CLINICAL TRIALS AND MEDICAL DEVICES IN EUROPE: INNOVATION AND HARMONIZATION
For several years now, European institutions and the European Commission in particular have been looking at the problems related to clinical tests and medical devices. The requirement for greater transparency and increased control of rules, conditions and criteria, and the need to make administrative procedures less rigid, have also become more urgent in the opinion of European citizens and health professionals, particularly following the case of the PIP prostheses, which revealed undeniable malfunction in the process of certification and control.

The European Commission therefore launched two initiatives to improve the efficiency and safety of these procedures: in July 2012, a draft regulation relative to clinical tests abrogating the 2001 directive, and in September 2012, two regulations covering medical devices and in vitro diagnostic medical devices. This issue of The European Files will therefore mention the modifications envisaged by this new legislative package proposed by the Commission (the systematic notification of all alerts, improvement of the "Eudamed" European database, etc.), while also exploring innovative avenues for discussion to enhance transparency and the traceability of ongoing processes (establishment of an expert group on medical equipment which will give an opinion on the medical devices most at risk, improvement of professional training on medical devices, etc.). One of the fundamental issues is also to clarify the administrative restrictions, both for health professionals and for patients, in order to facilitate carrying out clinical tests while ensuring maximum safety for users. In this respect, it is important not to slow research and development, for which innovation in industrial, scientific and medical matters is fundamental for the European Union, due to administrative frameworks that are too rigid. On the contrary, the legislator’s role should consist of promoting research and innovation while ensuring the safety of patients.

On the occasion of the reorganisation of this European legislation, the various contributors to this issue of The European Files give their insights into the current situation in the European Union and its development.
# Table of Contents

## Editorial

Laurent Ulmann, Editor-in-chief, The European Files

### Clinical Trials and Medical Devices in Europe

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laws on Clinical Trials and Medical Devices: Better, Stronger, Safer</td>
<td>6</td>
</tr>
<tr>
<td>For an Efficient Control System of Medical Devices</td>
<td>8</td>
</tr>
<tr>
<td>Improving the Safety of High-Risk Medical Devices</td>
<td>9</td>
</tr>
<tr>
<td>Clinical Research in the European Union</td>
<td>10</td>
</tr>
<tr>
<td>The Role of the Legislator to Increase Participation in Clinical Trials</td>
<td>12</td>
</tr>
<tr>
<td>Clinical Trials in Europe</td>
<td></td>
</tr>
<tr>
<td>All Drug Trial Results Must Be Reported</td>
<td>14</td>
</tr>
<tr>
<td>Providing Greater Transparency in Clinical Trials</td>
<td>15</td>
</tr>
<tr>
<td>The Future of Ethics Committees Within European Clinical Research</td>
<td>16</td>
</tr>
<tr>
<td>The Future of Clinical Research in Europe: How Can We Enhance the EU’s Innovative Edge?</td>
<td>18</td>
</tr>
<tr>
<td>A New Regulation for Clinical Trials in Europe: Opportunity or Threat? An Industry Perspective</td>
<td>20</td>
</tr>
<tr>
<td>Maintaining Europe’s Attractiveness as a Location for Investment in Research and Clinical Development</td>
<td>22</td>
</tr>
<tr>
<td>Simplification of Administrative Procedures Cannot Hamper Safety of Clinical Trials or Ethical Standards</td>
<td>23</td>
</tr>
<tr>
<td>Taking the Effective Clinical Trials Ahead</td>
<td>24</td>
</tr>
<tr>
<td>Clinical Trials and Europe’s Responsibility to Humanity</td>
<td>26</td>
</tr>
<tr>
<td>A Pan-European Perspective on the Challenges of Patient Recruitment for Clinical Trials in Rare Diseases</td>
<td>27</td>
</tr>
<tr>
<td>The Draft Regulation on Clinical Trials on Medicinal Products - A Second Chance for European Clinical Research</td>
<td>28</td>
</tr>
<tr>
<td>Revising the European Clinical Trials Legislation to Facilitate Trials for Rare Diseases</td>
<td>30</td>
</tr>
<tr>
<td>Ensuring Patients’ Trust in Medical Devices</td>
<td>33</td>
</tr>
<tr>
<td>PIPII Breast Implants: What Malfunctioning and What Remedies?</td>
<td>34</td>
</tr>
<tr>
<td>Medical Devices – Safeguarding Innovation and Patient Safety</td>
<td>35</td>
</tr>
<tr>
<td>Should We Set Up Premarket Authorizations for High-Risk Medical Devices?</td>
<td>37</td>
</tr>
<tr>
<td>Towards a Medical Device Regulation that Guarantees Patient Safety, Ensures Patient Access and Keeps Innovation in Europe</td>
<td>38</td>
</tr>
<tr>
<td>How Can we Ensure an Efficient Monitoring and Post-Market Surveillance of Medical Devices by Notified Bodies After Their Market Authorisation?</td>
<td>40</td>
</tr>
<tr>
<td>Should a Marketing Authorization BeImplemented for High-Risk Medical Devices?</td>
<td>41</td>
</tr>
<tr>
<td>Revise the Rules Relating to MD Advertising to Ensure the Right Information and Optimal Patients Protection</td>
<td>42</td>
</tr>
<tr>
<td>Regulated Reprocessing of Single Used Devices – Article 15 vs 10 years of Experience</td>
<td>43</td>
</tr>
<tr>
<td>Medical Devices: the Impossible Single Market</td>
<td>44</td>
</tr>
<tr>
<td>Implementing a Real Vocational Training for Using Medical Devices</td>
<td>45</td>
</tr>
<tr>
<td>How Depositaries’ Expertise Benefits Medical Devices Supply Chain</td>
<td>46</td>
</tr>
<tr>
<td>Team NB Perspective on the Medical Devices Regulation in Europe</td>
<td>48</td>
</tr>
<tr>
<td>Single Use Medical Device Reprocessing</td>
<td>49</td>
</tr>
<tr>
<td>Regulation on Medical Devices</td>
<td>50</td>
</tr>
</tbody>
</table>

## Medical Devices in Europe

### Ensuring Patients’ Trust in Medical Devices

Paola TESTORI COGGI, Director General of DG Health and Consumers, European Commission

### PIPII Breast Implants: What Malfunctioning and What Remedies?

Michèle RIVASI, MEP, vice-president Group of the Greens / European Free Alliance, European Parliament Co-sponsor for the “PIPII resolution”, Shadow rapporteur (ENVI)

### Medical Devices – Safeguarding Innovation and Patient Safety

Marina YANNAKODAKIS, MEP, European Conservatives and Reformists Group, European Parliament, Shadow rapporteur (ENVI)

### Should We Set Up Premarket Authorizations for High-Risk Medical Devices?

Nora BERRA, MEP, Group of the European People’s Party (Christian Democrats), European Parliament, Rapporteur for opinion (IMCO)

### Towards a Medical Device Regulation that Guarantees Patient Safety, Ensures Patient Access and Keeps Innovation in Europe

Serge BERNASCONI, Chief Executive Officer of the European Medical Technology Industry Association Eucomed

### How Can we Ensure an Efficient Monitoring and Post-Market Surveillance of Medical Devices by Notified Bodies After Their Market Authorisation?

Gilles PARGNEAUX, MEP, Group of the Progressive Alliance of Socialists and Democrats, European Parliament

### Should a Marketing Authorization Be Implemented for High-Risk Medical Devices?

Thomas ULMER, MEP, Group of the European People’s Party (Christian Democrats), European Parliament

### Revise the Rules Relating to MD Advertising to Ensure the Right Information and Optimal Patients Protection

Françoise GROSSETETE, MEP, Group of the European People’s Party (Christian Democrats), European Parliament

### Regulated Reprocessing of Single Used Devices – Article 15 vs 10 years of Experience

Marcus BRACKLÖ, Chief Executive Officer, Vanguard AG, Germany

### Medical Devices: the Impossible Single Market

Corinne LEPAGE, MEP, Group of the Alliance of Liberals and Democrats for Europe, European Parliament

### Implementing a Real Vocational Training for Using Medical Devices

Chantal JOUANNO, French Senator, Chairman of the Information Mission on Implantable Medical Devices

### How Depositaries’ Expertise Benefits Medical Devices Supply Chain

Jean-François FUSCO, Chairman of EALTH (European Association for Logistics and Transport in Healthcare), Chairman of LOGSanité and Pharma GM for AEXXDIS FM HEALTH

### Team NB Perspective on the Medical Devices Regulation in Europe

François SCHLEMMER, TEAM NB Director, Corinne DELORME (LINEG-MED Regulatory Affairs Manager TEAM NB Secretary)

### Single Use Medical Device Reprocessing

Frédérique PERLIER, Health Products Purchasers Association, Paris France, Project Manager, Medical Department, Capio Santé, France

### Regulation on Medical Devices

Dr. Franz TERNAY, President, European Social Insurance Platform ESP
Laws on Clinical Trials and Medical Devices: Better, Stronger, Safer

Tonio BORG
EU Commissioner for Health and Consumers, European Commission

The health of European citizens and the functioning of the internal market are high on Commission’s 2013 agenda, with the revision of the laws on clinical trials and medical devices. At this very moment, debates on the proposals are in full swing in Council and Parliament. Once adopted, the new laws will bring an end to pressing issues caused by the current legislations.

Clinical trials

Last summer, the Commission adopted a proposal for a regulation to replace the current Directive on clinical trials. Clinical trials are used to test the safety and efficacy of pharmaceuticals on human beings, and to secure innovative treatments and state-of-the art clinical practice. The current directive has ensured a high level of patient protection in the EU. However, in practice it also created a number of problems: excessive red tape, high administrative costs, and unnecessary delays to obtain the trial authorisation. In addition, the directive was implemented in very different ways in the 27 member states. The current directive has ensured a high level of patient protection in the EU. However, in practice it also created a number of problems: excessive red tape, high administrative costs, and unnecessary delays to obtain the trial authorisation. In addition, the directive was implemented in very different ways in the 27 member states. The current directive has ensured a high level of patient protection in the EU. However, in practice it also created a number of problems: excessive red tape, high administrative costs, and unnecessary delays to obtain the trial authorisation. In addition, the directive was implemented in very different ways in the 27 member states.

The Commission will be entitled to conduct controls in member states and other countries to ensure that the rules are being properly supervised and enforced.

Finally, the proposal also takes better account of the actual risk the subjects are exposed to during the clinical trial. It introduces the concept of ‘low-intervention clinical trials’, meaning that a clinical trial which poses only minimal risk to subject safety compared to normal clinical practice, will be subjected to a lighter procedure. Such trials, often conducted in a routine setting, will be subjected to a minimal risk to subject safety compared to normal clinical practice. Therefore, one of the major changes introduced by the regulations will affect the way notified bodies are appointed by member states, and will give notified bodies more powers as regards manufacturers. Furthermore, the notified bodies’ conformity assessments related to high-risk devices will be scrutinized on a case-by-case basis by government experts.

Medical devices

In September 2012, the Commission adopted a proposal for a regulation on medical devices and a proposal for a regulation on in vitro diagnostic medical devices to replace the current three directives on active implantable medical devices, on medical devices and on in vitro diagnostic medical devices.

Medical devices play a major part in the lives of patients, as well as in boosting the economy and innovation. They cover a huge spectrum of products used for prevention, monitoring and treatment of diseases or disabilities. We estimate at 500,000 the number of medical devices currently available on the EU market. They include, among others, bandages, X-ray machines, implants or pacemakers. All of them proceed from a dynamic network of 22,500 EU innovative businesses, 80% of them SMEs, that employ 500,000 people. In 2009, the sales of medical devices generated around €85 billion, of which around 8% were re-invested in R&D.

All of them proceed from a dynamic network of 22,500 EU innovative businesses, 80% of them SMEs, that employ 500,000 people. In 2009, the sales of medical devices generated around €85 billion, of which around 8% were re-invested in R&D.

In conclusion

Together with my team I am working hard to achieve adoption of these important proposals on medical devices and clinical trials by Council and Parliament by next year. The sooner the regulations are adopted, the faster they will help further enhance patients’ safety and promote growth and jobs in the area of public health and research.
For an Efficient Control System of Medical Devices

European Union has a low rate of notified incidents and this rate varies from country to country. There is a general feeling that the EU lacks homogeneity in incident notification and in the functioning of the control system, and that is the reason why we should introduce improvements in the new regulation.

An efficient surveillance system of medical devices is essential in order to get a study regulatory framework. The few elements after-specified can contribute to achieve this goal:

- The presence of an electronic system easing notification of incidents and corrective measures by manufacturers and enabling public authorities to be immediately informed. To do so, it would be useful to have a European centralised control platform.
- The availability of an European database of information on elements such as notified incidents, conclusions about performed examinations, safety corrective measures taken by manufacturers, as well as measures adopted and recommendations issued by authorities.
- The involvement of health professional, users and patients in the notification of serious incidents. In this respect, actions are required to be taken, both by national authorities and by the European Commission.
- The promotion of implant registers at a national level allowing early detection of complications, as well as the development of interoperability among these registers for data sharing.
- The cooperation of national authorities and scientific experts in the evaluation of incidents, especially when these incidents have significant effects on health or when they occurred in different member-states, in the search of the most efficient measures,

- The implementation by manufacturers of quality management systems and clinical after-sale follow-up programs adjusted to the category of risk and the type of health product to ensure compliance with standards and improve their conception and production through experience. Notified bodies should carry out audits on a regular basis to check the enforcement of these measures.
- The introduction of mechanisms ensuring the accountability of manufacturers in case of damages produced by faults or defects on their products, including costs caused by treatments and diagnosis needed by patients.
- The establishment of sanctions within national laws for the cases of non-compliance with the requirements imposed by the control system.

We have to seize the opportunity that offers the revision of the European regulation in order to introduce new elements, such as the above-mentioned, that allow the strengthening of the control system on medical devices in the interest of patients, health professionals and citizens of the European Union.

Improving the Safety of High-Risk Medical Devices

European health ministers are confronted with a complex balancing act, particularly in a period of crisis such as the one that we are undergoing: how to provide our fellow citizens with the best quality and safety in health care, while allowing innovation to be available as quickly as possible, and ensuring the sustainability of our social-security systems?

We are prepared to meet this triple challenge because our priorities are clear: the first is to ensure treatment of the best possible quality while guaranteeing our citizens maximum safety. Patients, medical staff and manufacturers have everything to gain from this.

Several recent problems related to implantable medical devices lead us to want to strengthen the regulation that governs the marketing of medical devices. The European health Commissioner shares this objective. The proposed regulation of medical devices that the European commissioners adopted in September 2012 largely meets our desire for improved supervision of notified bodies responsible for CE marking, increased control of the market and medical devices surveillance, and improved clinical evaluation of medical devices.

For this category of high-risk devices, the opinion given by the group of experts must be binding. It would be inconceivable to see products marketed for which the group of experts have given an unfavourable opinion after assessing the clinical dossier. This opinion, if it is negative, should lead the company to supplement the dossier, in order to provide the panel of European experts with the necessary guarantees. These are the conditions under which the trust of patients and doctors can be ensured. It is important that our companies continue to innovate, to provide patients with the necessary innovations to treat them. This is the second priority that we set ourselves. The medical devices sector is important for our economies. It has potential for job-creating economic growth that we wish to promote. Our ambition is therefore to secure the system, paying particular attention to the most sensitive medical devices, while allowing our companies to remain innovative and develop. This will make European products more attractive: the quality and safety of medical devices ought to be considered as a prime asset for European products.

The Commission and the Member States have already made significant efforts to implement immediate measures to secure our system of CE marking. Everyone is aware that the new regulation package must be adopted as quickly as possible, in order to use all the levers that can secure this market. Our objective is the adoption of the whole text before the end of the European Parliament’s term of office. This objective is achievable if the Member States and members of Parliament combine their efforts, with the help of the Commission. It is our ambition. We know that it is shared by all European health ministers. We will put all of our energy into it. Indeed, the safety of patients can wait no longer.
Clinical Research in the European Union

Clinical research is conducted in practically all areas of medicine. One important area in which clinical research is practised is the clinical trial of medicinal products. Without such research, there would be no further development of and no improvement in therapy with medicinal products, which is the most important tool in medical treatment. Many patients are placing their hopes for recovery in a broadening of the range of therapies.

At the same time, clinical research can also be an engine for economic development in the Member States of the European Union. It constitutes an important economic sector with ambitious tasks requiring highly qualified workers. For our economic future it is therefore important that we continue to develop and augment clinical research in the European Union. Harmonised framework conditions for the administrative details are absolutely imperative if we are to continue to secure the clinical research locations of the European Union.

Furthermore, this must all take place under strict observance of the indispensable ethical standards, in a regulatory environment that guarantees a high level of protection for the patients who make themselves available for a clinical trial.

For many years now, harmonised regulations on clinical trials of medicinal products have existed in the European Union. Council Directive 65/55/EEC\(^1\) specified for the first time that an application for the authorisation to place a medicinal product on the market was to be accompanied by documentation on the results of the tests and clinical trials conducted with the product in question. The requirements to be met by the documents to be submitted became more detailed with the adoption of Directive 75/318/EEC.\(^2\) Finally, the Directive currently in force, Directive 2001/20/EEC\(^3\), specifies that all finished medicinal products for human use, for which an official application for marketing authorisation is to be submitted, and for which there is insufficient experience to assess their efficacy and safety, must be subjected to a clinical trial. These provisions created a fundamentally uniform standard within the European Union, which does justice to the significance of the clinical trial as an indispensable component of the medicinal product safety system.

This notwithstanding, in some cases, different requirements continued to exist in the Member States with respect to clinical trials and how they are to be conducted. These led to delays and complications and, in the end, hindered the effective implementation of the regulations within the Community. As a result, Directive 2001/20/EC\(^4\) laid down legal and ethical framework conditions for clinical trials and further harmonised the corresponding administrative regulations. This Directive, which entered into force on 1 May 2001, contained the requirement that the Member States of the European Union incorporate the new regulations into national law within two years and apply them with effect, one year later, from 1 May 2004. In the Act on Medicinal Products and with the Ordinance on Good Clinical Practice,\(^5\) Germany incorporated this European requirement into national law.

Notwithstanding the degree of harmonisation achieved, the current regulations still leave room for differences in the national implementation and administrative enforcement by the Member States. This renders the conduct of multinational clinical trials more difficult.

On 17 July 2012, the European Commission submitted a Proposal for a Regulation of the European Parliament and the Council on clinical trials with medicinal products for human use and repealing Directive 2001/20/EG.\(^6\) This regulation is meant to replace Directive 2001/20/EG. This directly applicable regulation is meant to further harmonise the legal framework for clinical trials with medicinal products for human use, Europe-wide, divergent national regulations should be pre-empted. The proposal is currently being discussed in the Council by the Member States and the Commission.

The Commission’s proposal is also highly important for Germany from the point of view of securing clinical pharmaceutical research in the long term. Basically, the core elements of the proposal, such as the new concept for the regulation of multinational studies and the simplified and streamlined rules for low-risk studies involving authorised medicinal products, are commendable. However, the criticisms made by the European Commission to justify the new regulations do not, in this form, apply to the situation in Germany. According to both the national industry and our higher Federal authorities, the existing procedures for obtaining an authorisation and the approval of the ethics committees have proved their worth, the stipulated deadlines have been met, and there has been no recognisable decline in study numbers.

In Germany, the Commission’s proposal is being discussed on the technical and political levels. In the meantime, the Bundesrat has taken a decision on this proposed Regulation. Moreover, the proposal was under discussion in the Bundestag’s committees and has led to the adoption of a cross-party decision.\(^7\)

The reactions in Germany show that some provisions of the proposed Regulation have a polarising effect. A need for amendment has been identified, particularly, of the following aspects:

- Independent, interdisciplinary ethics committees must continue to be appropriately involved in the authorisation procedures for clinical trials.
- The level of protection afforded to particularly vulnerable groups may not be compromised. The level of protection that clinical trial subjects, especially children and adults who are unable to give their informed consent, are guaranteed under the German Medicinal Products Act and similar legislation in other Member States, must be upheld and, consequently, incorporated into the proposed Regulation; specifically, information and treatment must be provided by a doctor; research that benefits sick children as a group may only be permitted where the risks and burden involved are minimal.
- A workable timeline and reasonable deadlines that allow the submitted documentation to be properly examined must be fixed for assessing the applications for authorisation.
- The authorisation procedure must be more strongly geared to the intensified and effective co-operation among Member States in assessing the application, as is already the case with the voluntary harmonisation procedure that is successfully implemented by the Member States cooperating in this regard. Nevertheless, the responsibility of the individual Member States must be safeguarded.
- Technical support must work smoothly. By the time the Regulation enters into force, the envisaged single portal – through which all applications for authorisation will be submitted and accordingly communication will take place (for instance with the sponsor of a clinical trial and among the Member States concerned by a clinical trial) must have a sufficient degree of functionality.

- On matters of insurance, several approaches must be viable. The existing system of insurance for clinical trial subjects in Germany has essentially proved its worth. Therefore, the Member States should be granted some degree of latitude in organising the insurance coverage of trial subjects. Germany rejects any obligatory requirement for the establishment of a national indemnification mechanism.

The discussions on the Commission’s proposal at the national and international levels are on the right track for ensuring that the proposed Regulation will properly consider the interests of all stakeholders involved and will, overall, lead to the expected improvement in the conduct of clinical trials in the Member States.
The Role of the Legislator to Increase Participation in Clinical Trials

Astrid Krag
Danish Minister of Health

Clinical trials are part of the backbone in developing the European health care industry. Patients benefit from every single trial carried out. Every trial put into practice helps us to increase our knowledge on what works and what does not work – and thus helps us to find the very best treatments for all patients. Clinical trials are consequently a crucial part of the development of new treatments in the vast European health care industry. For that reason, I find it of great importance that the regulation of clinical trials is as well-functioning as possible. European patients, European industries and European economies will benefit from it.

Clinical trials on medical products for human use are currently regulated by Directive 2001/20/EC. The directive has lead to the implementing of good clinical practice in the conduct of clinical trials. It has, among other things, lead to important improvements regarding safety and ethical soundness of clinical trials and in the reliability of data from clinical trials. However, the legislation has not been able to prevent all problems. During recent years, the number of applications for clinical trials in the EU has decreased considerably. Simultaneously, the administrative costs for conducting a clinical trial by Member States. In addition, I would underline that no personal data and information relating to clinical trials. The intention is that the EU-database shall be established to enable the cooperation between Member States and sponsors. It also serves as a transparency mechanism to the public, which in the end could lead to a greater understanding and recognition of the high value that clinical trials bring to society.

Besides, damage compensation may be another tool to encourage the participation in clinical trials. An indemnification mechanism has existed in Denmark since 1992 and we deem it to be a successful mechanism that provides for a safety-net for trial subjects. The current directive has introduced an obligatory insurance, which has unfortunately substantially increased the costs of conducting clinical trials. However, there seems to be no evidence that the number of damages, or the amount, has increased with the entry into force of the directive.

In the future, the main focus in legislation on clinical trials of course ought to be on the clinical trial subjects – regardless of the involvement of patients or healthy trial subjects. In Denmark, citizens are highly motivated to participate in clinical trials. This motivation should be ensured also in the future – and preferably spill over to the rest of the EU Member States. Without persons who are willing to participate, there will be no clinical trials!

As I see it, we have the essential tools to encourage confidence – and thereby to motivate persons to offer their bodies in the service of science. If I look at the proposal for a new regulation, the main tools primarily will be: protection of subjects and informed consent, increased transparency and damage compensation.

Regarding the protection of the trial subjects, their rights and well-being are crucial in every single trial. Therefore, an important aim with the new legislation is to ensure the rights and the safety of the subject. I am content that clinical trials in emergency situations have been dealt with in a specific provision in the proposed regulation. The aim is to allow trials in emergency situations, on certain conditions, according to existing international conventions.

In my opinion, increased transparency should be one of the pillars in a new regulation. It follows from the proposal that the European Commission shall set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials. The intention is that the EU-database shall be established to enable the cooperation between the competent authorities in the Member States. I find it very positive that the database will be accessible to the public. This accessibility covers all or parts of the data contained in the database – unless confidentiality is justified due to the protection of commercially confidential information or to ensure effective supervision of the conduct of a clinical trial by Member States. In addition, I would underline that no personal data of data subjects participating in a clinical trial will be registered. There will thus be no public access to this information.

The proposal puts an obligation on the sponsor of the trial to permanently update the information in the EU-database regarding any changes to the clinical trial which are relevant for the supervision of the clinical trial by the Member States. This means that also negative results stemming from a clinical trial need to be reported via the database.

In summary, the EU-portal serves more purposes than being a tool for exchange of information between Member States and sponsors. It also serves as a transparency mechanism to the public, which in the end could lead to a greater understanding and recognition of the high value that clinical trials bring to society.

So, we will have to find better solutions to the question of compensation in the new legislation. Among other things, I find it acceptable with the proposed indemnification mechanism which works on a not-for-profit basis. The proposal puts Member States under an obligation to set up a national mechanism which shall help in particular “non-commercial sponsors” to obtain coverage for possible compensations.

I am sure that we, together – during the negotiations in progress – will succeed in agreeing on a future legislation on the conduct of clinical trials. An optimal legislation in view of the rights and safety of the trial subjects, and in view of the reliability and robustness of the data generated. All in all a legislation of great benefit to the peoples of the Union.
All Drug Trial Results Must Be Reported

Glenis WILLMOTT
MEP, Group of the Progressive Alliance of Socialists and Democrats, European Parliament
Labour's health spokesperson in Europe and Leader of Labour MEPs
Rapporteur (ENVI)

To many results from clinical trials are misleading, biased or missing. It is time that all pharmaceutical companies and researchers made the full results of studies on new and existing drugs publicly available.

In my role as the European Parliament rapporteur for the revision of the European rules on clinical trials, I am calling for wide-ranging transparency measures. My report was published a month ago and we now have all of the suggested amendments from other MEPs.

Along with many other colleagues in the Parliament, I want to see comprehensive results from clinical trials published on a public database. A summary of the results is not enough. Summaries written by those that carried out the research can be biased, and make a medicine sound more successful than it really is. Independent researchers need access to the results of the trial in order to verify the sponsor’s claims.

I am proposing that a full clinical study report is published on the new EU database. This is the same document that companies must submit to regulators for approval of their medicine, and therefore contains a full account of how the clinical trial was conducted and what the results were.

I also want to see financial penalties imposed on those that do not upload their results on time. The law in the US requires all trial results to be uploaded within a year, but a 2012 audit found that 80% of trials had failed to comply. If we are serious about openness in medicine then we have to levy fines on those not following the rules.

Numerous academic studies have found that around half of all trials are never published, usually those with negative or disappointing results. For too long unflattering studies have gone undisclosed. It is vital that we know about negative outcomes, otherwise trials can be conducted repeatedly before it becomes public knowledge that they are ineffective, or even dangerous.

There is still a long way to go, but it looks like we are making progress. The All Trials campaign is doing a great job of putting pressure on pharmaceutical companies, researchers and legislators to improve the system. The campaign was given a huge boost last month when pharmaceutical giant GSK signed up. I am determined to support these efforts by writing transparency measures into EU law, and creating a level playing field for all those who invest in clinical research.

Of course these are complex issues that need to be discussed further. Many non-commercial sponsors tell me that producing a Clinical Study Report might be too burdensome. I am happy to discuss ways to ensure that we have a workable system which is feasible for both non-commercial and commercial sponsors, but we must get an agreement that ensures true transparency.

Alongside new requirements for openness I am supporting many measures which should greatly reduce unnecessary bureaucracy and make it easier to carry out research into new and better medicines. These include setting up a single EU portal for trial applications, which will make cross-border trials much simpler. This is particularly important for rare diseases where trials cannot be carried out in one country alone. I am also supporting a reduction in bureaucracy for “low intervention trials”, the less risky studies often carried out by academics trying to improve standard treatments. And finally I am very supportive of the idea of national indemnification systems. Again this will benefit non-commercial researchers, as they will be able to use this scheme free of charge, rather than being forced to purchase extremely expensive insurance for their trials. High insurance costs can often prohibit essential research.

Now I must win the support of the rest of the European Parliament, across political groups, and that crucial vote will be at the end of April. Once I have that mandate I will need to convince EU governments that this is the way forward.

But it looks like the focus of clinical trials is shifting towards patient safety and knowledge-based medicine. Because when a patient makes the decision to take part in a clinical trial, they do so to help advance medicine, to improve treatment for themselves and for those in a similar situation.

Providing Greater Transparency in Clinical Trials

Cristian BUSOI
MEP, Alliance of Liberals and Democrats for Europe, European Parliament
Rapporteur for opinion (IMCO)

The revision of the legal framework for clinical trials is of paramount importance for the attractiveness of clinical research in the EU but also a great opportunity for stepping up transparency in clinical data trials.

Apart from providing for a single-entry point for the clinical trial applications, the EU Portal and the EU database, which will contain all the information submitted through the EU Portal, also have the advantage of providing for greater transparency in the whole process. From the very start of the debates on the Commission proposal in the European Parliament, this was a key point of discussion, namely when it comes to the transparency of the clinical trials results.

Pharmaceutical companies have been repeatedly accused of withholding information about the results of the clinical trials and in particular of not publishing the negative results of clinical trials. Some of them have also been involved in scandals generated by the overestimation of the effects of their medicines. While I consider that intellectually dishonest behaviours should be punished severely, I think we should avoid any emotional reaction to that. Therefore, I require that sponsors submit through the EU Portal a summary of the clinical trial results within one year after the end of the clinical trial.

Concerning this last aspect, I think there are two fundamental points to be clarified: what information is to be publicly accessible and at what point in time. The answer also depends on the purpose of transparency. One would not provide the same information to a patient or to an academic for scrutiny purposes, as their level of expertise and hence, their capacity to understand and exploit the data is different. Furthermore, the two questions are intertwined because the definition of what may be commercially confidential information actually depends on whether the medicine has already been granted a marketing authorisation or not.

Taking this into account, I don’t think the disclosure of raw data before marketing authorisation is a good idea. Apart from the costs involved, one cannot guarantee at this stage that the re-analysis will not be flawed or that the data will not be misused putting the protection of commercial interests is also at stake. Alternatively, I think we should rather go for a detailed summary of the results which would contain enough information to allow independent scientists to scrutinise the results presented by the sponsor. This is what I proposed in the Internal Market Committee by detailing the content of the summary in a new annex based on a technical guidance of the Commission. Moreover, this summary should also be offered in a version which is understandable to a layperson, including patients.

After marketing authorisation, the situation is a bit different, since the product is already on the market. This is probably also where the scrutiny of clinical trials results is most relevant and most needed. In this respect, the European Medicines Agency has been working on solutions for proactive disclosure of clinical trials data for such medicines which would address issues such as patient confidentiality, rules on meta-analyses and rules of engagement for sharing raw data.

The solution should flow from a thorough and informed debate on the matter and should be a balanced one. Transparency should be a means to ensure scrutiny where needed, not an objective per se. We should ensure transparency where it is really needed and relevant without disproportionate costs and burdens, especially for academia, since this would actually drive clinical research out of Europe.
Clinical Trials in Europe

The Future of Ethics Committees Within European Clinical Research

Philippe JUVIN
MD PhD
MEP, Group of the European People’s Party (Christian Democrats), European Parliament
Shadow rapporteur on the draft regulation “Clinical trials” (EWI)

The new proposal is now criticized by all the stakeholders, especially regarding the absence of the word “ethics committee” and any rules on their role within the assessment procedure of clinical trials in the draft regulation. Indeed, the European Commission did not include any measures either on their functioning nor their role within the assessment procedure.

This absence has led to a vast outcry and protests from academics and associations of patients, who feared a strong will of the European Commission to remove not only the ethics committees but also ethic assessment from European clinical trials. They claimed that this decision would jeopardize safety and health of patients. This is a serious misjudgement on the approach of the Commission. I deeply regret it.

Indeed, the European Commission never intended to remove ethics committees and to allow the conduct of clinical trials without preliminary ethical assessment. The European Commission would only like to get the European clinical research out from the impasse in which now it finds itself.

The draft regulation aims to standardize and simplify the assessment and authorisation rules. Furthermore, it is also urgent to shorten the assessment timelines and to align the draft regulation on international rules, by adjusting requirements on monitoring, labelling and patient consent in accordance with the risk added by the research.

The European Commission strategy is the following: oblige the Member States to collaborate and to rationalize their assessment procedures through a technical way (a European single portal, standardization of submission files, very short timelines, two-part assessment) while letting them organise and implement scientific and ethical assessments.

In the beginning I was really sceptic and cautious with this strategy. However, in my opinion, this approach seems now to be the most reasonable, reasoned and realistic. I do support this strategy that respects first of all the subsidiarity principle, and then, takes deeply the diversity of national rule for ethical assessment into account.

It would be useful to underline several differences and problems. First of all, the number of ethics committees from one Member State to another one. Striking example: in 2009 Hungary had only one ethics committee, while Italy had 264 ethics committees on its territory. Germany had 53 ethics committees.

Many scientific articles highlight the heterogeneous roles and prerogatives of ethics committees but also ethic assessment from a Member State to another one. Striking example: in 2009 Hungary had only one ethics committee, while Italy had 264 ethics committees on its territory. Germany had 53 ethics committees.

Many scientific articles highlight the heterogeneous roles and prerogatives of the ethics committees from a Member State to another one. We can also observe many double assessments by national competent authorities and ethics committees with frequent contradictory results.

Despite the obligation of transposing directives into national law, many Member States do not implement the principle of a single opinion per Member State within multicenter clinical trials (article 7 of Directive 2001/20/EC). This is unfortunate. In France for example, this measures has been implemented and has led to an improvement of ethic assessment and a speeding up of the assessment and authorisation process.

Regarding this heterogeneity and the national withdrawals of Member States, it is impossible and illogical to harmonise ethics assessments at the European level.

However, many colleagues call for including the expressions “ethical assessment” and “ethics committee” in the draft regulation. Moreover, they want to introduce an obligation of a preliminary favourable opinion from ethics committees before authorising and launching a clinical trial.

As shadow rapporteur for the EPP Group on this dossier, I am ready to consider this approach, but we must not jeopardize the strategy of the European Commission. Once again, in my opinion, this strategy is reasonable, reasoned and realistic and it would avoid repeating the same mistakes which has been done with Directive 2001/20/EC.

We have to keep in mind that the European clinical research involved in a globalized and competitive research. We must not repeat the same mistakes done by European decision-makers unable to understand the reality and complexity of procedures which European companies, academics and patients have been facing. The burden of responsibility which we carry is a heavy one: to ensure, at all costs, that the forthcoming regulation on clinical trials does not prove to be merely “a bandage on a wooden leg”.
Richard BERGSTROM
Director General, EFPIA

The proposed Regulation aims to make the processes for managing clinical trial applications more efficient and less bureaucratic, while maintaining a high level of patient protection. By doing so the Regulation would go a long way towards maintaining Europe’s status as an attractive centre for clinical research. Clinical trials play a large yet unrecognised role in the system of innovation and account for over €20 billion in investments throughout the EU. It needs to be recognised that the Commission proposal reflects a compromise of the diverse needs of various stakeholders, including patients, academia, healthcare professionals and the pharmaceutical industry.

EFPIA welcomes the Commission’s intent to streamline procedures for submission, assessment and authorisation of clinical trials, particularly the introduction of a single application with defined, harmonised requirements. A single decision per Member State, which is based on a review by ethics committees and competent authorities in line with their national organisation, represents a major step forward. Furthermore, the possibility for a sponsor to propose a reporting Member State for the coordinated assessment supports the process of excellence building and work sharing, which has already been started several years ago.

One of the key concepts is the harmonisation of scientific and administrative requirements for clinical trials between Member States. It is important that this is maintained throughout the legal debate as to allow for the basis of a coordinated assessment.

Enhancing cooperation between ethics committees

Ethics committees need to be included in the review process consistent with guidelines established on good clinical practice by the International Conference on Harmonisation of Technical Requirements (ICH) and the principles of the World Medical Association’s Declaration of Helsinki.

The new Clinical Trial Regulation introduces the single decision per clinical trial per Member State. This implies stronger interactions between ethics committees and regulatory agencies at a national level and the need for adjustment of national legislation in many countries. At the same time, it provides ethics committees with the unique opportunity to improve their processes, practices and organization and to enter a stronger cooperation, knowledge sharing and best practice exchange locally and across borders.

Streamlining documentation to encourage clinical trials applications

EFPIA welcomes a single set of requirements for the application dossier which requires a streamlined submission by companies and is expected to allow an assessment within competitive timelines.

Establishing competitive timelines to encourage efficiency by industry, national competent authorities and ethics committees

A system where decisions are made through co-operation between Member States and adhere to set timelines has the potential to improve the efficiency of the authorisation process and address shortcomings of the past. Tacit approval and withdrawal mechanisms are intended to ensure that Member States and sponsors comply with these timelines which have been proven to be achievable in some Member States in the past. Additionally, the proposed system offers Member States the option to conduct expedited assessments of single-country trials. At the end, the proposed concept is intended to ensure European approval times for CTAs will remain competitive compared to other regions in the world since they include both the review by competent authorities and by ethics committees.

Facilitating discussion to safeguard the EU’s innovative potential

There are important public health benefits associated with making clinical trial information more widely available. When doing so, it is imperative that individual privacy, commercially confidential information (such as on contracts), including intellectual property rights are protected while respecting international legislation. Amendments to the proposed Regulation, if realised, could make more information on clinical trials and development publicly available than in any other market. Towards this end, we are extensively engaging in the current EMA process, with all relevant stakeholders to discuss what type of clinical trial data could be made publicly available and the timing of its publication. Our belief is the EU’s innovative potential must be protected and hence that clinical data should only be made available after a product has been authorised.

Ensuring regular reviews to ensure continued success

The Regulation, once adopted, needs to support European clinical research to 2030 and beyond. Science is evolving quickly and examples include:

- novel designs (e.g. virtual recruitment, an increasing role for patients in the design and management of trials);
- the investigation of hugely innovative medicinal products (e.g. personalised healthcare, advanced therapies);
- advanced processes to manufacture medicinal products utilising increased scientific and technical knowledge.

A periodic assessment of the Regulation is needed to ensure it keeps pace with the actual scientific progress and continues to provide an appropriate framework to support European clinical research.

The Clinical Trial Regulation has the potential to make the Europe 2020 Agenda a reality – we must not miss this opportunity.
The single submission via the EU portal provides the opportunity to harmonise the application process and should be compulsory for both single country trials as well as those run in several Member States. Currently, sponsors have to submit clinical trial application dossiers to each individual National Competent Authority as well as to every individual Ethics Committee in each Member State where they intend to run the clinical trial. For sponsors of multi-country trials, the compliance with all these specific requirements results in an important extra workload without any added value for the patients.

In response, the proposal establishes the principle of a single submission for clinical trial applications so that the sponsor only has to submit one single clinical trial application dossier for all Member States concerned. However, to ensure that diverging national requirements will not persist for single country trials, the Regulation should specify the mandatory character of the EU portal for both single and multi-country trials. This would ensure genuine harmonisation of the submission requirements to National Competent Authorities and speed up the preparation time of the clinical trial application for sponsors.

A single final decision per Member State, with no additional assessment or decision at national level, is essential to streamline the approval process for clinical trials.

The approval process of a clinical trial application is complex and the process varies between the Member States. Sponsors do not only have to manage the complexity induced by the number of different stakeholders involved but also by the divergence of requirements between Member States. In our experience, the average time from submission to approval in the EU is around 70 days (excluding the time needed for ethical committees approval).

We welcome the coordinated assessment procedure, where each Member State will organise its assessment (including division of tasks between competent bodies). It will result in closer collaboration between National Competent Authorities and ethics committees at national level, and with one single decision per Member State.

It should be clear that after the decision is taken by a Member State on a clinical trial application, there should be no additional assessment or subsequent decision by national bodies. The approval therefore guaranteeing that the sponsor has the possibility to start the clinical trial in the Member State concerned.

Ethical opinion should be explicitly included in the coordinated assessment procedure

Ethics Committee opinion is an integral part of the evaluation of the relevance of a planned clinical trial, an international fundamental principle established in the ICH proceedings and the Helsinki Declaration. It is a cornerstone principle safeguarding patients’ rights. In the draft regulation, the Ethical opinion is implicitly referred to in several places and is an integral part of the single decision on the clinical trial application that shall be provided per Member State concerned. In spite of this, some stakeholders still expressed concerns that the Regulation would provide a lower level of patients’ rights protection. We do not feel that there are grounds for such concerns, however, it may be preferable to explicitly state that Ethics Committees should be subject to the provisions of the Regulation related to the coordinated assessment of the clinical trial application. Their review should be integrated in the coordinated assessment procedure and the final single decision.

A knowledge-based categorisation of clinical trials is essential to bring back academic research to Europe but to ensure a workable system, the categorisation should not be extended beyond that of low-intervention clinical trials and other clinical trials.

Currently, all clinical trials are subject to the same administrative requirements. It is not logical that the same requirements apply to a drug tested in humans for the first time versus to a trial adjusting the dosage scheme on a long time approved product.

The distinction between low-intervention clinical trials and other clinical trials, as proposed by the Commission, is strongly supported because this system would reduce the heavy administrative obligations and financial burden for low-intervention trials (of which most are conducted by academia) without compromising patient safety.

However, the introduction of further classifications would create a complex system with no real benefits, especially for the patients, and would be contrary to the objectives of the Regulation: simplification and harmonisation.

More generally, the rules contained in the Regulation should focus on patients’ rights, safety and data reliability, and should not address specific disease risks or classifications.

The timelines should remain competitive to place Europe at the forefront of research

As a result of different national requirements and different ways of organizing the scientific reviews and deliverance of the ethics assessment, there is a notable disparity amongst Member States in terms of the overall time needed to initiate a clinical trial. This certainly contributed to a decreased European competitiveness in comparison with other regions of the world.

The unified timelines proposed in the Regulation are not there to impose the utopian vision of a harmonised European ethical review. On the contrary, it accompanies the necessary differences across Europe in the ways to educate Ethics by leaving it up to each Member State to organize the relevant local processes. On the other hand, the concern of competitiveness is addressed via the application of a common timeline, imposed on all, to deliver the authorisation to start a given clinical trial. These different timelines (there are in fact several, adapted to the type of research) are challenging for all stakeholders but they are not unrealistic considering the evolution of the communication methods over the last decades. It is therefore of paramount importance to keep them competitive in the final text.

Systematic access to clinical trials results is a key element of improved knowledge for patient care and academic researchers. However, should the EMA ongoing transparency discussion really be merged with the Regulation parliamentary debate?

The systematic publication of a summary of results of all completed (or prematurely ended) EU clinical trials is a regulatory reality that started several years ago. The process is about to be achieved with the forthcoming implementation of version 9 of the EudraCT database that is currently in pilot phase. It will provide the required systematic public access to a summary of the results, one year after the completion of the trial (6 months for pediatric trials) and contribute to an improved level of general knowledge, particularly for patients, prescribers and academic researchers. The draft Regulation is perpetuating the same principle and enhancing the amount of documents to be published.

In parallel, for 2013 the EMA has launched a public consultation to discuss the parameters of systematic publication of full clinical study results (i.e. the documents submitted to the Agency in order to obtain the marketing authorisation). Importantly, in that transparency debate, the publication of full study results is meant to occur after the marketing authorisation has been granted.

Cautions should be exerted before introducing topics of the EMA transparency debate in the clinical trials Regulation. The consequences of public access to full clinical trial results prior to granting a marketing authorisation have not been fully evaluated. Is it really necessary to merge the two discussions? The question should be asked, especially when considering that the EMA transparency debate is tightly framed to deliver results by year end, i.e. even before the Regulation enters into force. We recommend that there is a clear distinction between the elements of discussion regarding the EMA policy to be developed and the clinical trials Regulation.

Opportunity or threat? The ultimate success depends on the protection of the confidentiality of the Regulation: a simplified and harmonised clinical trial application process

The competitiveness of EU medical research must be preserved and reinforced so that EU patients continue to benefit from the most innovative treatments. Now is the time to deliver legislation that will build on the important benefits brought by the 2001/20/EC Directive while correcting the difficulties that surfaced during its implementation. The European Commission issued a sound proposal following several years of analysis of the opinions of the stakeholders and iterative consultations. Staying within the framework defined during that evaluation period is already an extremely ambitious goal. Let us seize that chance to boost clinical research in Europe while putting in place a sound proposal that will accompany the upcoming evolution of the medical science.
The life sciences sector continues to develop new innovative therapies to address areas of unmet medical needs and improve patient outcomes globally. The sector is recognised as an important and sustainable knowledge based economy in the EU, providing opportunities for skilled workers in various stages of research and development (R&D).

EuropeBio supports the need for sensitive and proportionate regulatory policies underpinning the legal framework designed to promote openness and transparency in clinical development. Indeed, there are many existing provisions already in place to facilitate public access to relevant clinical trial information, for example the EU Clinical Trials Register and US ClinicalTrials.gov. Dedicated web portals have been created to facilitate public access to information pertaining to on-going clinical trials and their results, for example IFPMA Clinical Trials Portal.

We believe that a balanced approach should be taken to ensure that the means to achieve transparency and openness is not disproportionate and that the achievement of such an objective should not be done in such a way that undermines Europe’s international competitiveness in basic, applied and translational life sciences research.

Life sciences sector based on collaboration and partnerships

The changing nature of drug development puts increasing focus on collaborations and partnerships between a variety of stakeholders including academia, medical research charities, SMEs and multinational biopharmaceutical companies. This ensures drug development is more efficient and effective through better access to innovation and proper management of costs and risks. For example, a single drug could easily pass through the ownership of four or more organisations before it is finally available for patients.

Protection of know-how is a key factor underpinning the funding of such partnerships. We fear the loss of this protection would dramatically impact upon investment into the sector, which cannot be made up by public money alone, thus removing a key pillar for collaborative R&D designed to improve patient outcomes and care.

Impact of publicly accessible EU database containing commercially sensitive information

Unlike many other technology based sectors, the life sciences sector specialising in developing new medicines and technologies has a unique regulatory obligation to generate a substantial body of pharmaceutical and preclinical testing data and clinical trial data to the competent authorities to enable an appropriate assessment of safety, quality and efficacy for the purpose of obtaining a marketing authorisation.

It is important to recognise the value of know-how and R&D expertise of research based life sciences companies. To provide context, such know-how and trade secrets could relate to methods of manufacture and certain underlying technological approaches involved in the development of an innovative product. They represent a considerable investment in intellectual effort, inventive skill, time and money, but may not necessarily be capable of protection by the mainstream law of intellectual property. Nonetheless, such commercially confidential and sensitive information should be treated as a form of intellectual property.

These issues are relevant in so far as they relate to products in clinical development which do not benefit from regulatory data protection. The sponsor is required to provide an investigational medicinal product dossier (IMPD) which contains data relating to the quality and pre-clinical pharmacological/toxicological testing data, prior clinical trials and human exposure data and an assessment of the overall benefit:risk balance to support granting of a clinical trial authorisation. Certain strategic information and know-how (essentially a road-map to R&D of an innovative medicine) is often contained in the IMPD.

Moreover, expanding the amount of information that can be made public through the EU database in the proposed Regulation to revise the Clinical Trials Directive 2001/20/EC, could damage the value of the assets held by SMEs as well as the potential to obtain patent protection later in the product lifecycle. For example, an academic researcher or a spin-out company conducting a Phase I trial would be obliged to file a patent before the trial data are public. This means that mandatory early filing would not only eat into post-marketing patent protection, but might undermine the value of the patent.

EuropeBio and its membership therefore call on the European institutions to give proper consideration to this issue in the proposed Clinical Trials Regulation to ensure that commercially confidential and sensitive information arising from various stages of R&D before product approval is not disclosed unless such disclosure is justified on grounds relating to patient safety or public health and following consultation with the data owner.

In conclusion, the EU legislative proposal needs to stimulate the conduct of clinical trials in Europe to the benefit of patients and economic growth. If the commercial interests vested in product development is undermined this will dissuative investors and bring about seriously damaging consequences on Europe’s international competitiveness.

About EuropeBio: EuropeBio is the European Association for BioIndustries, bringing together bioscience companies from all fields of research and development, testing, manufacturing and distribution of biological products. It has 56 corporate members, 14 associate members and Bio Regions and 19 National Biotechnology Associations representing around 1800 small and medium sized enterprises across Europe.

Maintaining Europe’s Attractiveness as a Location for Investment in Research and Clinical Development

Christiane ABOUZEID
Chair of EuropeBio Clinical Trials Topic Group, and Head of Regulatory Affairs, BioIndustry Association (BIA)

Simplification of Administrative Procedures Cannot Hamper Safety of Clinical Trials or Ethical Standards

Alda SOUSA
MEP, Confederal Group of the European United Left - Nordic Green Left, European Parliament

Chair of EuropaBio Clinical Trials Topic Group, and Head of Regulatory Affairs, BioIndustry Association (BIA)

Last year, the Commission proposed the review of the Clinical Trials Directive. The Clinical Trials Directive 2001/20/EC has brought about important improvements in the safety, wellbeing and ethical soundness of clinical trials in the EU, setting patient wellbeing as its highest priority. Notwithstanding this contribution, the directive generated criticisms: the pharmaceutical industry said that it was too lengthy and academic sponsors stated that it was too expensive for their budgets. According to the data brought forward by the European Commission, the number of applications for clinical trials from 2007 until 2011 fell by 25%. However, even when confronted about the origin of this data, the Commission kept quiet and never released the study that contained this data. The argument of the "competitiveness" of the clinical trials has been consistently used, almost as if the new Directive for the Clinical Trials was a mere economic decision, whose success was to be measured by its economic indicators. Dramatically, the figures used by the Commission have been used as a justification for the lowering of the ethical standards of clinical trials. The World Medical Association issued a statement that reads: "the European Commission is proposing a revision of its Clinical Trials Directive (2001/20/EC) that if adopted by the European Union (EU) Parliament represents a change that puts the ethical principles for clinical research at great risk". It seems that the European Commission has solely the interests of the pharmaceutical industry in mind and this is unacceptable.

Less bureaucratic procedures are welcome as long as they not lower ethic standards, which was what proposed by the Commission. We must take into account the positive aspects of the current Clinical Trial Directive, such as ethical soundness that it introduced, and not discard it entirely. The future legislation has to ensure that no clinical trial can start without the prior approval by an independent ethics committee in any Member State concerned. This is the core issue, and it is this that is at stake. I am glad that several members of the ENVI committee from different groups tabled together amendments on this specific issue, and it is absolutely essential that these amendments be approved, thus rejecting the Commissions intuition to lower the ethical standards.

Another important issue is that the EU Portal on Clinical Trials should provide clinical reports and not just summaries of the results, whether they are positive, negative or inconclusive. A transparency procedure may be far more encouraging for researchers (and sponsors) to engage in clinical trials (and for subjects to accept to enter a trial) than the attempt of the Commission of jumping over decades of well-accepted international guidelines.

If the objective of the European Commission is to solely please Big Pharma, then we might as well keep the current directive.
Taking the Effective Clinical Trials Ahead

Karel VERKOOLEN, MD
Regional Medical Officer Europe, Sanofi

We need a modern, smart, flexible and competitive regulatory framework to accompany the development of the medical research and corresponding clinical trials in Europe. The inconsistent implementation of the current Clinical Trials Directive by the EU Member States has created a regulatory framework which is too fragmented, burdensome and costly to effectively support European therapeutic innovations. This difficult and uncompetitive environment is one of the reasons why clinical trials are gradually moving out of Europe. With the Commission’s proposal for new clinical trials regulatory framework, Europe has a unique chance to repurpose itself at the forefront of global R&D hub.

If the current Clinical Trials Directive 2001/20/EC goal “the protection of the health and safety of clinical trial subjects” has been achieved, the Commission’s statistics clearly confirm a general decline in Europe in many metrics we use to assess clinical trials and notably in multinational clinical trials. Most large clinical trials need to obtain a marketing authorisation of new medicinal products are conducted in several clinical research centers located in different countries. The benefits of multicenter trials include a larger number of participants, different geographic locations, the possibility of inclusion of a wider range of population groups, and the ability to compare results among centers, all of which increase the scope of the studies and the robustness of data used by the authorities to authorise an innovative medicinal product. Furthermore, all clinical trials bring important benefits and improvements to the Community like spreading and sharing of the state-of-the-art clinical practice across the EU medical community, fuelling innovative thinking in the clinical scientists’ teams for the benefit of patients and their relatives.

For all these reasons, the new legislative approach should reverse the current trend of the decrease in clinical trials conducted in Europe. Administrative simplification and standardisation can foster and facilitate patients’ access to large multinational trials conducted by commercial or non-commercial sponsors. At Sanofi, we think that the proposal submitted by the European Commission has the potential to deliver on this objective.

First and foremost, Sanofi is in favour of the proposed clinical trials assessment process which provides more harmonisation across the EU, moving towards a more integrated clinical trials research area. We support the creation of the EU portal which will enable a single submission of all clinical trials applications. The proposed joint scientific assessment is very promising and will help delivering a common technical assessment across Member States. Ethical assessment is also a key element of the authorisation process as it ensures that the rights, safety and wellbeing of patients in a clinical trial are adequately protected. At Sanofi, we believe that patient safety should be at the heart of all clinical trials. No clinical trial should start without being assessed and approved by an independent Ethics committee. To recognize the important role that the ethics committees play at national level, the EU legislation should respect Member States’ competence in this area leaving national competent authorities the freedom to organise themselves about to ensure the required ethical assessment.

Running in parallel, the joined scientific and the national ethical assessments – leading to a single decision at Member State level – have the potential to make a big difference provided that the process is framed by competitive and properly enforced timelines. We welcome the timelines and the tacit approval mechanism proposed by the Commission. Current experience of several EU member states shows that these timelines are not only achievable but also competitive as compared to the timelines used in other parts of the world, and therefore have the potential to help re-establish Europe as an attractive place for conduct of clinical trials.

At Sanofi we believe that such timely and more harmonised assessment of clinical trials applications will reduce fragmentation and red tape, offering a more coherent and competitive environment for researchers enabling patients to have a safe access to the latest medical innovations.

Last but not least, Sanofi is aware of the current debate on access to clinical trials information. We are supportive of the need of increased transparency regarding clinical trials and recognize the important benefits associated with it. We, therefore, welcome the proposed establishment of a new public EU Database which will serve as a repository for the trials summary results. Already today Sanofi publicly discloses results of phase 2, 3, and 4 (and phase 1 in patients) clinical trials conducted on products approved for marketing and on products which development has been discontinued.

Sanofi pursues publication via European and International Clinical Trials public registries and scientific medical journals. Once results of a clinical trial with a product under development are published, Sanofi submits all other results (positive or negative) of similar studies performed with that product. However we would like to caution that premature publication of comprehensive clinical trials information may be counterproductive in the sense that this information could be used for commercial purpose by third parties without having invested in clinical research, playing against the interests of the sponsors and the European medical research. The legislators should answer the following questions: What information should be released? When? To whom? For what reasons and how? Regarding the timing of disclosure, Sanofi believes that due attention should be given to the marketing authorization (MA) status of the product. As for information to be disclosed, notably from the Marketing authorization dossier, we believe that the MA Holder should always be consulted so that it has an opportunity to seek appropriate redactions so as to protect commercially confidential information, including intellectual property, and protected personal data. All stakeholders should work to develop clear and robust standards and operating procedures so as to provide meaningful information without promoting unfair competition.
F or drugs tested in the EU there are ethical concerns to be dealt with and we have the legal framework in place to do so. For drugs tested outside the EU, often in developing countries, the ethical concerns are even more numerous and the legal framework often weak or nonexistent. The questions that must be answered are difficult; how do you ensure informed consent if the trial subjects are illiterate and unequipped? How do you guarantee that the treatment offered is effective in countries without universal healthcare?

Clinical trials are a necessary evil. Drugs need to be tested on humans in a controlled environment before they can be deemed safe for the population at large. However, the pharmaceutical companies increasingly follow the profit margin to test drugs in poorer countries where the cost is lower, the regulations less stringent.

The large majority of people who suffer from the ailments the drug will treat in the phase 1 and maybe phase 2 clinical trials have been done in a developing country, phase 3 and 4 will then often be moved to a European country, which is where the drug will mostly be sold after it is authorized.

The main aspect that we as European legislators must consider is how we ensure that the well-being of our citizens is not based on the ill-treatment or even death of someone who is our only remaining option of survival. They are not informed about the dangers of participating in more than one trial at a time and it is almost certain that they will not receive follow-up treatment or compensation if something goes wrong.

And even more unfortunate, most of the drugs tested on poor people in developing countries will never benefit the people of those countries. There is far too little money to develop new medicine for the most common diseases in the world: Malaria, cholera, rotavirus etc. The large majority of people who suffer from them are poor. Most research is therefore meant for the European and American markets where there is money to be made. And yet the trials are only moved to Europe or America when many of the kinks have been worked out. We essentially use the poor people in Asia and Africa as modern day food tasters.

Over the last 10 years, we have seen many clinical trials move to countries like India or Uganda. Most of these are so-called phase 1 clinical trials which involve a group of people who are not necessarily suffering from the ailments the drug will treat in the phase 1 and maybe phase 2 clinical trials have been done in a developing country, phase 3 and 4 will then often be moved to a European country, which is where the drug will mostly be sold after it is authorized.

The results of clinical trials on humans belong to humanity at large, whether positive or negative, leading to publication or not. In the European Parliament, we are working on complete transparency when it comes to both results and patient data from trials in Europe so that independent researchers can check the findings and the pharmaceutical companies can benefit from each other’s knowledge. This is a small step towards what is really needed: complete global transparency on clinical trials. That will be a valid way to make sure that no poor person is harmed or exposed to drugs in vain due to pharmaceutical companies’ search for profit.

The Commission proposal moves in the right direction on this issue, but I believe that we must go even further. In the future, in order for phase 2, 3 and 4 clinical trials to be authorized in the EU, the previous phases must take place in a country with the same or an equivalent system as the one in place in Europe. It will be up to the Commission, together with the European Medicines Agency, to approve other countries’ legal frameworks to ensure that they live up to this standard.

This carrot and stick approach is a step in the right direction but I fear that it is not enough. We must ensure that the ethical considerations done prior to authorization of a clinical trial in Europe, include the practice and location of precious clinical trials. This involves total transparency into where and how clinical trials are conducted even abroad as well as a focus on the ethical aspects of clinical trials in the authorization process in general.

The main aspect that we as European legislators must consider is how we ensure that the well-being of our citizens is not based on the ill-treatment or even death of someone without a voice in Europe? Part of the answer must be to help the national authorities in the developing countries create a legal framework to protect their citizens where it does not exist and improved it where it does.

Clinical Trials and Europe’s Responsibility to Humanity

Margrete AUKEN
MEP, Group of the Greens / European Free Alliance, European Parliament
Shadow rapporteur (ENVI)

A Pan-European Perspective on the Challenges of Patient Recruitment for Clinical Trials in Rare Diseases

Dr. Alexander NATZ
Secretary General European Confederation of Pharmaceuticals Entrepreneurs (EUCOPÉ)

3. See European Commission Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and amending Directive 2001/20/EC, COM(2013) 389 final, page 3. Moreover, other causes (such as salary costs and the need to conduct multinational studies to reach enrollment targets) have been addressed through regulatory requirements and consequential costs of the Directive 2001/20/EC, where the Commission is recognizing the need for companies to reach recruitment targets as one problem of the existing legislation.
Clinical trials are important for Europe: for severely sick patients desperately looking for opportunities to gain access to therapeutic progress, for the academic discipline of clinical research which is a rapidly advancing area of human research providing an attractive research environment for scientifically interested and methodologically experienced physicians who want to develop reliable data for better treatments for their patients, and for the pharmaceutical industry and their service providers — an important economic factor in Europe with hundreds of thousands of jobs. But clinical trials are difficult to perform in Europe: the governing legislation is a Directive from 2001, implemented in 2004, the “Clinical Trials Directive”. This Directive was a big step forward in harmonizing the quality and supervisory procedures for clinical trials with medicinal products as before all European Member States had completely different legal conditions. This was particularly difficult and time-consuming for academic and industry sponsors when they wanted to perform clinical trials in several Member States in parallel to achieve faster patient recruitment and thus faster availability of results.

The Clinical Trials Directive set European standards and achieved harmonisation of the principle approaches to responsibilities in clinical trials, to study approval by competent authorities and ethics committees, to patient protection, quality of study performance as well as safety data handling and created an overview for the authorities of clinical trials with medicinal products organized in Europe by academic and industry sponsors. However, the Directive foresaw independent parallel approval in all Member States participating in a clinical trial by national competent authorities and ethics committees — and it was “only” a Directive and not a Regulation.

Thus implementation occurred in quite different ways in the different Member States and created a huge amount of multiple assessments and parallel activities in multinational clinical trials with parallel submission of differently constituted documentation dossiers and related resource needs for all parties involved.

As this complex and time-consuming regulatory system was considered to be an important factor for the marked reduction of clinical trials in Europe and all stakeholders involved called for reduction of bureaucracy, the European Commission decided to propose a new legislative environment for clinical trials: a Regulation with a radically streamlined study approval process and timelines, where the coordination of the assessment in multinational trials is shifted from the sponsor to the competent authorities, with differentiated risk considerations and related study conditions as well as with reduced administrative efforts in authorisation dossier preparation and safety reporting.

The new system foresees a “coordinated assessment procedure” amongst all Member States involved in a multinational trial including the patients’ voice. This assessment procedure is divided in a “Part 1” in which the scientific and ethical aspects of the trial are assessed with the result of a single decision on the acceptability of the trial and in a “Part 2” in which in parallel the suitability of the investigators and the trial’s national ethical acceptability are assessed.

This multinational autorisation procedure is enabled by a single electronic portal: the sponsor submits the authorisation request dossier once, the assessing bodies have access to this information and submit their reports to the system. The whole approval procedure is supposed to be completed within 25 days after a 6 days dossier validation period and only few days for sponsors to complete the dossier or answer additional questions. For so-called “low-interventional trials” with authorized medicinal products, investigations within their authorised label and only causing minimal risk and burden to the study participants, the assessment procedure will even only take 10 days.

It is left to the Member States to implement a collaboration system between competent authorities and ethics committees that enables national decision making as contribution to the coordinated assessment process in so short timelines.

The Regulation foresees that the sponsor selects one of the involved Member States as the “reporting Member State (rMS)” and all other countries involved are “concerned Member State (cMS)”. However, the Regulation does not define how the Member States will manage this coordination and how to ensure that the national opinions and concerns of the national competent authorities and ethics committees are taken into consideration by the rMS.

As ethical review systems are under national responsibility the Regulation does not explicitly mention “Ethics committees” and “independent ethical review” but refers to the Declaration of Helsinki and the ICH guideline on Good Clinical Practice and describes the constitution of the national assessing body in line with current practice of ethics committee constitutions in most countries.

The very narrow timelines, the unclear role and future of ethics committees in this process with the related concerns on patient protection and the difficulties to ensure a true multinational assessment and decision are the most frequently mentioned concerns of the stakeholders but also other aspects of the proposed Regulation like a national patient liability insurance system or the possibility to include patients in an emergency situation into a clinical trial without their informed consent raise intense debates.

Many comments and suggestions from different stakeholders like academic and industry sponsors, ethics committees, competent authorities, patient organisations, not-for-profit organisations, etc. have been sent to the European Parliament and were carefully considered by the Parliament’s Rapporteure’s. Many stakeholders in mid-2008 have been provided with a description of this Regulation and the Regulation work in daily practice.
Revising the European Clinical Trials Legislation to Facilitate Trials for Rare Diseases

Yann LE CAM
Chief Executive Officer, EURORDIS

EURORDIS has put forward specific amendments to the proposal that are designed to facilitate the process of initiating and conducting clinical trials for rare diseases:

EURORDIS, the European Organisation for Rare Diseases, is the non-governmental patient-driven alliance of patient organisations representing 581 rare disease patient organisations in 51 countries encompassing more than 4000 rare diseases. Since its creation in 1997, EURORDIS has been committed to facilitating the development of therapies for rare disease patients, which are characterised by small and geographically scattered patient populations and expertise. EURORDIS seeks to improve the quality of all aspects of clinical development by promoting the involvement of patients’ representatives in clinical development decision-making procedures, such as clinical protocols, ethical aspects, information on studies and the communication of results.

Clinical trial conduct in the European Union (EU) has specific requirements, which are delineated in the Directive 2001/20/EC of 4 April 2001, commonly known as the “Clinical Trials Directive.” This Directive encompasses the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Clinical trials performed in the EU are required to be conducted in accordance with the Clinical Trials Directive.

Similarly, trials conducted outside the EU and submitted in an application for marketing authorisation in the EU must follow principles equivalent to the Clinical Trials Directive provisions.

The Clinical Trials Directive has been criticised by researchers, patient organisation representatives and other stakeholders for slowing down clinical health research by requiring a burdensome amount of paperwork and bureaucratic legwork. Consequently, a Public Consultation was launched in February 2011 on a Concept Paper on the Revision of the Clinical Trials Directive, which set out to address some of the concerns of the Directive. EURORDIS submitted a contribution to this Consultation (learn more).

On 17 July 2012, the Commission adopted a Proposal for a Regulation on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC. This proposal has been submitted to the European Parliament and the Council. EURORDIS has put forward specific amendments to the proposal that are designed to facilitate the process of initiating and conducting clinical trials for rare diseases: Amendment on Article 7 bis (new): Assessment report on clinical trials in rare diseases

In the specific case of clinical trials in rare diseases - as defined in the EU Regulation on Orphan Medicinal Products - the reporting Member State shall seek expert opinion from the Protocol Assistance/Scientific Advice Working Party at the European Medicines Agency (EMA) on the disease or group of diseases concerned by the study, including on aspects covered by Part II.

The Rationale for this amendment proposal lies in the fact that for the overwhelming majority of rare diseases, the patients, data, and overall expertise are very limited and scattered, and must be gathered at the European level in order to reach well-informed decisions on the authorisation of clinical trials. The amendment proposal seeks to facilitate the decision-making process by introducing well-informed reports produced by EMA-level experts. For rare diseases, of which over 6000 have been identified to date, such reports can only be produced through cooperation at the EU level. The most relevant expert group to produce these reports is the Scientific Advice Working Party of the EMA because this group is in charge of the Protocol Assistance procedure specific for orphan medicinal products, providing scientific and expert advice on clinical trials for rare diseases. For multinational clinical trials involving rare diseases, the experts at the EMA would deliver an opinion based on their expertise and knowledge for each specific clinical trial to support the decision-making process, which would remain at the national level.

It should be noted that this proposed amendment results from extensive discussion with stakeholders, including researchers performing clinical trials in rare diseases, small populations. Members of the European Parliament, as well as the Commission.

Another proposal EURORDIS is promoting concerns Article 7: EU database

Article 7: EU database - The EU database should include information on the localisation of the investigation sites. The navigation tool should be available in all EU languages, as should information related to the title of the trial, the objectives, and the inclusion/exclusion criteria.

The Rationale for this proposal stems from the current situation, in which a patient who wishes to have more information on an on-going trial and/or who wishes to participate in a trial, must contact either the sponsor (which may dissuade patients), or search on a website that is based outside the European Union.

Finally, EURORDIS is putting forward one further amendment proposal specific to genetically modified organisms (GMO).

Article 7: Assessment report – Aspects covered by part II: 1. Each Member State concerned shall assess, for its own territory, the application with respect to following aspect:

(i) New: Compliance with genetically modified organisms (GMO) regulation

Rationale: Today there are more and more clinical trials involving advanced therapy medicinal products (ATMP) as defined in article 2 of Directive N°1394/2007 (gene therapy; cell therapy and tissue engineering) and most of these products are genetically modified organisms (GMO). Regarding European rules, each EU Member State shall designate a local competent Authority/Committee to authorise the use of GMO. As a consequence, GMO legislation applies to these products, when used in a clinical trial.

No mention of these Authorities/Committees is made in this future regulation. To improve the future system described in this regulation it is important to include the GMO aspect in part II of the Assessment report.

According to the Commission Proposal to revise the Clinical Trials legislation, approximately 24% of all clinical trials applied for in the EU are multinational clinical trials and these multinational trials involve approximately 67% of all subjects enrolled in a clinical trial. For low-prevalence rare disease and/or orphan medicine trials, which frequently involve very small and scattered patient populations, the number of trials that are multinational is much higher.

The revised proposal is to be voted at the Parliament Committee level on 24 April 2013. EURORDIS is confident that the amendment proposals put forward would facilitate clinical studies, particularly for trials involving low-prevalence diseases and hopes that the decision-makers will include them in the new Regulation.
Ensuring Patients’ Trust in Medical Devices

Paola Testori Coggi
Director General of DG Health and Consumers, European Commission

When the Commission started working on the revision of the medical devices directives in 2008, the aim was to bring the legal framework up to date with twenty years of constant technological progress. A stronger legislation on medical devices was indeed necessary to ensure a high level of patient safety, the smooth functioning of the internal market, and maintain the innovation and competitiveness of the European medical devices sector on top.

We estimate at about 500,000 the number of medical devices currently available in Europe, the world’s most innovative market. They range from low risk to high risk devices, depending on criteria such as the invasive character of the device, how long it is in contact with the body or which is the part of the body concerned. Hip implants, breast implants, intraocular lenses and pacemakers are examples of high risk devices.

In a rapidly ageing society, they offer cost-effective alternatives to systematic and long-term hospitalisation. Thanks to them, what we thought belonged to the realms of science-fiction has come true and changed patients’ lives. A typical example of such innovation is blind people recovering partial eyesight with a microchip inserted in their retina. This groundbreaking achievement could not have been possible without an eye chip, another high risk medical device.

Under the current directives, most high risk medical devices have proved to be safe and have served their purpose well. However, cases such as the PIP breast implants scandal or the metal-on-metal hip replacements problems have revealed shortcomings in the current regulation and have reminded us that high risk medical devices may pose a risk to patients. We learned from these lessons and added in our proposals a series of measures affecting, among others, notified bodies, market surveillance, transparency and traceability.

Notified bodies are organisations designated by Member States to assess whether a device meets EU safety and performance requirements, a prerequisite to the CE mark. Conformity assessments for high risk medical devices always involve notified bodies. If the assessment is positive, the manufacturer is authorized to label his product with the CE mark, required for placing the product on the Union market.

In our proposal, we strengthen the criteria used for Member States to monitor existing notified bodies and we propose that all new nominations be assessed on a joint basis, by a team of Member States’ experts and Commission experts. Together, they will examine whether the new notified bodies have the necessary competence to conduct conformity assessment of devices.

Notified bodies must be independent and meet high quality standards. Therefore, we also reinforce their powers vis-à-vis the manufacturers. In particular, we have introduced stricter requirements for unannounced inspections of manufacturing premises, as well as checks of device samples both before and after their placing on the market. To ensure the independence of notified bodies vis-à-vis manufacturers, we have introduced a requirement for rotation within its personnel.

A major novelty in our proposal is the mechanism for scrutiny of notified bodies’ assessments of some high risk medical devices.

The scrutiny mechanism will require notified bodies to inform the Member States’ Medical Devices Coordination Committee of all new applications for conformity assessment of high-risk devices. This committee will be entitled to request, on a case-by-case basis, a summary of the notified bodies preliminary conformity assessment. After an examination of this report, it will deliver its comments on this text.

This procedure is not a pre-market authorisation, as applies to medicines. It is first of all a tool for Member States to be informed at an early stage about high risk medical devices likely to reach the market. It will also enables Member States to check on the performance of notified bodies prior to the delivery of the EU certificate.

Moreover, the scrutiny mechanism will only apply to a small number of medical devices. We admit that the speed to market of some of these products may be slightly slowed down, by about three months. However, prevention is better than cure. A faulty procedure must be stopped before it is too late.

Once the product is on the market, we must ensure it is under proper surveillance. At present, the vigilance system is national; it is fragmented. We propose setting up an EU vigilance system that would funnel all serious incidents and make coordinated analyses possible by all Member States concerned. This could lead to a higher level of patient protection across the EU and harmonize the corrective actions pressed upon manufacturers by national authorities.

Closely related to vigilance, traceability of devices must be reinforced throughout the supply chain. We also suggest to have all manufacturers fit their devices with a Unique Device Identifier, mandatory for all high risk devices. This will allow for fast and effective measures in case of safety problems.

In addition to the aforementioned measures, we also stress the need to keep EU citizens informed on the available products, via a European database on medical devices and in vitro diagnostic medical devices. Transparency is yet another necessary step to restore trust and maintain European medical devices sector in poll position.

Safe, effective and innovative medical devices and in vitro diagnostic medical devices certainly bring important benefits to the health of European citizens and to their quality of life. They are also crucial in helping the European Union to meet current and upcoming demographic, societal and scientific challenges.
PIP Breast Implants: What Malfunctioning and What Remedies?

Michèle RIVASI
MEP, Vice-president Group of the Greens / European Free Alliance, European Parliament
Co-sponsor of the "PIP resolution", Shadow rapporteur (ENV)

An estimated 300,000 women, including 100,000 in Europe, received faulty breast implants from French company Poly Implant Prothèses (PIP). These medical devices had been secretly made using industrial silicone normally used in mattresses rather than material approved for medical surgery. This type of silicone contains components capable of passing through the shell of the implant, so they end up later in the body tissues.

Widely used in France, the UK, Spain and Germany, these implants appeared to be dangerous for women’s health, causing cancers. The fraud was discovered in early 2010, a huge scandal upon which the European Parliament could not remain silent.

Although national governments are responsible for public health policy, EU legislation covers over 10,000 medical devices sold in Europe. This is why, following the PIP scandal, the European Parliament adopted a resolution on June 14th 2012, on breast implants produced by the French company PIP.

Europe needs a more rigorous system for testing medical devices before they are approved.

I asked (through an amendment to the resolution) the European Commission to shift to a pre-market authorization system for these medical devices, because they can be as dangerous as medicines. While consumption of a drug can be stopped without delay in case of adverse effects, the removal/replac- ement of an implantable device requires surgical intervention: which means additional risks of infection and potential anesthetic rehabilitation etc. I was very satisfied to see that my colleagues decided to follow my request and to vote in favor of this proposal. It was necessary to send a clear signal to the European Commission asking for stricter rules in order to prevent such a scandal from ever happening again.

On the health side, I also asked the Commission to demand an appropriate toxicological assessment of all medical devices and to suggest the gradual phasing out of the use of substances that can prove carcinogenic, mutagenic or toxic for reproduction. The Greens also won on this important issue. If applied, that would mean a phase out of all kinds of soft PVC infusion devices containing DEHP (classified as toxic to reproduction).

We mustn’t forget that these devices enter the body and are in constant contact. Now that we know the danger of endocrine disrupters and other chemical products (long term effect with DEHP classified as toxic to reproduction),

Health authorities across Europe failed to give consistent information on what to do about defective PIP implants. This is why we need a system which allows consumers to defend their rights and obtain compensation for the damage they suffered.

The European Commission’s answer is to reform the current decentralised system by allowing a new Medical Device Coordination Group to request additional assessments – such as longer or larger clinical trials – for some “Class III”, or high-risk, devices. As the negotiation process between governments, parliament and the Commission is likely to be lengthy, and new legislation may not come into force across the EU until as late as 2019, we sincerely hope that no new scandal will appear in between.

We regret the fact that at present, there is no European guidance on the designation of notified bodies, nor on the audits that these bodies carry out. The case of PIP implants, like that of hip replacement prosthesis, have highlighted the failure of the current certification system and controls carried out by the notified bodies, as no authorization is required for the marketing of such products.

We also called for compulsory breast implant registers in all 27 Member States along with a mandatory patient-passport traceability system. A single European data base should be established to bring together information about medical devices on the market, regis- tration of economic operations, vigilance and market surveillance; clinical investigations, notified bodies and EC certificates issued. There must be more unannounced test visits by inspectors. A centralized European approval is important: the manufacturer must be able to provide the results of a positive risk-benefit ratio for patients in clinical trials. European citizens can not accept being treated as guinea pigs.

Any revision of the Medical Devices Directive must be proportional in its approach, restore the confidence of patients, consumers and healthcare professionals while not increasing bureaucracy or stifling innovation. At the same time we must not lose sight of the cornerstone of all health legislation, namely the safety of the patient.

In this context, I see the revision of the directive as a way to iron out the flaws and shortcomings within the current regulatory framework in order to ensure further progress in protecting patients from undue harm, while also fostering patient access to safe, timely and improved medical device technologies.

Recent scandals have made us all too aware of the flaws and gaps in the directive which we need to overcome. We need to strengthen the legislation in those areas where we need to increase patient safety.

As in all areas of health we need robust trans- parency. With medical devices the issue of transparency is more important as they are not subject to pre-market authorisation by a regulatory authority. Devices are at present grouped into four categories; the medium and high-risk categories have to be assessed by an independent third party known as ‘notified bodies’. This being the case, it is even more important that the process is transparent.

Notified bodies are member state-driven, and their position will be strengthened, giving their function some teeth in terms of their rights and duty to carry out unannounced factory inspections as well as other tests on devices. These inspections and tests, however important they may be, must not lead to unnecessary delays. And here I refer to the fact that the notified bodies will have to inform an expert committee of new applications for conformity assessments of high-risk devices.

The danger here is that this might cause delays in marketing devices without any real value-added to patient safety. We must also be conscious of creating additional burdens on SMEs who produce medical devices, especially at a time when small business is feeling the pinch from the economic crisis and is already weighed down by EU red tape.

We need to take into account the inherent differences between larger multi-national enterprises, and their smaller counterparts. Small businesses often do have a regulatory department and may not be able to meet the resulting costs of assisting such visits. This may unnecessarily drive up costs for small companies who may as a result be forced out of the market. I do welcome proposals to allow SMEs to ‘buy in’ the expertise and hope that the parliament will support them.

Medical Devices – Safeguarding Innovation and Patient Safety

Marina YANNAKOUDAKIS
MEP, European Conservatives and Reformists Group, European Parliament
Shadow rapporteur (ENV)

Following the scandal involving fraudulent breast implants which affected tens of thousands of women in Europe and around the world, the revision of the Medical Devices Directive must make certain this can never happen again. The revision of the directive comes not only in the wake of the breast implant scandal, but also follows reve- lations of potential problems in metal-on-metal hip replacements. Furthermore, the European Parliament will examine the directive at a time when healthcare systems across Europe are simultaneously facing greater demand for their services in a time of economic austerity.

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We need to take into account the inherent differences between larger multi-national enterprises, and their smaller counterparts. Small businesses often do have a regulatory department and may not be able to meet the resulting costs of assisting such visits. This may unnecessarily drive up costs for small companies who may as a result be forced out of the market. I do welcome proposals to allow SMEs to ‘buy in’ the expertise and hope that the parliament will support them.

One of the areas which I believe will add value to the legislation is the unique device identifier (UDI) on devices for purpose of traceability in the event of unforeseen problems. Identifying medical devices will reduce problems should a medical device need to be recalled, and will aid the important process of market surveillance.

To protect patients we must also have the best innovative and competitive products on the market without unnecessary time delays. This means that we should be very cautious in proposing a centralised European approach that could potentially see the European Medicines Agency (EMA), or a similar EU agency, taking a larger role in pre-market authorisation in the area of combination devices. We must be vigilant not create a burdensome layer of adminis- trative bureaucracy that could see us move away from overall management and coordi- nation of the system by the member states’ competent authorities, and their appointed notified bodies.

The current directive is far from perfect and there are areas we need to concentrate on in the new legislation. We need to work to ensure the patients, consumers and health care professionals have confidence in the systems and in the devices they use. At the same time we must work to allow industry to bring safe, effective and innovative products to the market. By doing this we will also have an industry which grows, attracts more investors and ultimately produces more affordable devices. All this while respecting the foundation of patient safety and overall patient wellbeing.
Safe Medical Devices Contribute Directly to Safe Working Environments

This Regulation aims to guarantee high standards of quality and safety for MDs allowing for a high level of protection of health and safety for patients, users and other persons. The term “user” is defined in the current proposal as “any healthcare professional or lay person who uses a device”. This includes not only frontline medical staff, such as nurses and doctors, but also caregivers in outpatient and alternative healthcare settings, laboratory staff and support workers such as cleaners, laundry workers, prison staff etc.

"Health and safety" is mentioned throughout the Regulation proposal as an overarching goal. In this spirit, the proposal includes the general safety and performance requirements for MDs, it explicitly stating that “the devices and manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and where applicable other persons”. It also underlines the need for devices to avoid risk of injury to patients, users and other persons.

The relationship between safe and high quality MDs and the overarching goal of ensuring health and safety for users, patients and other persons allows for this legislation to synergise with applicable EU legislation on occupational health. The regulation should therefore refer to legislation for high levels of safety for users and patients in healthcare settings including the design and performance characteristics of MDs cited. This is certainly the case with Directive 2010/32/EU on the prevention from sharp injuries in the hospital and healthcare sector, which aims to improve occupational safety following a framework agreement by the social partners at EU level which recognises the need to provide MDs incorporating safety-engineered protection mechanisms in order to limit risk of injuries and infections from medical sharp. Therefore, it is entirely logical for such a provision to be recognised in the general safety and performance requirements of the MDs regulation.

Healthcare institutions need to make sure that their employees receive the necessary training for the correct use of MDs, tools and practices that help reduce needlestick injuries, the transmission of healthcare associated infections and other adverse effects in order to ensure the safe use of new medical technology and surgical techniques.

All healthcare workers should also receive adequate protection, through vaccination, post-exposure prophylaxis, routine diagnostic screening, provision of personal protective equipment, and the use of medical technology that reduces exposure to blood-borne infections.

I believe that these proposals can have an important contribution for the safety of workers in the healthcare environment. As such, safe MDs contribute directly to working conditions and need to provide for the safest possible working environment.

Should We Set Up Premarket Authorizations for High-Risk Medical Devices?

Several Health Ministers and members of Parliament have legitimately advocated for the implementation of premarket authorizations after the PIP scandal. This call should not be analysed through this scandal, that a premarket authorization would not have permitted to avoid. Actually, this issue challenges us about the necessity of medical device evaluations and especially clinical evaluations (which importance has increase with therapeutic medical devices) and the necessity of harmonizing practices within the EU in this domain. Our fellow citizens, who have the right to obtain guarantees of high security, look forward to this demand.

Nowadays, almost 80 different certifying (notified) bodies intervene to evaluate clinical data from manufacturers and authorize their products to be disseminated in 27 different countries. It could be then difficult to homogenize the assessment requirements and methods especially as the good practice corpus in this domain remains very general, in particular because of the diversity of devices and their constant evolution (materials, ergonomics, surgical interventions...). In addition, the current state of market authorization procedures makes it difficult to ensure that the evidence used by manufacturers to justify the conduct of clinical trials (and approved by certifying bodies) is still up to date and the resort to equivalence (allowing to depart form the clinical investigation) still excessive.

The Commission decided in its proposal to favour a pragmatic approach. Without setting up a new agency such as the EMA, the Commission alternative is to establish a group of European experts (MDCG) whose function is to scrutinise high-risk devices through a control system that would have two advantages: implementing a kind of European public agreement in a process that is for now “privatized” (manufacturers and accredited bodies) and following the appearance of new sensitive medical devices on the market.

It seems though, in the current state of things, this procedure is not suitable for anyone:
- For some health authorities and consumer organisations, the mechanism dispositions are insufficient, especially because the conclusions of the control would not be binding. Thus, a device having a negative notice from the expert group could still be put on the market.
- For manufacturers, it will be a long process with an uncertain outcome. It would result in a significant burden for competitiveness which is crucial in this moving sector with short innovation cycles.

While giving answers to legitimate concerns of European patients about a public control on certain high risk categories medical devices, we have to find feasible solutions and improve the existing model as far as possible to encourage innovation and preserve rapid access for patient to innovative devices.

Thus, the European scrutiny should be automatic in order to guarantee that it constitutes a true control and not a simply consultation. Thus a negative opinion would prevent devices from being certified and introduced in the market.

Conclusions of this scrutiny should be binding in order to guarantee that it constitutes a true control and not a simply consultation. Thus a negative opinion would prevent devices from being certified and introduced in the market.

Once gained experience, some independent groups of clinical experts could probably go along with the Commission to help establish guidelines and common specifications addressed to manufacturers and accredited bodies for clinical evaluation and post-market follow-up and then progressively reduce the scope of this mechanism to start in class or very innovative devices.

We should not implement a rigid system in such a moving sector, but a system that would become stronger thanks to new data related to existing devices. It would then result in harmonized practices all across European Union.
Towards a Medical Device Regulation that Guarantees Patient Safety, Ensures Patient Access and Keeps Innovation in Europe

Serge BERNACONI
Chief Executive Officer of the European Medical Technology Industry Association Eucomed

European medical device manufacturers acknowledged that the current regulatory system in Europe needs an overhaul. It needs to be significantly improved to address safety concerns, meet increased expectations and take account of the advancements in healthcare technology. In particular, industry unanimously agrees that incidents like the fraudulent PIP breast implant case should never happen again.

What do we have and what do we need?

It is important to note that the European system is known for providing its citizens with timely access to safe technology thanks to the effective decentralised device-specific approval system. True, the system needs to be significantly improved but we should fix what’s broken and strengthen what works instead of radically changing the system. Through this approach we will be able to guarantee safety and provide Europe with a predictable and effective regulatory system for patients, healthcare professionals, healthcare systems and keep value-based innovation in Europe.

The Commission’s proposal

The Commission’s proposal represents a step in the right direction and many of the recommended measures are welcomed by industry as they: (1) improve patient safety; (2) do not unnecessarily delay patient access to medical devices that save or improve lives and (3) do not hamper innovation. However, more improvements are necessary, especially with regards to the controls and monitoring of Notified Bodies – professional organisations that are authorized by national governments to assess the safety of medical devices before allowing them to be made available to patients (pre-market approval).

More stringent control measures on Notified Bodies

Industry believes that more stringent control measures on Notified Bodies are necessary to ensure the highest safety of medical technology for patients in Europe. The current proposed measures such as the ability for the European Commission to further specify the regular checks of manufacturers by Notified Bodies are not sufficient. Industry believes that a comprehensive systematic control procedure is necessary that includes measures to ensure that Notified Bodies are meeting the highest quality standards as well as ensuring that the clinical evidence for medical devices is being properly reviewed by independent clinical experts. This systematic control procedure would replace the proposed ‘scrutiny procedure’ (article 44), which is essentially a duplication of reviews and checks and does not contribute to patient safety. The proposed scrutiny procedure is a ‘needle-in-a-haystack’ approach which should be replaced by a systematic procedure that prevents the ‘needle’ to land in the haystack in the first place. Only then will Europe successfully increase patient safety and prevent unnecessary delays of medical devices reaching patients.

Improvements on seven key focal areas

Besides the monitoring and control on Notified Bodies, industry suggests improvements on seven key focal areas and ten additional topics. The details can be found in our position paper “Towards a regulation that guarantees patient safety, ensures patient access and keeps innovation in Europe”. In summary the seven key focal areas are:

1. Only the best Notified Bodies should be allowed to approve medical devices to allow for rapid identification of adverse events and to ensure coherent and timely action by Member States.
2. A clear, predictable and effective regulatory system that works for patients and innovation – a regulation that works for Europe.
3. Clear science based classifications are needed to avoid the currently proposed arbitrary reclassification of families of medical devices without any scientific or other justification, which will lead to global confusion. Clear and science based procedures must be followed to ensure that devices are appropriately classified.

Listening to stakeholders

The revision of the EU medical device directives is a process that affects the whole spectrum of Europe’s healthcare stakeholders. Medical device manufacturers agree with the views of doctors, patients and some Members of European Parliament expressed at a hearing held in the European Parliament on 26 February that the current system must be significantly improved to increase patient safety, maintain timely patient access to the latest life-saving technology and keep medtech innovation in Europe. Panellists at the hearing proclaimed the need for greater transparency, traceability of devices and strict control of notified bodies – the entities charged with reviewing new medical devices.

A concern has been raised that European patients do not enjoy faster access than US counterparts because Europe’s national health systems are slow in reimbursing new technologies. While the approval of a medical device is for the whole of Europe, reimbursement is organised differently via national health systems. Early patient access in many EU countries is extremely low through special payment mechanisms and/or leveraging available reimbursement for innovative medical technologies. The existing special payment mechanisms accelerate access and bridge the period between product approval and new specific reimbursement for innovative technology. A recent study of the European Health Technology Institute (EHTI) conducted by the London School of Economics (LSE) reported that approximately 70% of countries surveyed use special payment mechanisms for innovative technologies and these are considered to be effective in integrating new technologies into the health system.

We acknowledge that national health systems reimburse devices in different ways and at different speeds, but there is simply no doubt that these life-saving devices are available to European patients sooner than anywhere in the world. The fact remains that a technology like renal denervation is already saving the lives of European hypertensive patients whose condition cannot be treated solely by pharmaceuticals, while an estimated 7 million Americans with the condition are still waiting for this procedure to be approved.

Tackling misconceptions

To clarify what is at stake with the current revision of the European medical device legislation, we have launched the campaign “Don’t lose the 3”. The campaign showcases the advantage that Europeans currently enjoy and explains what changes need to be made to the current European system to make sure that Europeans continue to have timely access to safe, life-saving medical devices.
How Can we Ensure an Efficient Monitoring and Post-Market Surveillance of Medical Devices by Notified Bodies After Their Market Authorisation?

Gilles PARGNEAUX
 MEP, Group of the Progressive Alliance of Socialists and Democrats, European Parliament

Along with manufacturers, notified bodies are the most fundamental part of devices market approval and monitoring. More than seventy notified bodies are in charge of the critical regulation of medical devices in Europe. While some argue that the current system is rather slick and efficient, making innovative technology available to people the fastest in the world, deep flaws have been revealed by the silicone-filled breast implants (PIPs) and the metal-on-metal hip scandals. As we stressed in the European Parliament’s resolution of 14 June 2012 on defective silicone gel breast implants made by the French company PIP, we need an improved post-market surveillance: this means an increased traceability for implanted medical devices, additional sample testing of products already on the market and a better coordination between Member States when it comes to reporting on, and warning about, serious side effects or damage caused by medical devices. As for notified bodies, we stressed that unannounced inspections should become mandatory.

I believe notified bodies lie at the heart of the problems within the current system. An enhanced control of their work should be on the agenda knowing that they can be very lax in some parts of Europe. We should even consider reducing their sheer number. As revealed by The Daily Telegraph and the British Medical Journal in an undercover investigation, some notified bodies in Europe were ready to give their CE certification to a fake diameter metal on metal total hip – called the Changi Total Metal Hip – that was based on a device which has been recalled globally for safety reason. Some notified bodies are reluctant to demand clinical data and lack the capacity to challenge or test the data against expert advice. Moreover, the current system is business-oriented while it should be focused on the safety of patients. Some notified bodies in Europe even offer consultancy services on how to market a product. Given their number they compete for business on the basis of fees and speed. This leads many manufacturers to “regulator shopping”.

Against such a dismal backdrop, change to the current marking and post-market surveillance is unavoidable for the sake of EU patients. It is necessary to improve the system by a proper use of evidence-based medicine and well-designed clinical tests before the devices are approved. Above all clinical registries to track outcomes in real time after they are approved should be the norm. This post-market surveillance has not been addressed sufficiently in the past and not monitored closely by notified bodies. It should thus be the cornerstone of the new regulation. Yet on many respects, the proposal of the European Commission falls short of providing the necessary guidelines to enhance the efficiency of notified bodies and how they should proceed with a better monitoring of the market.

Our current system of a complete delegation of responsibility to notified bodies leads to huge discrepancies between Member States. The regulatory framework is confusing, patchy and offers too many loopholes. In the future negotiations between the European Parliament, the European Commission and the Council, we will have to strike a political compromise between the EU-style of regulation made of a total delegation of powers and a more centralized system like in the US where the Food and Drug Administration (FDA) for instance maintains a database of reported adverse events and device malfunctions.

Should a Marketing Authorization Be Implemented for High-Risk Medical Devices?

Thomas ULMER
 MEP, Group of the European People’s Party (Christian Democrats), European Parliament

In the aftermath of the PIP scandal a lot was talked about the better patient safety we could have had in Europe if there had been a premarket authorization system like in the US. The reality, however, shows us that this is not true: there is no evidence that the US FDA would have detected the fraudulent PIP implants at an earlier stage.

There does exist an approval system in the EU for class IIb and III medical devices: it is called the “New Approach”. Under this approach, the “Notified Bodies” conduct the conformity assessment for high-risk MD. Given in particular the wide range of MD on the market this is a feasible solution for the manufacturers as well as for the patient. We must always keep in mind that medical devices represent a vast range of sciences and technologies. The personnel testing medical devices must have a high level of education and a vast set of know-how to handle the requirements of the conformity assessment of medical devices, covering the areas of Atomic Physics, Anatomy, Bioengineering, Mathematics and Acoustics to mention only a few. In order to have only the best Notified Bodies we have to elevate the highest requirements for them.

A centralized approval system similar to the system for medicines would require the establishment of a new EU public body, which would have an enormous impact on the EU budget as well as on manufactures in terms of costs and additional administrative burden. An argument often presented in support of such a centralized, EMA-like system is that there would be no conflict of interest with the industry because the industry would not pay the assessment. But a detailed report of the European Court of Auditors (Management of conflict of interest in selected EU agencies) notes that the EMA has around 3800 external health experts and scientific advisors who might have past or present connections to the industry. The MD industry is characterized by small and medium-sized enterprises. A higher regulatory and bureaucratic burden would impede the market access for products by this highly innovative manufactures.

From an ethical point of view it is important to keep in mind that we often do not have the possibility of clinical trials for medical devices. It is not possible to conduct double-blind studies on the functioning of a pacemaker or require a person without any problems to undergo another surgery after five years to see what has happened with the hip joint endoprosthesis.

In Europe patients have access to highly innovative medical devices on average two years faster than in the US. Other countries even copied our system of market approval.

In order to improve the European system, we should invest in innovation in the field of the non-destructive inspection of medical devices; this would allow for a higher level of safety of medical devices and a better means of monitoring them. The high criminal energy of the PIP scandal shows that we need intensified market surveillance and vigilance after a product is placed on the market.

Our highest aim therefore should be to establish a clear and effective legislative framework consistently implemented across the EU. Such a system should increase patient safety on the one hand and rapid access to new innovations on the other.
MediCal devices in Europe

Thanks to better incident reports, targeted market evaluation, and safety corrective measures and a better control by relevant authorities. The use of such a system should also improve the purchase policy and the stock management by hospitals.

Transparency and better information are crucial to give more autonomy to patients and health professionals and enable them to take decisions with full knowledge of the facts, in order to give a solid base to regulatory decision-making process and to make sure the latter is trust-worthy. To do so, it is essential that Eudamed electronic systems related to existing devices, concerned economic operators and certificates allow public opinion to be well informed about devices circulating on the market. The clinical investigation electronic system should serve as a tool for cooperation between Member States and enable promoters to deliberately introduce a unique application process for several Member-States, and in this case to report serious incidents. Otherwise, manufacturers should convey the main safety and performance characteristics and the clinical evaluation results for high-risk medical devices via a public document. The well functioning of notified bodies is also essential to guarantee a high level of health and safety protection, as well as citizen trust in the system.

Nomination and control of notified bodies by Member States according to precise and strict criteria should then be supervised by the European Union. We have to give notified bodies more power on manufacturers, especially the right and obligation to do unexpected inspections on site. Another option would be to submit medical devices to physical or laboratory trials to make sure that manufacturers keep on complying with the regulation after receiving the original certificate.

After the industrial fraud of the PIP affair, making many casualties in France, device vigilance issues have never been so important. Even if it is always difficult to solve a fraud issue a priori, it is essential to ensure a better traceability for this type of devices, following the example of the struggle to ensure a better traceability for this type of device for a long time.

Medical device traceability through a unique identification system based on international guidelines should significantly increase post-market effective safety of medical devices, thanks to better incident reports, targeted safety corrective measures and a better control by relevant authorities. The use of such a system should also improve the purchase policy and the stock management by hospitals.

Vanguard AG is the largest European medical device reprocessor. We undertake the complete reprocessing of used medical devices and assign them with a new useful life under substantially equivalent physical conditions that are applicable to the manufacturing of new devices. Vanguard AG has been operating under the German Regulatory System for the Reprocessing of Medical Devices (which covers both Single use and Multiple Use Devices) since its adoption in 2002.

Professionally reprocessed devices offer the same standard of safety as new products, as shown by extensive field data available both in Europe and in the US. In times of unpredicted economic crisis, reprocessing can produce significant cost-savings for healthcare institutions and reduce medical waste. Reprocessing is a means of cutting healthcare cost while maintaining patient safety and quality of care and is an environmentally responsible practice.

In Germany, reprocessing has been subject to monitoring and surveillance by public authorities and EU-accredited Notified Bodies. Rules on reprocessing of medical devices were put into place in 2002 through the joint recommendation, issued by the Commission for Hospital Hygiene and the prevention of Infection at the Robert Koch Institute in Berlin and the German Federal Institute for Drugs and Medical Devices, on hygienic requirements when reprocessing medical devices. While Germany has defined a tried and trusted regulatory path, this is still the exception in Europe.

While some other European countries prohibit reprocessing, it is our view that this prohibition is directed at the reprocessing of single used devices by hospital owned central sterilisation departments, which indeed should not be permitted given the inadequacy of such facilities for that purpose.

Vanguard AG supports the Commission’s initiative to introduce regulation to the field of medical device reprocessing. We believe that it is important that a consistent EU wide regulatory framework is adopted in order to allow all European countries to enjoy the benefits of reprocessing with patient safety being ensure. However we also have the view that overregulation should be avoided.

Vanguard AG’s position is that the current version of Article 15 of the Proposed Regulation unduly restricts the free circulation of reprocessing services and reprocessed devices, thereby unjustifiably restricting competition in the market and depriving European citizens of safe and cheaper alternatives to new devices. Vanguard AG therefore proposes to the Commission, the Parliament and the Council to consider changes to the current proposal of Article 15.

According to the provisions of the proposed regulation, manufacturers of reprocessed devices must be considered as manufacturers of new devices and accordingly must meet the “essential requirements” specified in the proposed regulations. As such, reprocessed devices will have to be CE-marked to be legally placed on the EU market.

If safety has been demonstrated through the CE marking process, then prohibiting the reprocessing of “critical” single use devices until further demonstrations of their safety is a disproportionate and excessive measure. Vanguard AG proposes that the ban on the reprocessing of “critical” SUDs should be replaced with measures that will allow only “professional” reprocessing, i.e. reprocessing carried out in a controlled environment and in full compliance with safety requirements.

The effect of Article 15 as currently drafted is to:

i) prohibit the reprocessing of “critical” SUDs;

ii) allow Member States to prohibit the free provision of reprocessing services on their territory;

iii) allow Member States to prohibit the free circulation of used devices;

iv) allow Member States to prohibit the free circulation of reprocessed devices.

These provisions are contrary to the fundamental freedoms of the internal market and violate the principle of proportionality and cannot be justified on grounds of protection of public health “specific to” any Member State. Article 72 of the proposed regulation provides for a safeguard clause. Thus, further restrictions on the free movement of services and goods as proposed in Article 15 are manifestly inappropriate and unlawful and should be removed in their entirety. It is Vanguard AG’s position that there are alternative and more proportionate measures which are less restrictive on intra-Community trade with which to achieve the Commission’s aim of the protection of public health.

Finally, the proposed regulation contains no provision which deals with the fact that a tried and proven regulatory system for medical device reprocessing exist in the largest EU Member State, Germany. Over 10 years experience and substantial evidence document that this system works. It would appear unreasonable to prevent Germany from continuing to use this regulation, or indeed to bar other Member States from adopting this regulatory regime if they so choose.
Medical Devices: the Impossible Single Market

What do financial crises, medical and food scandals have in common?

Corinne LEPAGE
MEP, Group of the Alliance of Liberals and Democrats for Europe, European Parliament

The Regulation philosophy is now based on stakeholders’ personal responsibility while public authorities always want to find the best framework possible. But without an effective control system, even the best legislation would remain virtual. As regards medical devices, we face a market in which margin for actors is important, though some of them decided to put the safety of patients using their products in jeopardy to obtain more profitability. In the case of the PIP breast implants, the Food and Drugs Administration of the United States rejected the authorization in 2000 because they were not complying with their standards. In a caustic letter, the agency established an eleven-bullet list of compliance upgrades after seeing the production factory and studying complaints related to the implants.

In 2005, several complaints were listed in the United Kingdom. In France, a doctor warned the AFSSAPS (the French Agency for the Safety of Health Products) early on in 2007 that the breast implant scandal had broader implications than expected by the media. The PIP case also underlines the shortcomings in market surveillance and here again, the European Commission proposal does not go far enough. We are far away from standards applicable in other fields; and the effective implementation is still unsatisfactory. The priority has to be given to patients instead of devices. At every step, manufacturers have to be inspected both on quality and methods on a regular and unexpected basis. Extraterritoriality in production must be included in control procedures for the product approval, including internet distribution.

The PIP case also highlighted serious gaps in medical device vigilance, especially due to under reported incidents by operators and prescribers. In this case, the operator did not report serious accidents and prescribers were facing unwieldy procedures as well as inadequate treatment from public authorities. We also have to consider the idea of making other stakeholders intervene in the evaluation process while ensuring a complete respect of private information, for instance by giving social security organisms a right of inspection with regards the cost per patient.

This kind of market intervention aims at improving public health standards and making the situation clearer for economic operators. A straight and demanding procedure is more interesting than a random one giving way to doubt and arbitrary. In a sector involving many innovative SMEs, it is important that we support research and development by implementing strict regulations while guaranteeing legal certainty and predictability for economic actors.

At the same time, we have to support and push forward an ambitious status for medical whistle-blowers. For more than ten years, employees of this company were probably aware of these wrong practices. Last but not least, thinking about all these women victims of the PIP prosthesis for aesthetic or medical reasons, the PIP case raises the question of sanctions and collective redress. If operators do not fear any exemplary sanction, then I am afraid we will keep on having such scandals.

In January 2012, an information mission on implantable medical devices and aesthetic surgical interventions was set up at the French Senate. This mission was aimed at responding to the disgraceful practices of the PIP society. At the end of its work, the mission for which I was responsible was convinced that the breast implant scandal had broader implications than expected by the media: the focus was exclusively on the bursting of the silicone implants and its dramatic consequences on the women who had them inserted. This tragic situation is actually the most tangible sign of a broader case that involves several steps of the process, from the medical devices certification to their prescription by health professionals.

This situation shows us that these products cannot stay out of the current health legislative process. Every single day, medical devices amongst the most complex ones contribute to extending patients’ life that had no alternative treatments or improving life quality of others. It is high time for policy-makers to understand that medical devices are not third-rate medicines but instead true and essential sanitary tools.

At the sources of market authorizations for medical devices stands the diversity of certification agencies, therefore the information mission established as first recommendation the setting up of a bill of specifications in order to standardize all certification agency criteria. There is demand for a true certification policy at the European level that has to go with reinforced controls on manufacturers, social security and professional organizations.

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Implementing a Real Vocational Training for Using Medical Devices

Chantal JOUANNO
French Senator, Chairman of the Information Mission on Implantable Medical Devices

Regarding health professionals, we have to rethink continuing education methods for doctors in relation with ordinal authorities, and simplify medical device alert procedures. One of the possibilities could be the Medical Board, as it is sometimes the case. It would be also necessary to improve teaching skills/ instruction by ordinal and public authorities towards doctors, through a national communication campaign focused on medical device alerts to identify faster the most hazardous medical devices for patient use. Increasing warnings and involvement of health professionals is thus essential to strengthen prescription of medical devices in optimal conditions.

More than lifelong learning on medical devices prescription, we should accentuate continuing education about the use of medical devices in general, by developing better medical device alerts and creating high-risk medical device registers in cooperation with the stakeholders. In the framework of the information mission, we recommended that the priority should be given to registers related to implantable medical devices requiring follow-up (also called risky medical devices), previously identified by health authorities and professionals. For such a measure to succeed, we need to get knowledgeable companies and interested doctors together. Indeed, hospitals and practitioners have to feed registers to give them the largest efficacy.
How Depositaries’ Expertise Benefits Medical Devices Supply Chain

Jean-François FUSCO
Chairman of EALTH (European Association for Logistics and Transport in Healthcare), Chairman of LOGSanté and Pharma GM for AEXXDIS FM HEALTH

Laurent ULMANN: Could you give us an update on EALTH activities?

Jean-François FUSCO: EALTH (European Association for Logistics and Transport in Healthcare) is a professional organisation established in Brussels and listed on the Transparency Register of the EU. From a historical point of view, LOGSanté, the French depositories association, took initiative in creating EALTH in 2010. The founding members decided to create a new relevant entity representing the full range of skills including logistics services as well as transport, up to the distributor or dispenser of healthcare products. So far all of the key players are members and we cover all of the EU territory.

L.U: What expertise do you provide to your customers?

J-F.F: You’re right when you talk of expertise due to the scope of our services, the range of products concerned and the expectation of our customers. It’s clear that our initial activity is based on warehousing operations but we evolved due to the market demand with additional services such as secondary packaging, customer service, tender support and management, invoicing, cash collection, transport optimisation, vigilances, market authorisation holding, and got the necessary legal authorizations.

Jean-François FUSCO: EALTH is the current market offer?

L.U: Following the previous question, what is the current market offer?

J-F.F: It is important to dissect the offer. Our clients come and look for optimization, i.e. how to comply with regulatory measures and how to find distribution methods that bring greater economic welfare. Our offer is de facto the result of a market study, which means that we look at the bill of specifications on the distribution of these products and then we build up an operable and practical model aimed at guaranteeing safety and deadlines as well as finding the appropriate economic process via new models such as European hubs, satellites, maximized means of transport or hospital distribution.

L.U: Is the legislative package on traceability taking the right direction according to you? Are these measures adapted to your means?

J-F.F: Yes, it is. Even if the unfortunate events that we know (I am talking about the PIP prosthesis, prosthesis with metal...) are the major initiators of these new measures, we are currently in a quite safe profession that just needed better harmonization and a reduction of legislative texts. The first major step is this legislative package with directives that brings more clarity and straightforwardness. There is a concentration of basic elements that have to be shared by most medical devices when others need more specific attention, which is the case for in vitro diagnostic medical devices. So I do think this reform takes the right direction: more clearness about medical devices in order to give patients better care. We make products because we contribute to a better health.

At this stage, it is important to keep in mind that it is not only about means, but also about how to use them. Indeed, we consider that we have three successful key factors: design capability and process command, availability of approved pharmaceutical tools (with IT enabling safety of transactions and traceability!); rigorous, regular, responsive and trained human resources. Our clients’ expectations and the regulatory compliance throughout the years led us to internalize these factors, which are essential to health products’ distribution. Our profession is used to putting these elements together.

L.U: What do you think about the precautionary principle with regards to the medical devices?

J-F.F: The revision procedure of the EU legislation on medical devices launched in Brussels, intends to reinforce traceability on these health products. Some stakeholders, such as the French Senate wants to accelerate the implementation of the Unique Device Identifier in the EU. This measure should go along with a reinforcement of distribution. Who better than a depositary can guarantee the storage and distribution of health products for companies? The depositary activity does not modify the price of medicine and medical devices distribution whatsoever. The neutrality about price comes from our specificity insofar as we do not buy stocks and we charge our clients on the Activity Based Costing (ABC) principle according to our maximized activities, instead of adding a margin on the purchase price. Furthermore, as health professionals, we are constantly aware of our clients’ expectations and needs based on their own clients mainly represented by hospitals, pharmacies and distributor wholesalers.

L.U: Do you think that the use of traceability techniques (Unique Identification System, serialisation, unique barcodes) is maximized?

J-F.F: The two regulation projects presented by the European Commission plan to improve medical devices traceability to respond more quickly and effectively to any safety problem throughout the supply range. Thus, chapter 3 of the two regulations related to identification, traceability and registration of devices and economic operators is essential. The EC highlights the fact that this chapter relates to one of the main shortcomings of the current system, which is the lack of transparency.

Chapter 3 has four main objectives:

1) a measure that forces economic operators to identify both suppliers and receivers of medical devices;
2) a demand that manufacturers append a unique identification on medical devices to make traceability possible;
3) a demand that manufacturers, authorized representatives and importers, as well as devices put in the European market, have to be registered in a European central database;
4) the development of the European database on medical devices (Eudamed), which will contain electronic integrated systems about the European Unique Identifier; the registration of devices, economic operators and certificates released by notified bodies; clinical investigations; vigilance and monitoring about markets; Who, other than depositaries, can carry out these serialization missions?

L.U: Can you explain to us the type of processes in your activity?

J-F.F: Traceability must not be merged with follow-up. If European institutions want to impose a complete follow-up on health products to secure pharmaceutical and health operations (including medical devices) through codification, they need to change their discourse towards all operators, including transporters. This follow-up has to rest on a globalized standardization system, such as the ISO norm or the Global Standards One (GS1) and has to fall within a quality and consultation approach to rally all the actors. Distribution fares should not be the only angle of attack of the “traceability file”; instead we should focus more on quality of service for patients and distribution netting all around the EU. Thus, it seems that depositaries are fully competent to respond to public authority preoccupations as regards traceability. Depositaries offer safety and control protections that can reassure medical device manufacturers and represent an additional guarantee in terms of activities and storage since they are submitted to controls and inspections by health authorities.
Team NB Perspective on the Medical Devices Regulation in Europe

Françoise SCHLEMMER
TEAM NB Director

Corinne DELORME
(LNE/G-MED Regulatory Affairs Manager
TEAM NB Secretary

Team NB is the European Association of Medical Devices Notified Bodies formed on 2001. It is a not for profit association. The 30 members are Notified Bodies under any or all of the three medical device new approach directives: 90/385/EEC; 93/42/EEC; 98/99/EC. Our aims are: to improve communications with the EC Commission, Industry, Competent Authorities and User Groups by acting as a focal point and the single voice of Notified Bodies, to promote high technical and ethical standards in the functioning of Notified Bodies, to protect the legal and commercial interests of Notified Bodies in their vital role in the functioning of the three of the medical device directives. Team-NB members wrote a position paper under the supervision of their president, Gert Bos (BSI), about the new draft regulations about Medical devices and in vitro diagnostic medical devices, which essentially expresses the following elements:

It is commonly agreed that the current European regulatory framework on medical devices has represented an improvement in the products control before their utilization over the last two decades. The ingenuity of the system is evidenced by the fact that it has served as a basis for global harmonization. It results in safe innovative products reaching European patients in a timely manner. This combination of safety and early availability to patients, is a unique and important feature. Team-NB welcomes the interim measures made by the European Commission, without waiting for the approval of the two new regulations, to review the designation of Notified Bodies, to precise the context of implementation of unannounced visits and to enhance the “hands on product” focus that is resulting from assessing the PIP case.

The current system combines short assessment times with a safety that equals the American FDA premarket approval system. Can we make it even better? Yes.

In the vision of Team NB, 3 key elements are needed:

1. More strict and uniform supervision on Notified Bodies. Team NB welcomes joint Member States audits, centrally coordinated and rotating. Member States should decide together on designation and details of the scope assigned to each Notified Body. This scope should be based on objective, demonstrated technical and medical expertise. Qualification requirements should at least meet the specifications in Team NB Code of Conduct, which is publicly available. Notified Bodies should focus on compliance, impartiality and high quality delivery. Appropriately 20% of the Notified Bodies review 80% of the products and the expertise of these Notified Bodies is well established. However, not all Notified Bodies are fully resourced with competent personnel matching their scope of designation. This can be changed, not by focusing on the number or the nature of Notified Bodies in Team NB, but on their quality and on restricting their scope to proven competence and available expertise. A clear window in which Notified Bodies are to operate, will be key to provide safe medical devices to European citizens in an affordable and timely manner in the years to come.

2. Secondly, all stakeholders should coordinate their market surveillance activities. It would be much more effective if all competent authorities were to investigate specific groups of products simultaneously. At the same time, Notified Bodies should focus on their unannounced visits on this same product group. Other stakeholders could then follow with their assessments and trend analyses. This way, input from all stakeholders, including medical practitioners and patients, can lead to more detailed product related safety and performance guidance.

3. Thirdly, the best way to enhance scrutiny is for Member States to do unannounced reviews of selected high risk design dossiers after CE marking. This forces Notified Bodies to excel in all their assessments. In addition, this will result in a more harmonized interpretation of the regulation. The Member States should focus on supervision and enforcement. To do so, they must have suitably competent resources. An added layer of review does not improve safety and will significantly delay the arrival of beneficial new treatments to patients.

In addition, TEAM-NB supports the concept of a “qualified person” that has been introduced into the draft legislation and considers that this will help to support regulatory compliance and consistently high standards across the industry. It is also likely to support notified bodies’ interactions with manufacturers and authorised representatives. Also, the regulations must clarify the roles and responsibilities of importers, authorised representatives and manufactures so that they each understand fully their obligations. The “qualified person” should be as equally well qualified as their counterparts in competent authorities and notified bodies.

All stakeholders need to cooperate in building and maintaining a fully transparent system that delivers safe, innovative devices to the patient and healthcare provider as efficiently as possible.

Single Use Medical Device Reprocessing:

considering latest process and success stories in Germany and the US, propose a safe and ambitious European legal frame

Frédérique PERRIER
Health Products Purchasers Association, Paris – France,
Project Manager, Medical Department, Capio Santé, France

Health spent is one of these tough topics where one must reconcile innovation, care outcome and efficiency at controlled cost. Despite being a difficult challenge, it is a tremendous source of innovation and job creation.

Reprocessing is one of the solutions found by several Western countries to meet this challenge. It consists in re-using Single Use medical Devices (“SUDs”) put on the market by original manufacturers. Germany and the USA among others have implemented and improved this process on more and more SUDs over the past 20 years.

How can a “Single Use” device be reused? Merely because the “Single Use” characteristic is decided by the original manufacturer no matter the device intrinsic properties. Indeed, marketing aspects (safety perception being higher for SUUs, sales rationale (Explosion of the turnover with SUUs) and study cost necessary to validate safe re-use processes are among factors discouraging the launch of reusable devices by the original manufacturer.

As far as France is concerned, old sanitary scandals (ex. Sport Clinic in Paris, contaminated blood) and the existence of uncontrolled SUUs reuse practices in the 90’s has led to a strong mistrust and French sanitary authorities have finally prohibited this process.

Moreover, the opinion published by SCENIH on April 15th 2010 concludes that “Despite the absence of data, a number of situations in which an increased risk from using a reprocessed SUD may have occurred be identified, ... pointing out specifically the issue with surgical SUUs, classified as “critical”.

Unfortunately, or (thank god for patients should we say), this definition does not mention the related but critical steps performed by AMDR (Association of Medical Device Reprocessors) and German reprocessing companies. Those steps include upstream validation studies to ensure the considered device can (or can not) be reprocessed, how many cycles it can be reprocessed, unit traceability/testing and last but not least excludes the critical devices which may have been in contact with organs potentially contaminated with prion.

In the US and Germany reprocessing has been successfully implemented with two different legal frames, both aiming at guarantying high standard of quality and traceability, but the removal of the OEM name could cause damage to the medical device therefore generating quality issues.

Significant and successful experiences exist in this area: let’s support its development and not reinvent the wheel or we will lose an opportunity to contribute to a more viable health system. Reprocessing is innovative and totally in line with the emerging paradigm of sustainable development, promoting local business and social utility.
The European Social Insurance Platform acts in the interest of its insured persons, particularly when they become patients, insofar as patient safety and good health is the highest goal of its work.

With view to the draft regulation to be discussed, our main concern focusses on high-risk medical devices. Those devices should be subject to strict requirements, comparable to the rules in the pharmaceutical sector, in order to keep the risk for the patient as low as possible.

The assessment of the safety of medical devices is a task of public responsibility, which is presently entrusted to private notified bodies within the framework of the relevant EU directives. This certification system is in our opinion insufficient. Several examples in the recent past show that the priorities in the certification system have shifted in the direction of a service concept to manufacturers with the effect that patient safety comes second. For the future, it must be ensured that notified bodies no longer compete with low prices and the promise of an accelerated assessment procedure for their clients.

The best and most effective way of ensuring patient safety is a centralized official authorization for high-risk medical devices. During the period necessary to build up such a system, the immediate improvement of the quality of the existing system is the highest priority.

The requirements for the conformity assessment procedures need to be increased and the quality of the assessments must be improved. For high-risk medical devices, a positive risk-benefit balance and the therapeutic value for patients must be proven by high quality clinical investigations before the products can be brought onto the market. This means to impose high quality controlled clinical investigations, i.e. generally randomised trials. For this evaluation the notified bodies need to have and must prove to have the necessary medical and scientific expertise. The proposed "medical device coordination group" needs to be entrusted with more authority and must be put in a position to intervene or to stop the ongoing conformity assessment procedure if necessary for reasons of patient safety. To that end, the coordination group needs to have the necessary, suitable and adequate personnel equipment.

Furthermore, from our perspective the rights of patients harmed need to be strengthened. Medical device manufacturers must be required to take out sufficient liability insurance against which the patients can take direct action in case of harm. It cannot be the patient’s risk that a manufacturer is unable to pay in case of harm caused by his product. Also, patients and payers liable for the cost of treatment, i.e. the social insurers, should be given the right to relevant information in case of harm in order to prepare a claim for compensation. And last but not least it is necessary that the burden of proof be facilitated for the patient in case of harm caused by a medical device. These are our main concerns, which we ask to be taken into consideration in the further legislative process.

Many groups and experts in Europe, including doctors, patients and industry, agree that the current system needs to be improved to cope with new medical technologies and innovations. But let’s keep what works and fix what needs to be improved instead of radically changing the system.

…ADVANTAGES OF THE EUROPEAN SYSTEM

1. LET’S MAKE THE SYSTEM EVEN SAFER
2. LET’S KEEP THE SYSTEM FAST
3. LET’S KEEP MEDICAL DEVICE INNOVATION IN EUROPE

…SOLUTIONS THAT WILL IMPROVE THE EUROPEAN SYSTEM

1. GET RID OF THE BAD APPLES
2. CHECK THE CHECKERS
3. GIVE PATIENTS THE INFORMATION THEY NEED

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