Challenges to borderline product classification in the EU

Lincoln Tsang and *Jacqueline Mulryne* address the difficulties involved in deciding whether a borderline product is a device or medicine in light of the current legislation, guidance and case law.

Proper classification of borderline products is a key aspect of research and development because it determines how the product should be regulated and what requirements should be applied.

Incorrect classification could bring about extremely costly consequences for a company, as it may delay a product's commercial launch and, in certain cases, wrongly classified products could be withdrawn from the market. For example, a combined advanced therapy product previously marketed by Anika Therapeutics in various EU member states, such as Austria, Germany, Italy and Poland, was withdrawn this year following the adoption of the EU Regulation 1394/2007 on advanced therapy medicinal products, which seeks to regulate all tissue engineered products as medicinal products[1,2]. Similarly, electrotechnical systems and equipment that have been developed to record human brain activity were challenged in the German lower courts, and subsequently before the German highest federal court, as to whether or not they should be properly regulated as a medical device.

Judicial decisions by national and European courts, as well as guidance issued by member state competent authorities and the European Commission, have sought to clarify the proper legal test that should be applied to borderline product classification, particularly in response to new scientific developments. For example, the UK Medicines and Healthcare products Regulatory Agency in November 2012 issued an updated guide on what is a medicinal product[3].

However, the borderline between medicinal products and other consumer or healthcare products remains unclear. Scientific advances, especially in the increasing convergence of physical and biological sciences relevant to research and development, have rendered proper interpretation and application of the regulatory rules challenging. At present, where there is an element of doubt, competent authorities generally favor classifying a relevant product as a medicinal product. However, this uncritical approach to classification of borderline products is not helpful without addressing the proper legal test that should be applied.

This article discusses the borderline between medicinal products and other consumer and healthcare products – in particular medical devices – and considers whether the current legislative approach adequately addresses the fast changing world of medical technologies where the demarcation between these product types becomes increasingly blurred.

The classification of products

Under EU law, ordinarily a product cannot be regulated by more than one regulatory regime. This is commonly known as the "non-cumulative" principle based upon the established case-law of the Court of Justice of the European Union. Instead, a given product can only be classified and regulated by one of the various frameworks. In addition, Directive 2001/83/EC[4] on medicinal products (through its amendment in 2004) states that in cases of doubt, where a product may fall within the definition of a medicinal product and a product covered by other legislation, the product will be classified as medicinal. This approach presupposes that borderline products would be most appropriately regulated as medicinal products for the purpose of public health protection, but this may not be appropriate. As noted by the CJEU in *Brain Products GmbH* (Case C-219/11)[5], the regulatory regime for medical devices also aims at achieving a high level of protection of health.

Classification of borderline products is carried out by the competent authorities of the country where the product is to be marketed. National authorities are given a very wide margin of discretion to make such a case-by-case assessment. On certain occasions, authorities may arrive at different conclusions on identical products with similar characteristics. This inconsistent approach to product classification adds legal uncertainty for manufacturers, particularly of innovative products.

The classification of products is based on the definitions contained in EU-wide legislation. The starting point is the definition of a medicinal product; Article 1(2) of Directive 2001/83/EC contains the definition for a medicinal product as follows:

> *(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*
> *(b) 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 relation to medical devices, Article 1(2)(a) of Directive 93/42/EEC[6] sets out the definition of a medical device:

> *any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:*
> - *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
> - *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
> - *investigation, replacement or modification of the anatomy or of a physiological process,*
> - *control of conception,*
>
> *and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means*

The definition of medicinal products is generally explained in two parts. One part relates to an assessment of the presentational aspect, whereas the other part relates to an assessment of the functional aspect. The definition of medical devices is arguably similar, in the sense that the classification ought to take into account the positioning of the product and its intended underlying mode of action.

Principal mode of action

One criterion the courts (and national competent authorities) use to determine the classification of a product is the principal mode of action, as stated in Article 1(5)(c) of Directive 93/42/EEC: "In deciding whether a product falls under [Directive 2001/83/EC] or [Directive 93/42/EEC], particular account shall be taken of the principal mode of action of the product".

Historically, medical devices achieve their function through physical means or mechanical action, whereas medicinal products act through pharmacological, immunological or metabolic means. Medical devices can be assisted in their primary function by pharmacological, immunological or metabolic means, as long as the primary action is not achieved via these (medicinal) means.

The commission has provided a definition of pharmacological, immunological and metabolic action in its MEDDEV guidance on borderline products. For a product to elicit a pharmacological action, the commission considers[7]:

> *interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.*

The underlying mode of action has also been the focus of a number of judicial decisions. In the recent decision in Case C-308/11, *Chemische Fabrik Kreussler*[8], the CJEU gave a very broad interpretation to the concept of "pharmacological action" to cover interactions between the molecule and the body that do not involve standard receptor theory. This case concerned whether a mouthwash solution containing 0.12% of chlorhexidine, an antibacterial, and marketed as a cosmetic product in Germany, could properly be said to exert a pharmacological action. By reference to a 1994 monograph on chlorhexidine, it appears that mouthwash solutions containing 0.2% of chlorhexidine could reduce salivary bacteria and in this way, have a therapeutic or clinical effect in cases of preventing or treating gingivitis.

The CJEU ruled that the commission's MEDDEV guidance could be relied upon in assessing whether a product could be said to exert a pharmacological action. However, the concept of "pharmacological action" should be interpreted broadly to include interaction between the molecules of a substance with cellular constituents present within the user, even if these cellular constituents are not human but bacteria, viruses or parasites harboring in the human subjects. Such interaction may nevertheless have the effect of restoring, correcting or modifying physiological functions in human beings.

Neither Directive 2001/83/EC nor the MEDDEV guidance prevents this type of interaction from being considered as a relevant interaction for the purpose of assessing whether a product mediates a pharmacological action. However, the interpretation is arguably broader than is intended in the legislation.

Practical implication for borderline classification

This decision, together with previous CJEU decisions, adds a further step to the guidance on classification of borderline products:

- each product should be assessed on a case-by-case basis, taking account of the product characteristics and underlying properties (*Hecht-Pharma*[9] and *BIOS Naturprodukte*[10]);
- a product, even if it falls within the definition of a different product, must nevertheless be treated as a medicinal product if it is presented as possessing properties for the treatment or prevention of illness or disease[11];
- product characteristics should be assessed with reference to its composition, the manner in which it is used, the extent of its distribution, its familiarity to consumers and the risks which its use may entail (*BIOS Naturprodukte*);
- in particular, the court will take into account the impression that consumers are likely to form as a result of the product's presentation or the historical classification of similar products[12];
- if the product has an effect on the human body, but only has a limited capacity to restore, correct or modify physiological functions, it should not be considered as a medicinal product (*Upjohn*[13] and *Hecht-Pharma*); and
- in deciding whether a product exerts a pharmacological action, it is not necessary for there to be a direct interaction between the constituent molecule of the product and the cellular constituent of the human body; an indirect interaction may be sufficient to infer a pharmacological action (*Chemische Fabrik Kreussler*).

The future

Each of these cases represents a small step in addressing technically complex and yet commercially important borderline questions. However, each case is decided on its own facts, and the court tends towards adopting a broader interpretation of the key legislative language.

In addition, the court tends to treat new products, with unknown technology, as medicinal products, so that they can be subject to stricter regulatory controls. This provides an awkward, and probably unsatisfactory, precedent for new and innovative products that do not neatly fit into the conventional definitions largely based on molecular characterisation according to whether or not the product exhibits a biological or a physical function.

For example, rare earth elements may be used to form particulate matters to promote the formation of new blood vessels. This technology platform may be deployed to develop innovative products for wound healing, diabetic foot ulcers and hair growth as well as in other therapeutic areas such as ischemic heart damage and orthopedics.

Nanoparticle radiosensitizers may be used to enhance electromagnetic radiation absorption to cause localized damage to DNA or other cellular structures for cancer therapy. Such radiosensitizers are made of spherical or near spherical pure gold nanoparticles where the surface is covered with a mixture of alkanethiol and trimethylammonium thiol ligands.

All these technological endeavors will present new challenges for industry and regulators as to the process that should be proportionately applied to their classification and regulatory oversight so that innovation is not unduly hampered.

References

1. *Europe's advanced therapies regulation claims its first victim, Scrip Regulatory Affairs, 8 March 2013*
2. *Regulation (EC) No 1394/2007 of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2007R1394:20120702:EN:PDF*
3. *MHRA Guidance Note 8: A guide to what is a medicinal product, Revised November 2012, www.mhra.gov.uk/home/groups/is-lic/documents/publication/con007544.pdf*
4. *Directive 2001/83/EC of 6 November 2001 on the community code relating to medicinal products for human use, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20121116:EN:PDF*
5. *Top EU court gives clarity on device "intended use", but grey areas remain, Scrip Regulatory Affairs, 23 November 2012*
6. *Directive 93/42/EEC of 14 June 1993 concerning medical devices, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF*
7. *MEDDEV 2.1/3 rev.3, Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative, December 2009, http://ec.europa.eu/health/medical-devices/files/meddev/2_1_3_rev_3-12_2009_en.pdf*
8. *Case C-308/11, Chemische Fabrik Kreussler & Co GmbH v Sunstar Deutschland GmbH, 6 September 2012*
9. *Case C-140/07, Hecht-Pharma GmbH v Staatliches Gewerbeaufsichtsamt Lüneburg, 15 January 2009*
10. *Case C-27/08, BIOS Naturprodukte GmbH v Saarland, 30 April 2009*
11. *Case C-369/88, Criminal proceedings against Jean-Marie Delattre, 21 March 1991*
12. *Case 227/82, Criminal proceedings against Leendert van Bennekom, 30 November 1983*
13. *Case C-112/89, Upjohn Company and Upjohn NV v Farzoo Inc and J Kortmann, 16 April 1991*

Lincoln Tsang is a partner and **Jacqueline Mulryne** is an associate in the law firm Arnold & Porter (UK) LLP. Email: lincoln.tsang@aporter.com and jacqueline.mulryne@aporter.com.