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Faculty of Pharmaceutical Medicine submission to the House of Commons Science and Technology Select Committee's Inquiry into the regulation of medical implants

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A medical device, is any device that is used for diagnosis, prevention, monitoring, treatment and alleviation of diseases. In the EU, the government of each member state is required to appoint a competent authority responsible for medical devices. In the UK, it is the Medicines and Healthcare products Regulatory Agency (MHRA) which acts as the competent authority. The competent authority in one member state does not have jurisdiction in any other member state but they do exchange information and try to reach common positions.

Medical devices are classified into Class I, IIa, IIb and Class III. The classification of medical devices is risk-based, dependent on the device's duration of body contact, its invasive character, its use of energy source, its effect on the central nervous system and the central circulation, its diagnostic impact, or its incorporation of a medicinal product. To simplify the discussion, the focus of this feedback is mainly on Class IIb and Class III, which are the implantable medical devices. Below is the summary of the feedback from the members of the Medical Devices Special Interest Network of the Faculty of Pharmaceutical Medicine to the four questions of the House of Commons Science and Technology Inquiry on medical devices.

1) Are current legislation and regulations on the safety and effectiveness of medical implants fit for purpose?

Safety and Effectiveness

- In order to assess whether the current EU legislation/regulation of medical implants is fit for purpose, we need to assess other regulatory regimes and whether they are better or worse that the current state of affairs in the EU.
- The US Food and Drug Administration (FDA) makes much greater demands for non-clinical and clinical testing of medical implants than do notified bodies in the EU. These demands usually manifest as insistence on controlled data and on long-term follow up data. This begs the question of whether this increased stringency by the FDA prevents unsafe or ineffective devices reaching the US market. Or put another way; do the lesser demands for non-clinical and clinical data made by notified bodies result in unsafe or less effective devices being placed on the market in the EU?
- Advamed (the US medical device trade association and lobbying group) released a report in November 2010, which summarized a survey of over 200 medical device firms. The report claims that on average, the FDA process delays approval of medical implants (or at least of medical devices needing a premarket approval (PMA) in the US) by two years compared to the EU, and that there have been no safety issues identified post-approval in the EU that were "caught" by the longer and more rigorous approval process in the US. We believe that these latter data were based on comparing medical device withdrawals from the market in the US and EU.

- Examples of medical devices that have been approved in the EU on little or no clinical data but which are being or were subjected to extensive clinical trialling in the US include:
    - Dural sealant: approved with no clinical trial data in the EU; controlled trial versus current standard of care with 12 month follow up in the US.
    - Intra-abdominal pump: approved with uncontrolled clinical study data in 30 subjects followed for six months in the EU; controlled trial with larger numbers of patients and follow up for 12 months in the US.
    - Intra-articular injection: approved in the EU with marginally positive clinical trial data; large, controlled trial ongoing in the US with six months' follow up and stringent statistical demands on the analysis.
- None of these three products has so far resulted in any safety concerns or field safety corrective actions in the EU. All three devices are apparently effective in that market uptake has approximated what was predicted by the manufacturer.
- Recent examples of major safety issues on marketed products in the EU include hip implants (metal on metal and leachable substances from plastics in the devices), breast implants, and drug-eluting cardiac stents. These long-term safety problems with devices were apparently not found sooner by the more rigorous FDA process.
- Despite the lack of hard evidence that the current system of approving implanted devices for marketing within the EU, there is concern that the current system of competent authorities being involved at the clinical trial approval stage and with post-market vigilance, but not directly with product approvals, is unsatisfactory. For instance, the recent recall of metal-on-metal hip prostheses demonstrated a mismatch between the competent authorities' assessment of post-market vigilance reports and the notified bodies' assessment of risk at the product approval stage. It would seem that the vigilance expertise within competent authorities is not directly brought to bear on the product approval process, which may expose patients implanted with medical devices to additional risk.
- The current Medical Device Directive (MDD) is clear about how to reach a decision about whether a specific clinical trial is needed for a particular medical device. A clinical evaluation report is written, which assesses all known published and unpublished safety and effectiveness data for the device in question and devices similar enough for meaningful extrapolations to be made. The conclusions of the clinical evaluation report include an assessment of whether all the essential requirements appropriate for the class and type of device can be met using current information, or whether additional clinical testing is needed. From members' experience, it is clear that some notified bodies are not expert enough in the assessment of clinical data, of likely safety risks in clinical use, and of issues such as "dose" ranging, to make an effective critical assessment of whether a de-novo clinical trial is needed and whether long-term safety data should be gathered in a formal way.
- The current MDD relies on the ability for manufacturers to claim similarity to other devices on the market in order to demonstrate safety and effectiveness/performance. In other words, Device Y is going to be used for the same indication, is made of the same materials, is the same shape, and has the same action as Device X: since Device X is on the market with no published safety issues, Device Y should be approved for use in the same indication. The flaw in this logic is that:
    - there may be unpublished safety issues with Device X;
    - there may be subtle differences in the use of Devices X and Y which result in safety and effectiveness differences that are not explored clinically prior to marketing the device;
    - no two devices are exactly the same and so extrapolating data from one device to another may be flawed (for example, subtle changes in the shape of a hip prosthesis may result in dramatically different wear patterns, with subsequent safety issues for patients implanted with those devices);
    - as time goes on, each iteration of a device rests its case on a previous iteration, each a little different to the next one: after several years, devices may be approved that are

very different to the original marketed device and currently there does not seem to be a good assessment of the clinical implications of such iterative changes in device design.

- When there are product recalls, the responsibilities of the manufacturer, the competent authority, the health care professional using the device, and the notified body need to be very clearly defined to ensure that patients who have been implanted with concerning devices have recourse to continuing care.
- The Faculty believes that formal periodic safety reporting should be a requirement for higher risk medical devices. Currently we believe that periodic assessment is undertaken by notified bodies during their ongoing audit programmes, but that periodic safety reporting and assessment does not have to be submitted to the competent authorities, which receive the expedited safety reports for marketed products.
- Members also felt that whichever body was approving higher risk medical devices for marketing should have the power to demand post-market surveillance programmes and be able to undertake minimum notice audits of manufacturers to ensure their compliance. An increased use of registries to gather long-term safety data on implanted devices was considered to be a useful addition to safety monitoring.

Inconsistency and Unfairness

- A likely issue with the current EU system for medical implant approval is inconsistency. There are many notified bodies and it is possible that different NBs could make different demands on companies for clinical trial data for similar devices. This would certainly be unfair as companies try to get their devices approved in the EU.
- In theory, any inconsistency could have an impact on the assessment of safety and effectiveness of medical implants.

The Future

- As medical devices become more sophisticated, it is unknown whether the assessors within the notified bodies are going to be able to assess safety and effectiveness effectively. The devices themselves are more complex from an engineering and programming stance; they are often combined with medicinal products and biologics, whose contribution to safety and effectiveness may be difficult to assess; devices are being used now to treat more and more chronic conditions, for which gathering meaningful clinical data is increasingly challenging.
- We conclude that there is some evidence that the current system allows unsafe or ineffective devices onto the EU market, and there is little confidence that notified bodies have the internal expertise and ability to assess complex devices for chronic conditions, often with medicinal products as part of the mix, in the future.

2) How effectively does the MHRA implement the Medical Device Directive?

- This is an odd question in the context of approval of medical devices in the EU: the competent authorities are removed from the assessment and approval of individual devices and have input only to clinical trials (via clinical trial approvals) and post-market safety (via vigilance reports for marketed devices).
- In terms of clinical trial approvals, the MHRA implements the Medical Device Directive appropriately. However, their input to clinical trial design and execution is limited, since the MHRA is not the audience for the final clinical data during the product approval process.
- Competent authorities do control, audit and license the notified bodies in their country, so the MHRA may be very active at making sure the UK-based notified bodies are up to scratch. However the MHRA is powerless to take direct action against a notified body from another country if it approves devices that should not be approved, and the local competent authority takes no action.

- The MHRA was noted to have been very active in closely monitoring various sources of safety signals in the case of metal on metal hip prostheses, including various national joint registries. The MHRA implemented medical device safety alerts as a result of this.

3) How could the legislation and regulations be improved?

- The scope of this inquiry should have been Class III devices, not just medical implants.
- Any issues with inconsistency and the inability (perceived or real) of notified bodies to adequately assess complex medical devices, devices used to treat chronic conditions, or combination products (not already regulated as drugs), would be addressed by having Class III devices assessed by a central agency, staffed with experts in medical device regulation including those with expertise in assessing clinical data. This central agency could also be responsible for licensing notified bodies throughout the EU, which would ensure consistency of standards across borders.
- It may not be necessary to change the conformity assessment pathway for Class III devices; it would just be that one organisation instead of potentially a hundred organisations would be responsible for the assessment.
- The current system does not really allow a transparent translation of medical policy from public opinion to legal implementation. In other words, notified bodies are a large step away from government control as they are private commercial companies that undergo periodic licensing by the competent authorities. In the recent public furore about hip prostheses, the notified body that actually approved the device for marketing was not mentioned in all the media coverage. Too much public pressure may be a bad thing, but no public accountability is equally dangerous.
- A central body approving and overseeing notified bodies may be not be readily accepted by industry, although it would reduce inconsistency and increase fairness. It would likely increase the demand for clinical trial data for some Class IIb and Class III devices, which industry may see as overly onerous. However, if a new system of approving higher risk devices increases patient safety and public confidence, this would have long-term societal and industrial benefits.
- A central body, perhaps part of the European Medicines Agency (EMA), overseeing higher risk device approvals would facilitate designation of combination products. These products are well-defined and their regulatory path clearly laid out by the FDA, but in Europe there is much confusion as to how to define a combination product and which regulatory path (device or drug or both) is appropriate. As medical devices become more complex and incorporate biological, pharmaceutical, and cellular products, a central body that could be consulted to determine the appropriate regulatory and developmental pathway will be helpful in commercialising innovation at the same time as protecting patients.

4) How could the European Commission ensure that potential changes to the MDD do not hinder the introduction of innovations in medical implants to the market?

- If a product is truly innovative, and has incremental benefit to patients, it is unlikely that increased regulation will hinder its introduction to the EU market.
- The primary driver for regulatory oversight must be patient safety. There is evidence that the current system sometimes fails patients in this regard. Therefore a clearly defined and robust regulatory framework with a focus on short and long term patient safety, should serve patients and industry well.
- However increasing the bureaucracy surrounding product development is seen as a negative influence on introducing innovative products to the EU market. Often increasing layers of bureaucracy slow research and increase costs, without adding any appreciable benefit in terms of increased patient safety. So great care must be taken to increase the quality of regulatory

oversight, without increasing bureaucratic hurdles to the point of blocking ground-breaking research from proceeding at a reasonable pace.

- The main issue with devices that are subjected to large clinical trials is that they are rather similar to their competition or controls, and therefore not that innovative!