medicinal products currently developed by members of the IMM-ETG.

Following on from this, there is also a need to define what is meant by *'industrial process'* or *'industrial manufacture'*, given these terms give the demarcation between the blood, tissue and cell, and medicinal product legislations. Nevertheless, no legal definition is provided in any of the legislative instruments, which led to differences in interpretation and the need for clarification by the European Court of Justice.[2] With reference to stool banks, the nature of the systematic manufacture in a batch-wise process on a routine basis bears the hallmarks of an 'industrial process'. Certainly, manufacture prior to identification of a patient implies this practice does not fall under the magistral formula exemption from Directive 2001/83/EC. Allowing this practice to continue unchanged in the future could provide a loophole in the regulation of large-scale entities providing products for human use.

Regulation is critical to ensure the safety of healthcare products, including those based on human stool. The existing Directive 2001/83/EC covers the use of 'industrially processed' products based on human stool, making them medicinal products. Efforts should be made to set an EU-wide harmonisation regulatory framework for this novel starting material and derived medicinal products.

ORCID iD

Tue Anker Mikkelsen https://orcid.org/0000-0001-6788-3969

References

1. Keller JJ, Vehreschild MJGT, Hvas CL, et al. On behalf of the UEG working group of the standards and guidelines initiative stool banking for FMT: Stool for fecal microbiota transplantation should be classified as a transplant product and not as a drug. *United European Gastroenterol J* 2019; 14: 1–3.
2. European Commission. *Study supporting the evaluation of the EU legislation on blood and tissues and cells. SANTE/2017/B4/010*. Final report. Available at https://op.europa.eu/en/publication-detail/-/publication/c1c3414c-ec23-11e9-9c4e-01aa75ed71a1/language-en/format-PDF/source-106664789 (2018, accessed 10 October 2019).
3. European Commission. *Directorate-General for Health and Food Safety. Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718)*. Meeting of the Competent Authorities for Tissues and Cells. Summary Report. 3–4 December 2014.
4. Directive 2004/23/EC of The European Parliament and of The Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official Journal of the European Union*, L 102, 07 April 2004.
5. Human Tissue Authority. *Regulation of faecal microbiota transplants*. Available at https://www.hta.gov.uk/policies/regulation-faecal-microbiota-transplant (2015, accessed 4 December 2019).
6. European Commission. *Directorate-General for Health and Food Safety. Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718)*. Meeting of the Competent Authorities for Tissues and Cells, Summary Minutes. 13–14 May 2019.
7. Intestinal Microbiome-based Medicines European Task Group (IMM-ETG). https://www.pharmabiotic.org/2019/05/20/imm-etg-a-new-european-initiative-for-intestinal-microbiome-medicinal-products/ (May 2019, accessed 27 June 2019).
8. Terveer EM, van Beurden YH, Goorhuis A, et al. How to: Establish and run a stool bank. *Clin Microbiol Infect* 2017; 23: 924–930.
9. European Commission. *Commission Staff Working Document. Evaluation of Union legislation on blood, tissues and cells. SWD (2019) 376 final*. Brussels. https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/swd_2019_376_en.pdf (2019, accessed 10 October 2019).
10. Directive 2001/83/EC of The European Parliament and of The Council of 6 November 2001 on the Community code relating to medicinal products for human use, Annex I, Part I, Section 3.2.1.1 (b). *Official Journal of the European Communities*, L 311, 28 November 2001.