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Pre-Market Authorization And Other Sweeping Proposals Unveiled In EU Parliament

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High-risk medical devices would for the first time be subject to a government pre-market authorization process before being allowed to launch in the European Union under a proposal issued April 12 by a key legislator in the EU Parliament.

The proposal comes from Dagmar Roth-Behrendt of Germany, who was designated rapporteur, or liaison, for medical device reform legislation in the Parliament's Public Health, Environment and Food Safety Committee. The Public Health committee's proposal could be central in shaping the package that is ultimately voted on by the full Parliament.

The report goes much further than device regulatory reform recommendations issued last year by the European Commission. Regarding new pre-market requirements, the Commission's proposal would create a new centralized "scrutiny mechanism," establishing a new EU Medical Device Coordination Group with authority to review notified bodies' conformity assessments for certain high-risk products, but its recommendations would be nonbinding. (See *"EU Device Reform Proposal Adds More Government Scrutiny, But No FDA-Like Review Body" – "The Gray Sheet," Oct. 1, 2012.*) Currently, notified bodies, which are hired by device makers to review their products and/or facilities, provide the only stamp of approval necessary to launch a device in the EU.

Device makers have come out against the EC's scrutiny mechanism proposal and view outright pre-market approval as an even worse option.

The rapporteur's report also advances more far-reaching proposals compared to the European Commission on clinical trial requirements, the oversight of notified bodies, reprocessing of single-use devices and post-market surveillance.

Pre-Market Approval: Centralized And Decentralized Processes

The report's strong call for pre-market authorization comes in response to concerns among legislators with the current process of conformity assessments conducted by third-party notified bodies for high-risk devices in the EU.

"The conformity assessment procedure has shown substantial weaknesses over the past years, such as the lack of transparency, swift approval and placing on the market of medical devices despite insufficient investigations on patients and therefore insufficient clinical data, consequently putting patients at risk," the report declares. As a result, formal pre-market review by government bodies, either at the European or member-state level, is needed for high-risk products, the report argues.

Specifically, devices that would be subject to the new regulatory scheme are those "listed in class III, those implanted into the body, incorporating a substance considered to be a medicinal product, intended to administer a medicinal product, or utilizing nonviable tissues or cells of human or animal origin, or their derivatives," according the report.

Under Roth-Behrendt's proposal, devices that fit this description and are also deemed "innovative" would need to undergo pre-market authorization by a newly established Committee for the Authorization of Medical Devices, housed in the centralized European Medicines Agency, which currently performs pre-market drug reviews.

Authorizations granted through the "innovative" process would last five years, the report notes. At the end of this period, the authorizations could be renewed on the basis of a re-evaluation of the risks and benefits of the device, as demonstrated in the field.

High-risk devices deemed "noninnovative" would be subject to a decentralized approval process conducted by competent authorities in individual member states of the EU. Generally, though not always, the approval would be accepted by other EU countries through a harmonization process.

The proposal promises that reviews conducted by both the centralized and de-centralized processes will be completed within 210 days following receipt of a valid application. Under the centralized process, the Committee would be allowed one request of additional information – including on-site inspections or samples – during the review process.

"These provisions have been introduced to ensure swift procedures and quick decisions for the benefit of manufacturers and patients," the report concludes.

Industry Skepticism

But experts close to the device industry are skeptical of that claim.

Eucomed, the European medical device trade group, issued

a strong warning about the proposed legislation, saying that centralized approval would "create an enormous bureaucracy" and "delay access to lifesaving medical innovations."

BVMed, the German Medical Technology Association, noted April 17, "We reject mandatory official approval, since it would neither increase patient safety nor accelerate market access."

Erik Vollebregt, a medical device attorney with Axon Lawyers in Amsterdam, called the proposed 210-day review a "magical number," noting in an interview that that figure was simply copied from the EU's medicinal products legislation.

The 210 days, Vollebregt emphasizes, only concerns the time to an initial decision by the EU committee or member state authority. There are multiple provisions within the legislative recommendations that could prolong the process significantly, or even linger indefinitely, Vollebregt suggests.

For instance, the centralized committee would need to seek the opinion of the European Commission and member states before its approval decision can be finalized. In the decentralized process, the approving member state needs to send its detailed decision to other countries where marketing is sought by the manufacturer, potentially triggering a protracted back-and-forth process that could also involve EU-wide groups. (See box.)

There is also concern that the process for designating devices as innovative or noninnovative would be clumsy. The report does not describe the standards for making the determination or list particular devices that would be considered innovative. Instead, the matter is left to the European Commission, which would categorize devices via a regulatory maneuver called "delegated acts."

This maneuver involves the Commission defining a particular medical device as innovative, whereupon the Parliament and member state leaders would get a chance to comment on any particular decision. "It'll become a completely politicized process," Vollebregt predicted, suggesting that public entities will interfere with decisions based on short-term considerations.

Furthermore, he argues that Roth-Behrendt's proposal has no mechanism for deciding which approval path a device will travel if it has not previously been categorized by the European Commission.

Questions also continue to circulate about the feasibility of established government review processes in Europe, particularly under the persisting austere economic environment.

"Of course you can wave your magic wand and say, 'Let there be an agency,' but if nobody is going to pay for it, then how is it going to work?" Vollebregt said.

This viewpoint mirrors concerns expressed by some members of Parliament at recent hearings on the device reforms. (See *"EU Parliament Considers More Stringent Medical Device Regulations" – "The Gray Sheet," Apr. 1, 2013.*)

The report does not specify how the new EU medical device review Committee would be funded. With regard to the increased activities necessary of member states' competent authorities, the recommendations empower them to "levy fees for activities on the national level," provided they are comparable with other member states' fees and made transparent.

Members of Parliament also questioned whether there would be a sufficient volume of expertise in the government to handle all of the new review requirements. "Does Europe have the expertise, sufficiently, to do all this scrutiny?" Mairead MacGuinness of Ireland asked at a hearing last month.

Emphasis On Randomized Trials

Also potentially impacting a company's ability to launch a new device in the EU would be heightened clinical-trial standards detailed in the rapporteur report. Specifically, the report installs a presumption that randomized controlled trials

After The 210 Days: Extra Review Steps In Place For High-Risk Devices

In the centralized pathway for "innovative" devices that is proposed, after the EU medical device review committee reaches a decision, it transmits its opinion to the European Commission. The Commission then has 15 days to prepare a report concerning the reasons for the decision, which it transmits to the member states. After receiving the report, the member states have 22 days for "written observations" on the draft decision; they can also request that the opinion be discussed at a plenary meeting of the Committee on Medical Devices.

If the written observations "raise important new questions of a scientific or technical nature" at the plenary meeting, the European Commission may decide to refer the matter back to the European Medicines Agency for further consideration.

Similar, though not identical, obstacles may delay device-makers' trip on the "non-innovative" pathway. After the 210 days for the initial review process, the national competent authority (assuming approval) prepares a dossier to send to other member states when the device-maker plans to launch its product. After receipt of the dossier, the member states have 90 days to make a decision; if they decide in the negative, another 60 days is taken to coordinate and resolve whatever disagreements they might have via the Medical Device Coordination Group.

Should no agreement prove to be possible, the matter will go to arbitration before the Committee on Medical Devices, which will appoint a rapporteur, along with any necessary individual experts; the applicant will be allowed time to submit an opinion supporting approval. The report specifies that any arbitration decision should be issued within 60 days; if the decision isn't to the applicant's liking, it can submit a request for a reexamination of the opinion within 60 days.

Any draft opinion emerging out of the Committee is subject to opinions from the member states, within 22 days. Any new questions may trigger a referral to the EMA for further consideration.

should be the primary method of assessing the safety and efficacy of a device.

"As randomized controlled investigations usually generate a higher level of evidence for clinical efficacy and safety, the use of any other design or study has to be justified. Also the choice of the control intervention shall be justified. Both justifications shall be provided by independent experts with the necessary qualifications and expertise," the report states.

Device makers in Europe have already been resisting calls by some policymakers and clinicians for more randomized trials, arguing that it is often not possible or appropriate to perform such a study for a device.

"Most devices cannot be evaluated with randomized clinical trials as it is hard to blind and randomize due to strong ethical and practical issues in the choice of the 'comparator' (e.g. what would have been a comparator for an implantable cardiac defibrillator? How would one implant a placebo hip?)," writes John Brennan, Eucomed's director of regulatory and technical affairs, in a January 2012 blog post.

"We therefore believe that 'real world' data from observational studies performed under routine conditions are equally important [as pre-approval clinical trials] (structured post-market surveillance)," concludes Brennan.

Roth-Behrendt also inserts a provision calling for ethics committees to approve clinical studies. This is one of the few proposals in the report that Vollebregt labels as positive based on his experience in the Netherlands. "The Netherlands is actually one of the few countries in Europe that already has such a model with ethics boards. That model seems to work quite well, actually," he said, although he warned against conflicts of interest on the boards.

Personnel Standards For Notified Bodies

Despite the emphasis on pre-market approval, notified bodies would retain a core function in the EU's medical device regulatory structure under the public health committee's proposal. The third-party groups that are contracted by manufacturers would still provide the needed regulatory clearance for lower-risk products to enter the market and retain strong auditing authority for all devices.

Last year's European Commission proposal would establish stronger authority for the EU national governments to oversee notified bodies and heighten the standards that the groups must meet to maintain auditing certification. The government aims to implement some of these changes even before the comprehensive medical device reform legislation is enacted. (See *"Surprise Inspections, And More, Coming Soon To The EU" – "The Gray Sheet," Oct. 29, 2012.*)

The rapporteur report acknowledges these recommendations as big improvements over the status quo, but says they don't go far enough.

"Both the functioning of notified bodies and their monitoring by national authorities have shown huge weaknesses over the past years," the report states.

The parliamentary recommendations put more emphasis on regulating the expertise of personnel who work at both the notified bodies and at the competent authorities that oversee them.

"Notified Bodies shall have available, on a permanent basis, personnel with expertise in clinical investigation design, medical statistics, clinical patient management, [and] Good Clinical Practice in the field of clinical investigations and pharmacology," the report states.

The bodies are also required to subcontract with "public entities" or "external experts"; the list of these entities and their tasks must be made available.

And permanent, in-house personnel at national authorities must have "proven qualifications equivalent to those of the personnel of the notified bodies." Progress on securing such personnel is subject to peer review among EU member countries, with the results shared publicly.

Roth-Behrendt's report also includes directives to make certain that notified bodies charge fees that are more comparable to manufacturers.

With a goal of a creating a "level playing field across Member States," the legislative proposal includes provisions that would require fees charged by both notified bodies and national competent authorities to be comparable and publicly reported, under enforcement by the European Commission.

Industry attorney Vollebregt says this is a form a price-fixing that is inappropriate. "Price is something that should regulate itself if it's a true market," he contends. "If it's not a true market – like the rapporteur is apparently going to propose – then why not turn the Notified Bodies into government agencies in the first place if you don't want them to compete…?"

He suggests that higher-quality notified bodies should be allowed to compete by charging a higher price; otherwise, he argues, there will be a race to the bottom as the bodies try and reorganize in a fixed-price setup.

Reprocessing Versus Single-Use

A particularly dramatic proposal in the public health committee rapporteur's report that caught the attention of some in industry addresses the issue of reprocessing single-use devices.

EU authorities have been weighing for some time the right approach to overseeing the practice of reprocessing of disposable devices. A 2010 report from the European Commission concluded that the practice poses health risks and that at least some element of validation for the process is needed to ensure patient safety. (See *"Europe Questions Safety Of Reprocessed Devices, But Holds Off On Action" – "The Gray Sheet," Sep. 6, 2010.*)

Some countries in Europe ban the practice, while some others regulate it. Eucomed, representing original equipment manufacturers, has pushed for a Europe-wide ban of the practice.

But the April 12 report from the public health committee turns the issue on its head, emphasizing an assumption that in most cases device manufactures are labeling devices as single use for pure profit motives, rather than patient safety.

Roth-Behrendt's recommendation states that all medical devices should be presumed reprocessable, unless the manufacturer specifically applies for a single-use indication.

Manufacturers' preference for such labels is sometimes "the result of economic considerations," she states in the report. "In [the] recent past, manufacturers have started to label their devices as single use too systematically."

Under the proposal, manufacturers would have to provide evidence for their device's single-use status, and for class III devices, a new panel called the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) would be required to provide an opinion to the European Commission on the request within 90 days of an application.

SCENIHR is empowered to seek additional evidence from an applicant; a request from the panel has a 30-day deadline upon receipt.

Moreover, single-use devices can be reclassified as reusable devices. Any entity can apply to SCENIHR to reprocess a single-use device; if the panel agrees, the device is relabeled as reusable. Appeal processes are available to the applicant, but not the manufacturer.

However, the proposal "entails an automatic shift of responsibility from the manufacturer to the reprocessor," the report states, when a reprocessor decides to reprocess a device.

"I was appalled, actually," Vollebregt said of the reprocessing proposal. He called it a "literal translation" of "what must have been a complete lobbying proposal" by forces in the reprocessing lobby.

Post-Market Surveillance

In the realm of post-market surveillance, the Roth-Behrendt report is a less dramatic departure from plans presented by the European Commission. The report attempts to build on the Commission's proposals to strengthen the EU-wide Eudamed clinical database by allowing better access by patients to known information about the risks and benefits of devices.

Specifically, her recommendation would require a manufacturer, for any device submitted for marketing authorization, to draw up a report on the safety and performance of the device that is "easy for a lay person to understand." The report will be submitted along with the other application materials, and will be made available on Eudamed.

Similarly, adverse event reports will be posted to Eudamed and be available to the public. The report states that "While the public might have more differentiated access [than medical professionals], if there is a legitimate interest in gaining knowledge of serious incidents concerning certain medical devices at an early stage, a comprehensive right to information must therefore be created."

Political Next Steps

The rapporteur's report is an important milestone in the ongoing process in Europe to reform device and diagnostic regulations that has gained momentum in the wake of scandals with defective breast implants and metal-on-metal hips. (See *"EU Parliament Considers More Stringent Medical Device Regulations" – "The Gray Sheet," Apr. 1, 2013.*) A debate in the public health committee on Roth-Behrendt's sweeping proposal is scheduled for April 24.

The public health committee is not the only body with jurisdiction for the medical device legislation. The Internal Market and Consumer Protection Committee's rapporteur, Nora Berra – a French parliamentarian from that country's right-wing UMP Party – released her own report April 4 on the reform package.

Critically, Berra's report does not include a centralized pre-market authorization procedure, but it does include recommendations that would strengthen pre-market oversight compared with the European Commission's earlier proposals. She recommends a more systemic review of notified body conformity assessments by the Commission-proposed Medical Device Coordination Group than proposed by the commission. And, significantly, Berra would make the ruling by this EU-wide group binding, i.e., if the experts decided to reverse a notified body's positive review, the device would be blocked from launching on the EU market.

The Coordination Group would also be tasked with reviewing periodic safety reports compiled by manufactures of class III devices and assessing whether the risk/benefit ratio of a product has changed, and thereby whether a change in its approval status is necessary.

How controlling each of the proposals will be of the overall legislative process still remains to be seen. Attorney Vollebregt suggests that the socialist parties in the European Parliament are committed to some sort of pre-market approval process, while the free-market parties are as yet uncommitted. He says it is possible that the Roth-Behrendt proposal is purposefully extreme as a negotiating tactic, but he remains uneasy about the potential of the provisions becoming law.

In addition to Parliament, the EU Council, which represents the heads of each member state, will also need to take up the legislation before it can be implemented.