

Medical Technology

The borderline between medicines and medical devices – the handling of combination products

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Introduction

Recent advances in technology have made the borderline between medical products and medical devices increasingly complex. At the same time there has been a considerable increase in the number and sophistication of drug/device combination products being brought to the market. Many of these are posing new issues for the regulators. Industry is showing much interest in delivering a new generation of advanced drug/device combination products along with device/drug systems. The importance of this area for improving healthcare has been highlighted during the recent UK Healthcare Industry Task Force Review¹ and in discussions within the Medical Device Expert Group (MDEG) of the European Commission.

This article considers the borderline between pharmaceutical products and medical devices and assesses the handling of combination products. It looks at the challenges posed by the new technologies and the initiatives being developed to address these.

The borderline

The definitions of a medical product and of a medical device are set out in the relevant legislation. These have been made as clear as possible but nevertheless are constantly being challenged by advances in technology and science:

- The use of miniaturisation technology such as nanotechnology or nanobiotechnology for drug delivery
- Guiding tissue regeneration
- As a vehicle for site-specific targeting for subsequent thermal ablation of tumour tissues by means of external energy source.

How does one characterise the primary mode of action and assess the clinical safety

and efficacy of such products? Do these act physically or metabolically? What happens if they become incorporated into cells that may lead to interference with the cellular functions and apparatus?

The definition of a medicinal product is set out in article 1 of the new Directive 2004/27/EC, which amends the previous Directive 2001/83/EC. Member States are required to transpose the amending Directive by the end of October 2005. For the purpose of our discussion in this article, the new definition is not materially different from the current definition save that paragraph (b) clarifies the use of a medicinal substance or combination of substances from a functional perspective. The amending Directive defines a medicinal product as:

- 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.

Directive 93/42 defines a medical device and deliberately excludes those products acting by pharmacological, metabolic or immunological means. Although this Directive is currently being revised, the definition, at the time of writing this article, remains unchanged.

"Medical device" means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

1. diagnosis, prevention, monitoring, treatment or alleviation of disease
2. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
3. investigation, replacement or modification of the anatomy or of a physiological process
4. 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 European jurisprudence makes clear that classification of a relevant product takes account of two aspects: one relating to the presentational aspect and the other relating to the functional aspect. The latter must take into consideration the underlying characteristics of the product.

The phrase "used in or administered to..." in Article 1 of the amending Directive 2004/27 may help to address these issues as regards use of certain devices for drug delivery. However, this does not appear to solve the underlying tension in relation to classification of combination products where the device component is not designed for drug delivery but is active in alleviation of disease. In this situation, the drug component is incorporated to assist the function of the device.

Amending Directive 2004/27 also includes a new article 2.2, which states "in cases of doubt, where, taking account of all its characteristics, a product may fall within the definition of a 'medical product' and within the definition of a product covered by other Community Legislation, the provisions of the Directive shall apply".

The introduction of this article caused considerable concern to many within the medical devices industry and led to the then Commissioner for Enterprise offering during the final European Parliament debate, a conference on borderline issues. This conference duly took place on October 28, 2004. The interpretation of this article 2.2 ought to provide some comfort, since it has made clear that it should not be seen as a "catch-all", but rather as a final arbitration point. The words "taking account all its characteristics" are important, because in most instances the characteristics will help differentiate between a medicine and a device. However, the conclusions of this workshop fall short of identifying who has the legal power of making the final determination of the classification of a relevant product. It is desirable to have a clearer procedure for handling such determination to reduce delay in approval of such products that appears to be a significant regulatory impasse in the European Union.

So called "human tissue engineering products" are said to fall outside the current regulations and will be controlled through separate legislation. This will also provide an opportunity to tidy up issues for cell therapy and non-viable human tissue products. The proposed new legislation is discussed later in this article.

The current advice on borderline issues is set out in a guideline from the MDEG (MEDDEV2 1/3 rev 2 July 2001) following initial consultation with the Commission services, the Competent Authorities and industry. This is currently being revised in light of recent changes in the legislation. The current guideline highlights a group of products, which are controlled either as pharmaceuticals or as medical devices by precedent and consensus decision. Some of these decisions could be challenged and/or changed as a result of the recent legislative changes. It is to be hoped that pragmatism will be employed in the revision of this guideline, which will be agreed between the two sectors.

There will inevitably be problems on the borderline between pharmaceuticals and medical devices. The importance of these decisions partly reflects the substantial difference in the cost of complying with the different regulatory regimes. A change

between the controlling legislation often has a marked impact on the time to market, the development costs and the cost for regulatory compliance. These are particularly significant for SME (small and medium sized enterprises), which make up the majority of medical device and innovative companies.

In the USA, an office of combination products has been created within the FDA. The creation of this office has proved to be of benefit by streamlining the regulatory process and in identifying the "right track" for borderline products. In Europe the situation is much more complex. A company can consult the competent authorities for medicines and devices, or a Notified Body. Often this will reveal a difference of view, and even if not, there may be a need to establish a "European" single market view. In the devices sector, the MDEG has become the forum to discuss such issues and it seeks to establish a consensus position. An e-mail discussion network has been set up to help accelerate discussion between the Member States. The MDEG has also created a borderline working group. Nevertheless, all this takes time and needs to work better. The difficulties are highlighted in Sharon Frank's book² in which she sets out the case for a European Medical Devices Agency. Similar arguments are advanced in Chris Hodges' recent paper³, which analyses the case for a European Agency.

Tissue and cell products

Advanced cell therapy, gene therapy and xenotransplantation products are currently defined as pharmaceuticals in an annex to the Pharmaceutical Legislation, adopted through Directive 2003/63/EC. Viable human tissue products, which do not meet the definition of a "cell therapy medicinal product" according to Directive 2003/63, are currently unregulated. This area has been much debated in recent years following a report from the Scientific Steering Committee in 2001⁴. This report concluded that such products should be regulated through specific legislation in the interest of public health protection, incorporating a "third pillar" using the best features of the pharmaceutical and medical device regulatory regimes.

The EU Commission has consulted widely on proposed new legislation governing so-

called "tissue engineering products" for this sector and is shortly to bring forward a draft regulation. This will probably differentiate between allogeneic and autologous products. A new definition is being crafted to characterise this class of products with respect to the underlying mode of action. The EMEA (The European Medicines Agency) will be involved in co-ordinating the evaluation of such products through a new Committee and involving a network of experts. It has been said that some cell therapy products may revert from the current pharmaceutical regime to this new legislative control. There will be an "ombudsman" role for the EMEA to resolve borderline issues and this will apply a "*lex specialis*" approach, ie, in cases of doubt the product should fall under the jurisdiction of the specialist legislation.

In addition, the recently adopted Directive 2004/23, which must be transposed into the domestic laws of the Member States in 2006, will regulate standards of quality and safety of human tissues and cells for human application. The definition of "human application" is broad to cover use of tissues or cells on or in a human recipient. The recitals make clear that the Directive does not distinguish between tissues or cells used for treatment and those developed for cosmetic purpose.

Currently, non-viable human tissues remain outside legislative control, since these are specifically excluded under the Device Directive 93/42 and are not proposed to be covered under the human viable tissue legislation. This anomaly will need to be speedily resolved given recent questions over these products. One way would be to remove the current exclusion in Directive 93/42.

The Medical Devices Directive (MDD) and the Active Implantable Medical Devices Directive (AIMD) both require combination products to be considered in Class III. There is, however, currently insufficient guidance regarding how combinations for pharmaceutical products with an *in vitro* diagnostic are likely to be regulated. For example, the drug and the diagnostic components are presented in a single pack or with a linked service where the diagnostic kits have been dedicated for use only in a specific combination with the drug component. Ordinarily, for a drug-

device combination, it is necessary for an appropriately designated Notified Body to either undertake testing or to evaluate the design dossier to assess the quality, safety and performance of the device incorporating a medicinal substance. The manufacturer affixes the CE mark after receiving the permission of the Notified Body. The company can select any Notified Body to undertake the evaluation, taking account of the designation of the Notified Body (NB) (ie, is it designated to perform such evaluations?). Once the CE mark is affixed the product can freely circulate within the European Union (EU) and the European Economic Area (EEA), without any further evaluation or regulatory requirements.

The Notified Body is responsible for evaluating the device incorporating the medicinal product and is required to evaluate the performance against the proposed/claimed indications. Much debate can be made over the terms performance and efficacy, in truth this is often semantics, since the performance has to be evaluated against the claimed indications.

An important feature of the regulatory procedures for medical devices containing ancillary medicinal substances, is that the Notified Body is required to consult with a medicines competent authority in order to verify the quality, safety and usefulness of the substance in question. The Community law makes clear that the role of the Medicines Competent Authority (MedCA) is advisory. It should be noted that the Notified Body can select the MedCA – except in the case of blood derivatives where an EMEA consultation is mandatory – and is not bound to accept the advice or opinion given.

The system raises a number of questions:

- What are the respective roles of the NB and the MedCA?
- Which MedCA should be selected for different types of product?
- What documentation is required?
- What type of report is to be delivered to the NB?
- What are the differences, if any, for stable blood products covered under Directive 2000/70?
- What happens over post marketing issues, variations etc?
- What are future foreseeable developments?

The role of the Notified Body

The NB retains the overall responsibility for the approval of the device containing the ancillary substance. Arguably this includes the decision as to whether it is indeed a medical device or is in fact a medicinal product.

The legislation did not intend there to be duplicate work and assessment. Rather, it is suggested that the intention was for there to be complementary working. The NB, if it has been appropriately designated, has the expertise and competence to evaluate the device including biocompatibility (pre-clinical safety issues) and the clinical evaluation/claimed performance. The reason for the involvement of the MedCAs is to undertake the following tasks.

First, it has to check on the provenance and quantity of the ancillary substance. Is the substance of appropriate quality to be used in the product and for the claimed indication? The Notified Body probably does not have this expertise and hence the need to seek the opinion of a MedCA.

Secondly, it has to check the pre-clinical/biocompatibility documentation, which is more complex. The NB does have such expertise available. Indeed, there are already established international standards against which "Essential Requirements" are assessed to ensure safety under normal conditions of use. The evaluation should concentrate upon the wider issues, which might not be apparent from the dossier, and upon the relevance of any toxicological findings for the proposed clinical use.

Particular focus should be on local toxicity and the extent of systemic absorption. This is difficult, since the device may deliver a high concentration of the drug to a local and/or privileged site. In summary the question being asked concerns the relevance of the pre-clinical dossier data for the proposed use.

Thirdly, in considering the clinical data, the MedCA is being asked to highlight issues it is aware of which may be relevant to the consultation. These will often be potential

safety concerns. Examples would be the possible relevance of drug/drug interactions, allergic reactions/hypersensitivity reactions, inappropriate use of antibiotics, secondary pharmacological reactions. Possible comments on the Post Marketing Surveillance (PMS) proposals might be made.

The vexed question is whether there should be a full evaluation or simply "remarks" on the efficacy/performance. It is suggested that a full evaluation is not required, this might be offered in some cases, but in general would be provided as remarks for the NB to consider further.

Directive 2000/70, which covers stable blood products, gives a defined role to the EMEA in the determination of the marketing of the combination. The text specifically includes reference to the "usefulness" of the stable blood component. In Directive 93/42 the term "usefulness" is mentioned only in the recitals to the Directive. This term has also been the subject of some debate recently. The term is perhaps best understood to give it a natural meaning as regards the rationale for incorporating the blood component in the combination product. This is to take account of, among others, the potential risk from any blood component and therefore the need to ensure that there is an appropriate justification for the combination and the "usefulness" of the component. This is being clarified for other medicinal products through the revision of Directive 93/42, in the context of "chemical" ancillary substances, including those prepared by recombinant DNA methods as well as by more conventional synthetic processes.

Which MedCA is to undertake the evaluation?

Directive 2000/70 requires a Notified Body to consult the EMEA over any combination containing a stable blood product.

For other combination products, the NB can select any competent authority for human medicinal products. Directive 93/42 was written before the introduction of the Centralised Procedure and Regulation 93/2309, now Regulation 726/2004, which will come into full effect in November 2005. Hence there is no reference to the EMEA or centrally authorised products. Several

scenarios can be envisaged. The medicinal product may be new to the EMEA and to the Member States, the product may have been centrally authorised, authorised through the Mutual Recognition (MR) Procedure or through national routes. The Community law permits the NB to select any CA irrespective of the original approval procedure. Should this be regularised?

Combination products

Combination products represent a special group within the division between medicines and devices. As mentioned in the introduction, there is considerable interest and research activity in this area from both industries and from new specific combination therapy companies as a strategy for product life cycle management.

The regulation of such products is essentially harmonised across the major regulatory authorities. The European legislation makes clear that if the pharmaceutical component (medicinal substance) exerts the primary mode of action, then the product (perhaps to be appropriately called drug/device combinations) will be assessed and authorised as a medicinal product. In such circumstances the relevant medicines competent authority (MedCA) is advised to consult with a medical device competent authority or an appropriate Notified Body. Currently, this consultation appears to work well but a device/drug combination product is likely to fall under the provisions of either the general Medical Device Directive 93/42 or under the scope of the Active Implantable Directive 90/385. Should the product incorporate a stable blood product, then it is regulated under the Stable Blood Products/Medical Device Directive 2000/70EC.

However, some companies have experienced considerable delay in commencing the consultation procedure because certain medicines competent authorities take the view that the drug/device combination is a medicinal product. It is strongly desirable that a regulatory path should be created for the determination of such products by a body consisting of representatives from the device and medicine sectors.

Arguably since the process is one of consultation, it would make sense if the

consultation were with the most expert Competent Authority, ie, the one that performed the "initial" evaluation of the medicinal product containing the substance in question.

This logic would suggest that for all centrally approved substances the consultation should be with the EMEA, and involve the rapporteur/co-rapporteur. For substances approved through the MR Procedure, the consultation should be with the Reference Member State. For nationally approved substances, the NB should be free to select the competent authority for consultation.

For new substances (ie, those not previously authorised in the EU) the consultation might be with the EMEA in the future.

The MDD is currently being reviewed and the Commission will shortly be submitted to the Council and to the Parliament. This therefore provides an opportunity to introduce changes into the legislation if this is desired.

In vitro diagnostics

An additional important area for combination products will be the integration of a diagnostic with a pharmaceutical. This could be the use of a specific diagnostic for an infectious agent, targeting therapy for a specific viral strain or species of bacteria. Increasingly the combination may be with a bio-marker or a linkage with a pharmacogenetic/pharmacogenomic test or service. Such tests are likely to be used to select patients who will respond to the targeted therapeutic, to identify those at risk from certain side effects or those requiring a reduced dosage. The handling of such tests and services will be another challenge and will open up the issue of so called "traceability". It remains to be seen how these will be addressed. Most such tests will be Class I, self certification IVDs.

Documentation

The required documentation for products covered under the Stable Blood Products Directive 2000/70 has been elaborated in the EMEA document of August 26, 2004, which provides the application form.

Perhaps a similar approach is followed for the documentation for other substances. It has to be remembered that for most applications the

EMA or the national MedCA already holds the full documentation on the substance.

What documentation is required/appropriate for the pre-clinical and clinical areas?

Here there appears to be little consensus. Feedback from the Notified Bodies suggests that the documentation required is highly variable between the Member States. There is therefore an opportunity to rationalise and standardise the requirements.

Again it has to be appreciated that the Member States hold the original documentation. The Notified Body also receives the full design dossier from the applicant. It therefore seems reasonable for the consultation, that the Notified Body should provide a summary/overview of the pre-clinical data and the clinical file. For the pre-clinical area, this could take the form of the former pre-clinical expert report and for more recent/current applications, the overview summary in the Common Technical Document (CTD) format. A further suggestion is that the Notified Body sets out the question it wishes the MedCA to focus upon and address during the consultation.

The recently constituted Notified Body Association might provide a suitable vehicle through which to develop such proposals.

Post marketing issues and variations

This is a difficult area for combination products since the medical device regulatory procedure does not have a formal system for considering and approving changes/variations. For Class III products, the manufacturer is required to consult with the NB about major changes, but these are not defined as they are for pharmaceuticals.

The questions are:

- How should variations for these products be handled?
- Is a procedure required for consultation over variations to the pharmaceutical component?
- How should any post authorisation commitments be handled?

The reporting of adverse incidents also needs some clarification. Under which jurisdiction

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should the reports be made? This is likely to be through the Device Vigilance route, but how will any relevant links be set up?

How will Vigilance/Pharmacovigilance issues be optimally handled? These issues will need to be debated, especially if this is a growing sector, as the experts predict.

Future developments

The debate has already highlighted that combination products are an area of considerable interest and research. The current revision of the MDD 93/42 provides an opportunity to clarify some procedural issues.

Future combination products are likely to involve tissue engineering components. Human tissue engineering products are to be the subject of a Regulation, which is expected to be introduced to the Council and Parliament by DG Enterprise before the end of the year. This will give a new competence to the EMEA. The new legislation will also open up a new interaction and borderline for combination products.

In the US FDA, an office for combination products was established two years ago. This currently has a co-ordinating role between the existing centres, but has expanded. Some predict that this may become a centre in its own right.

Within Europe, the handling of combination products has been debated by Device Competent Authorities at their meetings under the Irish and the Dutch Presidencies last year. There has been some concern expressed that the current system is not sufficiently robust. The possibility of establishing a scientific committee to be available for Notified Bodies to consult about advanced technology products has been discussed. This might consider all aspects of the drug/device combination products. The debate is continuing. It is desirable to have this particular issue resolved as soon as possible. Otherwise, Europe is at risk of becoming less competitive in bringing this class of products on the market as compared with the situation in the United States. Moreover, it does not chime with the recommendations made by the Competitiveness Council following the Lisbon Summit and the recently published UK Healthcare Industry Task Force (HITF) Report.

A further element is the need for scientific advice and dialogue during development. This is currently not available in the device sector, but is through the FDA. It is likely therefore that Europe will eventually have to consider this aspect, which has been raised by industry. All of this may fuel the debate about the possible need for a European Devices Agency to co-ordinate Member State

activities and to provide a focus for emerging and novel technologies, which increasingly sit on the border between devices and pharmaceuticals.

There is also the interesting question of whether there might be a need for a smoother transition between the two regulatory regimes. At present the requirements and approaches are very different and yet the products represent a continuous spectrum of technology. There might be a need for a single over-arching legislation for healthcare products, some being up-regulated within the legislation and some being down regulated. The advances in technology may force this debate. In the meantime the various actors are endeavouring to make the complex borderline work and to facilitate the approval of combination products, which seem likely to play an important role in the advance of medical care.

Disclaimers

David Jefferys is Senior Strategic Regulatory Adviser to the Eisai Board. Lincoln Tsang practises regulatory and product liability law at Arnold & Porter LLP. The views expressed are personal and do not represent the position of any regulatory agency or advisory committee(s) with which the authors were previously affiliated.

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