EU drug and medtech regulation: a deliberate shift in power away from member states

In the field of pharmaceutical and medical device regulation in the EU, power is increasingly moving from member states to Brussels. This is largely a good thing for the life sciences industry as it will make Europe more competitive internationally, ***Vincenzo Salvatore*** tells ***Maureen Kenny***.

A major innovation in recent years concerning pharmaceutical and medtech legislative proposals coming out of Brussels is the move from directives to regulations. This change – from a co-ordinated to a harmonized approach – is not just academic, according to Vincenzo Salvatore, head of legal service at the European Medicines Agency until a year ago and now senior counsel at law firm Sidley Austin. It should, Professor Salvatore told *Scrip Regulatory Affairs* in an exclusive interview, result in a more competitive EU.

Regulations are directly binding on member states. Directives, by contrast, must be transposed into domestic law in each member state. In the area of pharmaceutical and medical device regulation, directives allow national competent authorities to fine-tune provisions according to their specific needs. Having regulations rather than directives means there will be far less chance of this happening. "You have the same rules applicable across all the member states rather than [having] 27* different procedures, different rules, different time frames….That's a way to make Europe more competitive," Professor Salvatore commented.

"The more you are able to harmonize rules across the board the more you make Europe a reality... this way you strengthen Europe and offer stakeholders a more reliable and more competitive system."

Most major EU legislative proposals of the past five years affecting pharmaceuticals and medical devices have involved the transfer of additional responsibilities from member states to the EU through the use of regulations. Specifically, these are:

- the new pharmacovigilance legislation (in place, a directive accompanied by a regulation);
- the (drug) information to patients legislation (ultimately shelved, but this was to have been a directive accompanied by a regulation);
- the review of the (drug) Clinical Trials Directive (under way, directive to be replaced by a regulation);
- the review of EU medical device legislation (under way, the Medical Devices Directive and the In Vitro Diagnostics Directive both to be replaced by regulations); and
- the review of the Processing of Personal Data Directive (also known as the General Data Protection Directive) (under way, directive to be replaced by a regulation).

The only piece of legislation from the so-called "pharmaceutical package" of proposals in 2008 that was not accompanied by a regulation was the Falsified Medicines Directive (the other two strands of the package were the pharmacovigilance legislation and the information to patients proposals). In the case of the FMD, the European Commission's hands were tied. "It could not propose a regulation because this directive has an impact on some areas of responsibility that fall outside the power of the European Union, that remain within the responsibility of member states," Professor Salvatore remarked. These include judicial responsibilities, police co-ordination, customs official training, etc. Also, the situation regarding the import and export of goods from non-EU countries may vary significantly from member state to state; a regulation was not therefore possible.

Professor Salvatore sees the shift in approach as largely positive. "I have spent all my life working on European law so I am very fond of the idea of this [transfer of power] – as long as the EU is not a federal state," he said. "Wherever it is possible, I definitely agree it should happen… you may not like some EU rules, but the benefits you get from having harmonized rules definitely outweigh the sacrifices and risks [there would be] if you had no harmonization."

Acting when things go wrong

The EU works on the principle of subsidiarity, which essentially means that it may only intervene if it is able to act more effectively than member states. When the commission supports the introduction of a regulation, therefore, "it may mean that something is wrong at national level or that member states didn't prove to be in the position to tackle a specific issue in an adequate and appropriate way," Professor Salvatore commented.

Pharmacovigilance

On the pharma side, the case involving the diabetes drug Mediator (benfluorex) in France was one of the reasons the pharmacovigilance legislation was reformed and a regulation introduced, with the accompanying centralization of responsibilities. The Mediator case proved that for products authorized at national level, there may be a need for co-ordination at the European level. For example, an urgent safety procedure may need to be triggered at EU level.

Clinical trials

In the case of pharmaceutical clinical trials, applications for new trials had dropped by around 25% over a 4-5 year period, from more than 5,200 in 2007 to 3,700 in 2011. Companies were looking at other markets to develop their clinical strategy, Professor Salvatore commented.

The existence of different national laws meant there was unpredictability in terms of approval times and potential inconsistencies in terms of outcomes of assessment procedure; the commission had to act. The result is that one of the more important elements of the proposed legislation is that, for clinical trial applications, there will be "a single EU portal; a single gateway, a European hub, with clear deadlines" that member states will need to meet. Professor Salvatore is confident this will facilitate the industry "in keeping on doing trials in Europe".

Medical devices

On the medical devices front, the PIP breast implants case speeded up the process of introducing a regulation – the idea behind the proposed Medical Device Regulation being to be able to track devices and better monitor the safety of devices at EU level.

In the case of device regulatory reform, the commission felt it needed to recover the trust of patients in the reliability of the medical device regulatory system. "When accidents occur… you need to convince people you have appropriate rules in place to guarantee that the health of patients is being protected," Professor Salvatore commented. "[This] goes also with the aim of making Europe more competitive because if the system doesn't work properly, it may result in a reluctance of industry – mainly based outside Europe – [and cause it to] consider alternative markets rather than the EU."

PPD

The replacement of the PPD Directive with a regulation will have an impact on the pharmaceutical industry in terms of, among other things, the acquisition of informed consent and the protection of personal data when companies are disclosing information relating to the safety of medicines.

Transparency and CCI

The protection of personal data is a key point in ongoing discussions over the EMA's clinical trial data disclosure plans. Starting January 2014, the EMA plans to proactively publish clinical trial data submitted in support of a marketing authorization application once the decision-making process has ended; under its 2010 access-to-documents policy it currently only supplies such data reactively, ie on request.

Another major point in the debate over transparency, of course, is the protection of commercially confidential information (CCI). In this area, Professor Salvatore noted, the real issue is that there is no real definition of CCI. This is why "everybody [the EMA, the industry, research organizations] is looking forward to receiving interpretative guidance from Luxembourg" that will clarify to what extent certain kinds of information can be made accessible, he said.

Here, the Sidley Austin lawyer is referring to the case of two companies, AbbVie and InterMune, filing suit at the EU General Court seeking to prevent the EMA from disclosing data on their products – Humira (adalimumab) and Esbriet (pirfenidone) respectively – and the court subsequently issuing interim rulings in the cases ordering the EMA to refrain from publishing the clinical trial data pending a final decision from the court.

In accordance with its 2010 access-to-documents policy, the EMA had been preparing to release certain clinical and non-clinical information submitted by the companies as part of marketing authorizations. AbbVie claims that the documents in question are commercially confidential and also that releasing them would be a breach of copyright law. InterMune says that the public disclosure of data on its product would wrongly undermine the protection of its intellectual property rights and damage its commercial interests.

Transparency is a "positive value per se but you have to consider that [there are] additional interests that deserve at least equal protection", Professor Salvatore said, commenting that, under the international IP trade agreement, TRIPS, there is a legal obligation on regulatory authorities to protect CCI received from industry in support of a marketing authorization.

While the EMA's move from reactive to proactive disclosure is "a good approach", one has to "ensure a fair balance between the interests at stake". Industry can participate in the debate over what constitutes CCI, but in the end it is up to the "requested institution" to provide clear guidance on what should be meant by CCI. Where there is disagreement, as there is here, "the only institution which is in a position to provide an interpretation… is the court".

Despite the court cases, the EMA has gone ahead with its planned public consultation on its draft policy on the publication and access to clinical trials data. When finalized, the policy will support the agency's existing access-to-documents policy.

The EMA plans to start proactive publication in January 2014. However, while the agency says its policy has been designed to "give widest possible access to data for independent scrutiny with the need to protect personal data as well as legitimate commercially confidential information", it accepts that final implementation of its policy will be impacted by the outcome of the aforementioned court cases and also by the ongoing legislative process regarding the Clinical Trials Regulation that contains several provisions on greater disclosure of clinical research data.

Professor Salvatore said he hoped to be proved wrong, but that he does not realistically expect the Luxemboug ruling to be issued "before next Spring". The court is aware of the importance of the ruling and of the impact it will have, he said, and while it is likely that it will try to "speed up proceedings", there are no set deadlines.

In the meantime, Professor Salvatore remarked, the EMA continues with its "tricky exercise" of working on its new policy without knowing what the approach of the judge will be.

A broader issue at stake, Professor Salvatore suggests. If a regulatory authority either at national or EU level is unable to protect CCI submitted by applicants, "I'm pretty sure that industry will become more and more reluctant" to provide information to the regulatory authority in question. "That could undermine the assessment itself," he suggests, "because at the end of the day assessors have to judge based on limited information… more limited than they could have discussed had they been able to ensure that no CCI would be disclosed".

Since this interview, the EMA has submitted an appeal against the interim rulings.

Single biggest issue for industry

I asked Professor Salvatore what the single biggest issue is for the pharmaceutical industry at this time. "Compliance with the new pharmacovigilance legislation," he says. The legislation necessitated "dramatic change" in some companies – internal reorganization, new training requirements, revision of contracts, reconsideration of outsourcing activities with regard to pharmacovigilance, exposure to enforcement procedure in case of infringement, etc. "That's the piece of legislation that's keeping industry awake at night and [it] will continue to do so for the next couple of years."

Adaptive licensing – new legislation needed?

We move on to the subject of adaptive licensing, and whether this new approach to new drug evaluation might be possible in Europe within the existing legal framework.

There is nothing in existing legislation about adaptive licensing per se, Professor Salvatore notes. However, the fact that the pharmacovigilance legislation introduced the possibility of imposing post-authorization safety studies (PASS) or post-authorization efficacy studies (PAES) conveyed the idea that risk-benefit assessment "is a continuous exercise and not an exercise that stops at the time the licence is granted". That, he says, could be a "precursor to a revision of the moment when the product can be placed on the market".

While he accepts that it may be possible with the existing framework, Professor Salvatore says he is "more inclined to think that, to support an adaptive licensing approach, you would have to have a clear legal basis" for it. It may come, he surmises, in a future proposal to revise the current legislation, now 12 years old (ie Directive 2001/83/EC). Sooner or later, he remarks, this directive will have to be revised.

In the meantime, "the current legislation never speaks about adaptive licensing. There is no adaptive licensing; there is the marketing authorization."

Thoughts on the network

Professor Salvatore is sanguine about the future of the European drug regulatory network. With such a large group – it now comprises 28 national competent authorities, the EMA and the commission – it is inevitable that the various partners will at times be more reluctant to work together than at others, he says.

The network does need to "keep on persuading even the more reluctant national competent authorities of the need to work together and not revert back to national legislation", but this is not "a particularly critical moment" for the network, Professor Salvatore says. "It is exposed to criticism, it's facing an economic crisis, but in general it works well,".

"The more you raise the bar of challenges, the more the system is able to react irrespective of the financial crisis and the lack of resources. If you [consider] what the EMA [and the network as a whole] has delivered… it's impressive," Professor Salvatore concludes.

**This interview took place in June; Croatia joined the EU on 1 July, becoming the bloc's 28th member.*

Maureen Kenny is the editor of *Scrip Regulatory Affairs*.