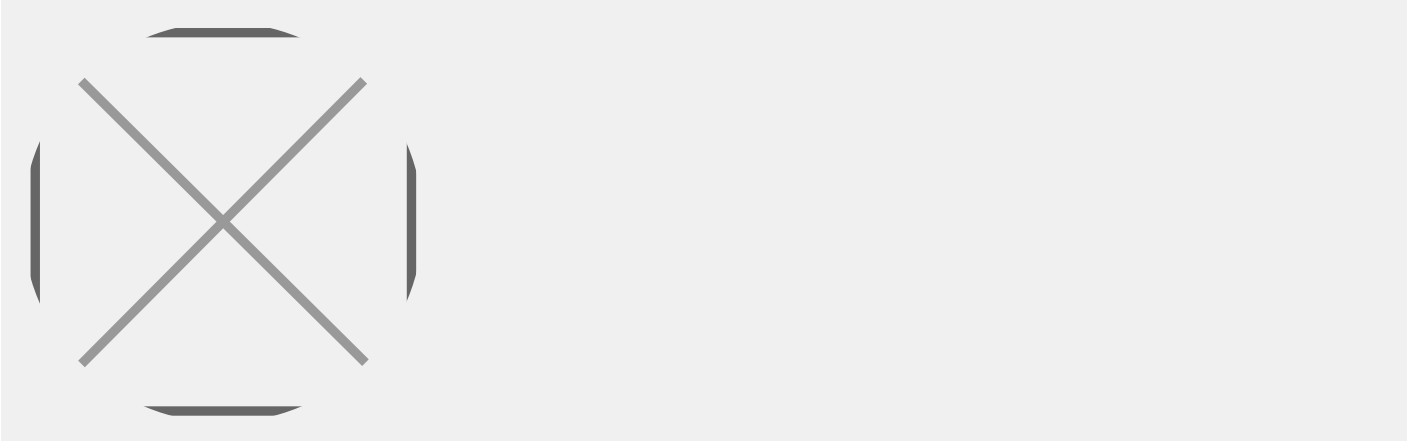
Interview with Jean Marimbert, Director General, Agence Française de Sécurité Sanitaire des Produits de Santé



04.11.2009

The creation of AFSSAPS in 1999 was a milestone for the industry as it became the organism which gives authorization to enter a drug into the market. Can you explain to our readers the main differences between this organization in France and the US FDA?

AFSSAPS was created in 1999 in response to a French law enacted in 1998 but the groundwork for the agency had been established on January 4 1993 under what was referred to as la loi Kouchner. 1999 represented the second stage where the assignments, scope and remit of the agency were broadened to other issues such as medical devices, cosmetics, gene therapy, etc. The agency has a rather wide scope but unlike the USFDA we are not responsible for food related regulation.

Throughout Europe the model merging foods with drugs is not widespread as the majority of countries medical agencies will focus on drugs and devices. When you look inside FDA operations there is a very stark difference between the way food and health products are handled. Even if there are interrelations between the two such as food supplements these two fields are very different in terms of issues which means on a day to day basis a unified body typically has to work in different directions. I’m not questioning the validity of the model but stressing the differences from the French system however our model is sufficient to cover 95% of the daily activities and regular contacts with the French Food Safety agency secure necessary coordination on some border issues and common stakes, so I’m not promoting a merger of our agencies in France.

There are several common traits between our agencies as well. The picture is rather similar in regard to scientific and operational independence from industry and government yet we are both part of the public health system. Therefore I am accountable in regulatory terms before public opinion and parliament as well, especially as the French system is becoming more Americanized in terms of parliamentary scrutiny and overview of health safety system. We have regular and close relations with the FDA which includes a confidentiality agreement since 2006.

The acceleration of European integration in recent years has led to greater cooperation between various national agencies through the European Medicines Agency (EMEA). What forms of further cooperation would you like to see between these agencies?

Currently, there is a European network which is one of agencies, not experts that shares its scientific expertise for the sake of European public health. This follows the original vision for the EMEA which was established in 1995 and historically has had a lot of French influence within the association. From the outset we have been heavily involved in the building of the EMEA to make sure it does not become a separate body disconnected from national agencies but rather is the product of common work and expertise. The composition of the EMEA has also changed over time as the EU has expanded from 15 to 27 countries and the association now includes associate members from Norway, Iceland and Lichtenstein. Additionally, in some countries veterinary agencies are distinct from medicine, as in France, so the membership has grown to reflect this. The result is a center of scientific excellence that is mainly derived from the contributions of national agencies with additional contributions from some experts.

EMEA has also grown as an institution since I took office in February of 2004. At that time the workforce of the association was approximately 300 persons and today stands over 600 persons. While the regulatory and scientific expertise within the organization’s staff has likely grown to some degree, the core source of knowledge is in the scientific bodies and committees. This is an important fact to consider in the debate on centralization. Industry and in particular major firms tend to think in terms of centralization which can produce positive results up to a certain stage but can also be counterproductive after a point. If you want national agencies, as collective centers of expertise to be able to bring added value to EMEA then they have to remain individual centers of knowledge. National agencies remain able to provide expertise by keeping a minimum of scientific assignments so if you centralize all assignments then you kill national agencies ability to be collective centers, as well as their creditworthiness as channels of information to health professionals, and active players of crisis management when it is needed.

Inevitably this is a question of dosage in order to ensure national agencies do not become little more than regulatory branches. However, such a drastic situation is impossible because it would mean national institutions such as AFSSAPS will have resigned themselves to being solely bodies dedicated to purely regulatory tasks in the future. Such submissions may work in some nations as

the pharmaceutical landscape is different everywhere but countries that have historically played a major role in the industry have a strong public opinion on the matter and thus they will not accept a purely regulatory role that would sound passive. For instance, after the withdrawal of Vioxx there were intensive and difficult parliamentary hearings in France, the UK and the US where agencies had to explain the situation and why they had not been previously aware of the intention of the firm to withdraw its product. I was able to be accountable because I had a strong scientific workforce on which I could rely to explain to me and the media what had happened. Should a situation like this occur in a centralized system, there would not be a cushion at the national level. Due to the current scientific significance of national agencies they are seen by lawmakers, media and general public as being reliable institutions that can explain complex issues. This capacity would diminish should policies move to a fully centralized model because at the end of the day there is no truly European scene for public health, most of the controversial debates still taking place mostly at national level.

It’s true that the basic law comes from the European level and we have more than 40 years of implementing it. The first European directive which dates back to 1965 was free market in nature and this mentality is embedded in Europe. However, in terms of accountability we still think mainly in terms of national responsibility. There are debates in European Parliament and press conferences in Brussels but at the end of the day, when a drug is withdrawn the lawmakers, health professionals and media turn to us for answers.

Apart from crisis, national agencies play a significant role in conveying information to the public and translate the differences in the distribution chain between countries as this is not a harmonized process through Europe. This is all due to the fact that public health remains largely in the domain of national rather than European remit. There are three levels of commitment for agencies, the first being the European level which is part of the day to day operations. Secondly, the national roots which should not be forgotten because there will be backlash if you do. Lastly there is the global dimension that lays over Europe and is strengthening as regulators across the world become more aware of the need to exchange information. This can be exemplified by the confidentiality agreement between our agency and the FDA of which there are 15 or 20 agencies with similar agreements: that is a network, although informal.

We have met four times since 2006 in summit events that are informal, that examine operational issues and try to foster cooperation at a worldwide level. It is truly necessary to create these ties because we are witnessing a shift towards globalization of the entire pharmaceutical chain. Many of the activities that are crucial to the safety of the products depend not only on operations in Europe or North America but also on regulations in distant territories. Therefore we need to cooperate for example with authorities in the China, India, Brazil and other emerging pharmaceutical powers. We are currently organizing the flow of information between regulators on all continents for all issues, particularly in case of emergencies. Moreover we have organized

intercontinental training sessions such as one AFSSAPS conducted on bioequivalence two years ago and with our support our Singaporean colleagues will do the same very soon. The next stage is to foster work sharing at global level like that which we have embarked on at a European level. On the inspection front, we have to rely more on international cooperation without short-circuiting local regulators. This is because safety will always rely on the combination of three factors, namely the ability of local regulators to meet the challenges they are confronted with, the accountability of the producers in monitoring their suppliers, and the effectiveness of international cooperation.

At the national level, associations such as Sicos in the chemical industry believe it is necessary make the patient more aware of the source of their products. Is AFSSAPS doing anything to inform the public? Is this an important clarification?

Information is very important but I am not sure that knowing the source of a product in itself gives an additional guarantee to the patient. The product may come from part of Europe where there may also be quality issues and I believe it would be unfair to depict a country as a source of danger. Quality has to be monitored everywhere even though the most recent problems have been occurring particularly in China. But it has become obvious there is a specific monitoring issue in countries where the number of pharmaceutical sites are rapidly increasing. It does not mean that all producers in China or India are bad guys because there are many competent people in these locations. The problem of course is to ensure that the level of quality and reliability becomes as homogeneous as it has progressively become in Europe. Conversely, problems can exist in Europe as well so we have to be very careful not to appear as if we are giving lessons to others.

One of the problems faced by agencies, especially in developing markets, is the rise of counterfeit drugs. It seems that this issue is spilling into developed regions as well and was recently commented on by former president Chirac just a few days ago. What impact on agencies in Europe Counterfeiting is really a plague to the healthcare community. I really admire my former counterpart in Nigeria at the NAFDAC, Dora Akunyili, an energetic and tremendous woman who has since gone on to become Minister in her country. When she took on her job nearly 10 years ago, the proportion of counterfeit medicine was deemed to be nearly 80%, but thanks to her actions it is deemed to be around 50% today. While this may still seem high it has been a big achievement in such a short period and she has had to pay a high tribute by losing a family member in an act of retaliation for her policies. This is just one example of how this epidemic weighs on the medical system throughout the world and in particular Africa. We have to work cautiously in collaboration with local officials to monitor and punish counterfeiters in severe terms.

In Europe, when I took my job five years ago this was perceived as a distant threat and a problem of the developing world. I cannot same the same today because some European states have been faced with counterfeit situations within the legal chain which has luckily not been the case in France but may be so in the future. The lesson we have already learned is that it is important to strengthen

the reliability of the pharmaceutical chain in what is a converging effort between local authorities in distant countries, traditional pharmaceutical countries and producers of drugs.

What is your final message to the readers of Pharmaceutical Executive?

I would stress that AFSSAPS has invested heavily in several sectors over the past few years and have exhibited a significant role in these fields. Firstly, there has been a lot of effort in post-marketing surveillance with several risk management plans developed since 2005 including strengthening pharmacovigilance, thanks to an intensive commitment of Doctors Anne Castot, Carmen Kreft-Jaïs and their dedicated teams.

Secondly, we have taken initiative in transparency and I am personally convinced that this is a necessary action if we want the outside world to trust regulators. Transparency requires agencies not only to publish more information on drugs but also to be clear about the way they assess products. Therefore, in 2005 before any legal obligation, AFSSAPS began to publish online all the minutes of our pharmacovigilance committees and later many other commissions such as diagnostics and market authorization. After four years of this practice we have had almost no controversy of what has been published online from either the labs or the general public. This is proof that transparency pays off at the end of the day.

Thirdly, in clinical trials we have had to implement the 2001 directive from 2006 on because the national regulations became effective then. Dr Chantal Belorgey who happened to be Chair of the Clinical Trials Facilitation Group (CTFG) in 2008 and implemented with its European colleagues a voluntary harmonized procedure (VHP) available to promoters for assessment of their multicentric clinical trials, has succeeded with her national team in implementing the directive while keeping assessment timelines will below the 60 days limit set in the directive. This was a big challenge to shift from a simple declaration system to a prior assessment model which is now widely recognized as accomplishment in the industry. Clinical trials are one of the areas where agencies overlap directly with the laboratories so we have scientific advice discussions with firms which are appreciated and complementary to EMEA advice.

Additionally we are developing our role in innovation and in the last few days have setup a specific assignment for interfacing innovators in our organization. In the last two years we have organized a number of meetings with biotech companies because one of the biggest problems faced in development of these technologies is the complexity of the regulatory landscape. We are trying to facilitate their operations while not giving up our assignment as a health safety agency. AFSSAPS is looking to guide them towards choices that may be more favorable for the development of their product and will help them avoid problems at later stages of assessment.

In conclusion, in order for national agencies to be an active partner and influence the way industry evolves they need to meet three challenges. The first is transparency which I already mentioned.

Second, competence is a factor which means adapting your skills to meet the changes in the regulatory and scientific fields. This is why over the past few years we have developed ambitious training policies for assessors, inspectors and laboratory workforce in order to match the scientific evolutions.

The third challenge is efficiency, as the format of our agency is stable due to a public workforce policy. This is very restrictive in an environment that demands additional missions involving for example authorization of clinical trials and ‘before-the-counter’ medicines. Submission volume in the field of marketing authorization alone has increased 30% in 2008 which includes the routes of centralization, mutual recognition, decentralization and national. In some countries, the level of national submission is decreasing why decentralized submission is steeply increasing. While there was a brief rise in centralized from 2005 to 2008 there is has been an ebbing which displays an evident problem in the pipeline. Today, the proportion of generic products in the centralized procedure is increasing which provides a stable level in the centralized process. France cannot rely on a substitution effect between national procedures and other routes of authorization, and has thus to cope with an at least a stable number of national submissions and a significantly increasing number of variations.

Efficiency is the key to handling this rising demand for processing which means constant reengineering and higher selectiveness when it comes to choosing the actions we implement on a risk basis. Moreover, revamping our information systems have to be a priority and in 2006 we implemented a comprehensive system which is just now reaping benefits. For example, in the middle of 2008 we began offering electronic submission which now makes up 50% of new submissions. Not only does this make life easier for industry but it has an added value for us as well.

To sum things up, I would meadily say that Afssaps clearly see the need to move and adapt to meet scientific and regulatory challenges. This is a powerful driver for the daily operation of our agency, and a key requirement which inspires its “Projet d’établissement” (Road Map) 2008-2010 and the “Contrat de Performance” (Performance contract) 2007-2010 which I signed with the Ministers of Health and Budget.

See more interviews