

# Mark of Approval

A year on since the 2010 Recast to the Medical Device Directive, and it seems the legislation has had a positive effect on patient safety for the countries that have enacted the changes. However, whether all countries will ever have the same procedure for the approval of medical device trials remains in doubt.

As CRO professionals working on clinical trials for medical devices, the main objective is to support sponsors in their task of collecting data for the CE mark applications and subsequently post-marketing data. Besides that, a good portion of work has always been to support post-marketing trials. After the new MDD 2007/47/EC came into force in March 2010, the landscape changed significantly for device manufacturers.

In the past, not all products required clinical evidence and many used literature reviews to show equivalence to products with existing CE markings. But with the new MDD reinforcing the need for clinical data, this route is increasingly being blocked, leading some manufacturers to have to foresee this and adapt their ways. Others learnt the hard way: when their notified body rejected their submissions or informed them they were not accepting the 'classic way'. This is quite burdensome for companies – especially the small ones struggling to meet these new requirements and cope with the associated costs.

The other big change that we have seen is the growing demand for post-marketing trials and data. Manufacturers are now adopting the demands of the new directive to actively follow up the safety and performance of their devices in the market after obtaining the CE mark. Besides this need to satisfy the regulations and meet their notified body's criteria for re-certification, there are other reasons for undertaking clinical trials including:

- Marketing benefits, such as the use of the post-marketing trial to support penetration of the markets
- Data requirements for regulatory approvals in other

jurisdictions/countries, particularly in the US

- For reimbursement and HTA approvals
- Compilation of user feedback in a uniformed way to collect data for improving devices and procedures

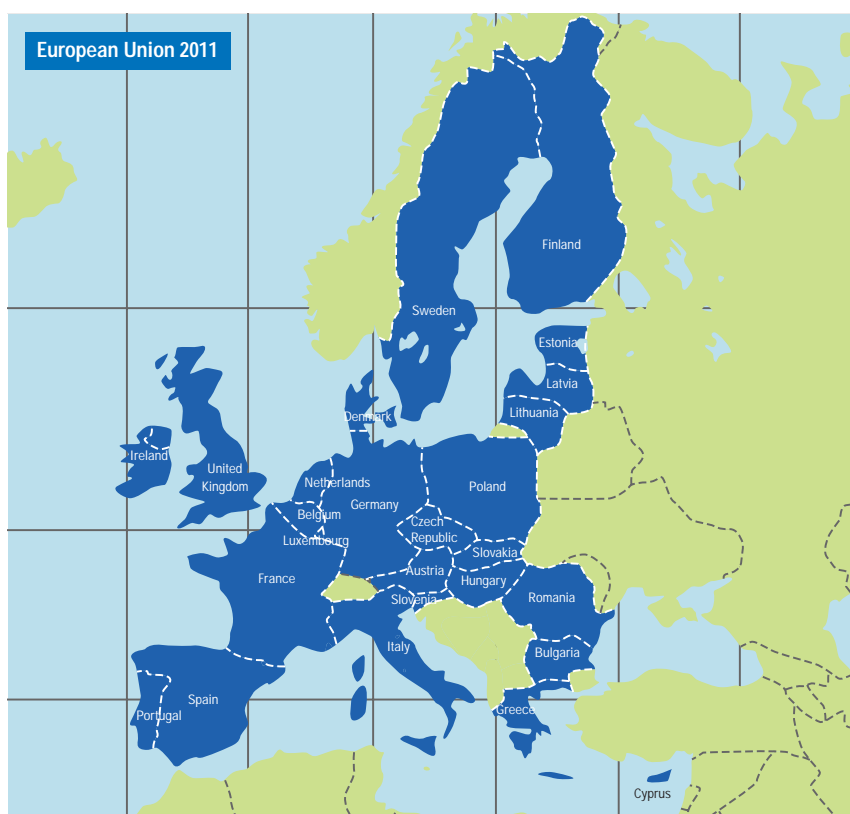
Quite often an approach is recommended that meets a variety of needs, combining a CE mark trial with long-term follow ups. For example, this could mean an endpoint at six to 12 months to support the CE mark, but yearly patient follow up thereafter for up to five years to collect the post-marketing data to meet one or more of these other requirements. The same patient cohort can be used, thus saving time and money by avoiding additional trials.

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As mentioned above, the changes are not made in favour of the manufacturers. One needs to appreciate, especially after the recent recalls of devices of hip implants, that there is logic behind it. The changes will improve device and patient safety, leading to a strengthening of the device industry's image as the one that cares about patient's welfare.

### Why Did This Happen?

The Medical Device Directive 93/42/EEC (MDD) – a directive adopted by the Council of the European Communities in



1993 – is responsible for regulating medical devices in the EU. Its influence extends outside the EU boundaries, as associated countries like Switzerland and Norway also base their national legislation on medical devices on this directive.

Directive 2007/47/EC amends not only the 93/42/EEC medical device directive, but also Directive 90/385/EEC on active implantable medical devices, and Directive 98/8/EC concerning biocidal products, such as disinfectants and insecticides. On 21 December 2008 this last revision of the directives came into force, with member states expected to implement into their national legislations by 21 March 2010. However, countries such as Poland, Italy, Slovenia, Finland and Czech Republic were late in meeting this requirement.

The main objective of this amendment was to improve the conformity assessment through increasing the amount of products and depth of clinical evidence, heightening the demand for risk management through the product life cycle, and introducing the need for post-market surveillance.

This amendment enforces the use of clinical data to confirm the performance and safety of a device, even adding clinical evaluation to the list of essential requirements to which all must comply with regardless of device classification. In order to avoid using a clinical trial, it will be necessary for the manufacturer to justify their decision to their notified body.

Furthermore, a “post-market clinical follow-up plan and the results of post-market clinical follow-up” have now been introduced in Annex II 5.2 as part of the information the manufacturer must supply to the notified body. Notified bodies can use the directive as a base to demand post-market clinical data if they consider it necessary for the extension of the CE mark on the device they are reviewing.

### **Has the Amendment Changed the Approval Process?**

The simple answer is no; however, major changes have come not from

the directive, but from the local competent authorities who have taken the opportunity to add in changes when implementing the new directive into local law. As always, although all countries follow the same directive, there are 27 different implementations into national legislation.

Regarding the notification dossier to the competent authorities, there are changes which are a direct consequence of the directive amendment. For example, manufacturers must submit a declaration of conformity to the essential requirements, except for those which will be tested during the clinical evaluation. However, this declaration now corresponds to a longer list of essential requirements. Also, some authorities, such as in Belgium and Italy, clearly request two new statements, introduced with the amendment to Annex VIII 2.2 devices for clinical investigations, as part of the dossier. The first statement indicating whether or not the device incorporates as an integral part, “a substance or human blood derivative”; and the second indicating whether or not the device is manufactured using tissues of animal origin”. Finally, safety reporting sections in protocol are reviewed by the competent authority to ensure they comply with the new 2.5 Annex X where all serious adverse events have to be reported to all competent authorities of all countries where the trial takes place, whereas before it was only necessary to report incidents. We have also seen requests from competent authorities to use/follow their reporting templates.

### **Germany**

Germany used to be, without a doubt, the first choice for clinical trials with its authority notification only process for interventional studies. A speedy ethics approval from Feki (professional Freiburg Ethics committee) was typically measured in a day and a simple notification to the competent authority has been replaced with a request for authorisation by Bfarm via the DIMDI online system: Feki EC is nowhere to be seen anymore. Ethical

approvals are now handled in a similar manner to pharmaceutical clinical trials with one lead ethics committee coordinating the approval process centrally, which is quite effective since one gets all approvals at once. Although the 30-day Bfarm approval timeline still should keep Germany theoretically in first position, in practice, the transition to the new system has complicated and extended the original timeline, bringing Germany in line with other countries. There is hope that the timelines will shorten once the process is well in place.

### **Italy**

In Italy, the requirements to start a clinical trial were stricter than the average EU country, as an approval from the Ministry of Health was required to start a trial with a CE-marked medical device at a private hospital. Fortunately, with the new Italian legislation, most private hospitals participating in device trials can now replace the 90-day approval process with a simple notification letter to the Italian Ministero della Salute.

### **New Member States**

Concerning the new EU member states (Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia, Romania and Bulgaria), the general impression is that they have done a good job in modifying and adjusting their regulatory landscapes. Despite the fact that in some cases there is still scope for improvements on the organisational and resource levels, these countries can no longer be treated as less strict in the regulatory sense. Therefore, it is not advisable to choose one of these countries with a hope that one can slip through the regulatory review with certain key documents missing or some important testing not yet fully completed. However, the fact that there is room for improvement in the new member states does not really imply that the system works perfectly in the old part of the EU.

### **Netherlands**

The Dutch competent authority (Dutch Health Care Inspectorate (DHCI)) confirms, based on relevant Dutch legislation that an ethics committee

approval and a valid insurance is sufficient to start the investigational device study only after DHCI has been notified. However, DHCI still reviews the documents and, in some cases, may put the study on hold and consequently it is advisable to wait until the official approval is issued. The timeline for this approval is not defined and with the heavy workload of the device department of the CA it can take more than three months.

### United Kingdom

Another example comes from the UK. The NIHR Coordinated System for gaining NHS permission was introduced after the changes in the Medical Device Directive but not as a result of it. Although it cannot be considered as an integral part of the regulatory landscape *sensu stricto*, it is in the end affecting the process of gaining the necessary approvals before the study starts. This coordinated system was heavily advertised from the beginning as being

a simple and fast way to start a study. Although not obligatory, this process has been adopted by the majority of sites. First experiences have shown that this system is complicated and slow, requiring extra administrative effort and resulting in delays in comparison to the old system. Perhaps this is due to the fact that it has only been recently implemented and hopefully over time will bring a real advantage to companies willing to perform their clinical studies in the UK.

### Conclusion

More than a year after the changes in the directive, it seems there has been a positive effect on patient safety as the need for clinical trials slowly increased. Also, while enacting the amendment into their national legislations, Italy and Germany have both made particular changes to their approval processes eliminating their differences with the rest of the EU countries. The younger members of the

EU have generally seemed to follow the same pathway. However, we are still left asking the same question: will the day come when all countries have the same procedures?

### About the author



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