Marketing certification of bioimplants: feasible or not?

The number of medical devices containing a biologically active component will rise in the future. An issue that a manufacturer can hardly delay addressing is that of the class to which his product belongs. Is it still a medical device, is it now a drug, a mixed form or an advanced therapy medicinal product – an ATMP? The answer impacts significantly on the action to be taken before the product can be marketed.

Which applies – the Medical Devices Act [MPG] or the Drugs Act [AMG]? The shortest possible answer runs as follows: if the main mechanism of effect of a product is mechanical, chemical or biological, then the product is a medical device. If the main mechanism of effect is pharmacological, immunological or metabolic, the product is a drug. So far, so good. However, this classification is often neither simple nor unambiguous. In the crossover area between the two, there is plenty of room for uncertainty. In addition, there are special rules and standards for ATMPs. The main products to come under this heading are those that contain viable cells or tissue in addition to the medical device component.

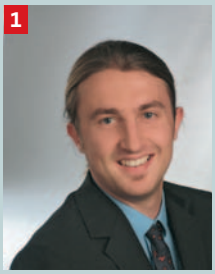
The deciding factor for classification is ultimately a clear statement of the purpose for which the product is intended. The active principle, the proper use, the intended use, the indication – these are the issues which must be addressed conclusively as early and as precisely as possible because these determine which laws and which other standards fundamentally apply. In ideal conditions, the actual development process would not start till then. Among the appropriate authorities, there are a number of bodies to turn to for clarifi-

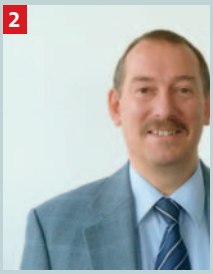
German Summary

Zulassung von Bioimplantaten: Machbar oder nicht?
Die Zahl von Medizinprodukten, die einen biologisch wirksamen Bestandteil enthalten, wird zukünftig zunehmen. Die Frage, ob es sich dann noch um ein Medizinprodukt, schon ein Arzneimittel, eine Mischform oder um ein Arzneimittel für neuartige Therapien (Advanced Therapy Medicinal Products - ATMP) handelt, kann sich ein Hersteller gar nicht früh genug stellen, denn die Antwort hat erhebliche Konsequenzen auf die notwendigen Schritte bis zum In-Verkehr-Bringen. Der deutschsprachige Beitrag ist nachzulesen auf www.meditec-international.com/0312rr

cation if in doubt. If the issue concerns distinguishing between a drug or medical device, advice can be sought from the Federal Institute for Drugs and Medical Devices [BfArM]. If a product is suspected of being an ATMP, the innovations office at the Paul Ehrlich Institute would be a suitable body to contact. Alternatively, a scientific opinion could be obtained from the European Medicines Agency [EMA]. Since ATMPs come with quite new and special standards, a group (the EMA/CAT-NB) was set up to act as the interface between the EMA and the Notified Bodies. This group addresses these standards and also the fact that until now the Notified Bodies had never previously had to deal with drugs. EC Regulation 1394/2007 contains details of the processes involved and explains how to integrate the Notified Bodies into the ATMP marketing certification procedure.

So everything is clear – theoretically. Yet researchers and manufacturers are beset with uncertainty. Sebastian Geismann, lawyer at the Freiburg University Medical Centre, confirms an increase in the number of enquiries received by the Clinical Trials centre there from various clinical departments on combination products. "There is an increased need for advice, especially on ATMPs. Often, all that is needed is some initial information on basics. But it is quite noticeable that many scientists are currently thinking about projects." The Clinical Trials centre is making preparations for this. "At the moment, the situation is a learning curve for everyone. Researchers and companies are not alone in entering virgin territory as regards ATMPs and changes in legislation – it's new ground for the authorities as well," continues Geismann. "The authorities do not have much in the way of prior experience to refer to as they seek to apply the new, abstract statutory rules. And that is not always straightforward because very many combination products have no blue print."





1) "There is an increased need for advice, especially on ATMPs. Often, all that is needed is some initial information on basics. But it is quite noticeable that many scientists are currently thinking about projects," explains Sebastian Geismann, lawyer at the Freiburg University Medical Centre.

2) "It makes no difference whether it is a medical device or a drug, it always makes good sense to have prior discussions with the appropriate authorities, for example a consultation with a test centre to coordinate and negotiate the test programmes," says Michael Schrack from Schrack & Partner.

Helpful links

Explanatory notes on the scientific and procedural advice given by the BfArM on 30.03.2012: **http://www.bfarm.de/cae/servlet/contentblob/1013496/publicationFile/65705/Erlaeuterungen_fuer_Antragst.pdf**
Draft guideline on the classification of ATMPs published by the EMA – deadline for submission of comments is 31st July 2012:
http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500126681&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc))

Direct communication is recommended

This is why his colleague, Jürgen Kätzler, clinical studies project coordinator, advises early discussion with the authorities, "Direct contact gives the parties involved, including the authorities, the best opportunity to learn the issues as fully and quickly as possible. Through direct, practical experience, they learn where the problems lie. Of course, there are rules and guidelines to refer to or indications of chemical-defined substances, but this is true only to a limited degree, or not at all, for ATMPS. We should all have the same aim, i.e. to have the necessary degree of certainty to rely on for clinical trials or marketing authorisations. On the other hand, the whole issue needs to stay realistic and feasible." In his view, a timely telephone call to enquire about some specific issue or obtain scientific advice from the competent authority is a good way of smoothing the approval or marketing certification process as much as possible.

Michael Schrack from Schrack & Partner agrees with him, "It makes no difference whether it is a medical device or a drug, it always makes good sense to have prior discussions with the appropriate authorities, for example a consultation with a test centre to coordinate and negotiate the test programmes. Of course, everyone should do their homework before contacting the authorities. But if the competent body at a later stage is presented with a full test programme and accepts it, then you are practically certain that everything will be accepted in the same way at the end of the road – always provided that the results are reliable and add up."

Some of the differences affecting marketing certification are in the mandatory documentation. For medical devices, the technical file acts as the official quality record whereas with drugs a CTD (common technical documentation) is required. "These two are fundamentally different. The content is structured so differently that it is important to distinguish between them at an early stage," explains Schrack. "Even the way that quality records are kept is different in some respects, for example with medical devices artificial product ageing is all that is required in many cases, whereas with drugs you need real time data." This prolongs the procedure, firstly because the trials needed last longer and secondly because they are structured differently. And quality management is handled differently, too. With medical devices, DIN EN ISO 13485 is the basic standard, whereas with drugs it's the EU GMP guideline (GMP – good manufacturing practice).

There are also specific differences in the organisational structure the manufacturer is required to have. With medical devices, a safety officer and medical device adviser are needed. With drugs, a qualified person (e.g. a pharmacist) and a qualified person for pharmacovigilance are specified. With drugs, the licensing authority is the BfArM or at executive level, the Regional Councils, which issue the production permits. Here, a manufacturing permit for drugs is an official act, whereas the conformity assessment procedure for medical devices is monitored by the Notified Body which in this respect acts under private law.

One problem which medtech producers never tire of mentioning is that

many medical devices – even ones with a pharmaceutical component – simply do not come within the scope of the AMG. This may make itself apparent in clinical trials, the conduct of which has been adjusted since the 4th MPG amendment to meet pharmaceuticals legislation. "Initially, this actually caused difficulties of legal interpretation, especially when the issues could not be transferred on a one-to-one basis from the pharmaceutical sector to the medical device sector," explains Geismann.

Unlike the pharmaceuticals sector, the medical technology industry features many small and medium-sized companies. In the view of these companies, the necessary powers of endurance and the associated capital base needed for the development of a combination product pose a great challenge. This is all the more true since the vast majority of these products require a clinical trial. A major producer of pharmaceuticals certainly has it easier than a medtech start up company. Even so, Kätzler does not regard the difference between the expense of an ATMP and that of developing and obtaining marketing certification for a medical device requiring a clinical trial as being all that big, "As soon as data is needed from clinical trials, the expense is quite similar. However, if simple medical devices are compared with ATMPs, things look different. It can take five to six years before the data from a clinical trial of an ATMP can be submitted to the authority – which marks only the beginning of the marketing certification procedure."

No need for intimidation

So is the expense still appropriate? According to Schrack, manufacturers should not be dismayed. He believes in the potential of combination products and ATMPs. "Of course, it does depend on quantities. With a niche product, it is getting difficult to refinance the expense of the development and marketing certification process. However, if a company operates in a sector where large patient numbers or many different application opportunities can be anticipated, things will work out. Because they save on second operations, and reduce infection risks etc, bio-resorbable materials in particular have a significant cost reducing impact and therefore justify a higher product price. This is where it becomes lucrative." Both the expense and the opportunities of success depend on the individual product. So the best rule for manufacturers is probably keep their eyes wide open when choosing the products to develop to market maturity.

Ramona Riesterer ←

With medical devices, DIN EN ISO 13485 is the basic standard. Photo: TÜV Sued