

# Phacilitate

Setting a New Standard for Pharmaceutical Industry Events

Advisory Boards

News & Views

Phacilitate Events

R&D Leaders' Forum

Autumn 2004

Vaccine Forum

Fall 2004

Cell & Gene Therapy

Forum 2005

R&D Leaders' Forum

Spring 2005

Vaccine Forum

Spring 2005

Home

Back ◀◀

## Dream or Nightmare?

In recent years we have seen great progress in updating regulation and the development of guidelines for the use of vaccines. Nevertheless, the vaccine industry and regulatory authorities still face some major challenges. **Dr Anne-Marie Georges holds the position of Director, Regulatory Affairs, Legal and Information within GlaxoSmithKline Biologicals.** Recently, she discussed with Phacilitate some current advances and problems and explained how some regulatory 'nightmares' are set to be banished forever.

**Phacilitate** What preparations are underway in Europe to respond to any potential bioterror crisis?

**Georges** Most discussion regarding anti-bioterror vaccines has revolved around the issue of the supply of smallpox vaccine. In Europe, it is not possible at the level of European Commission to force member states to accept Europe-wide proposals because public health policy still lies within the competencies of those member states. In fact, what has happened so far is that member states have individually entered into dialogue with vaccine manufacturers to investigate the feasibility of obtaining the relevant numbers of doses of smallpox vaccine in order to stockpile in case of emergency. How advanced this process is varies significantly between countries. The European Commission is strongly in favor of a stockpiling operation and, together with the vaccine companies, has created a task force to address the issue. Financial support will be needed because, although companies are prepared to develop a smallpox vaccine quickly to meet the requirements of the Europe Union, they also need to be sure that they can market the vaccine. Without financial support, companies face a situation whereby they develop a vaccine but may never be able to market a single dose. The European Commission is proposing, amid ongoing discussions, to block a certain amount of money to enable companies to tender for development of a smallpox vaccine stockpile. If accepted by the Commission, the proposal will later need to be ratified by the European Parliament, which controls the budget.

At the level of the EMEA, a new vaccine expert group, chaired by Mr Dobbelaer, has been asked to develop a new guideline on smallpox vaccines. Representatives of the vaccine companies have met with the group, and the guideline has now been finalized and is posted on the EMEA website. The guideline stipulates exactly what is expected of a smallpox vaccine and covers all aspects including quality, safety and efficacy.

**Phacilitate** What are the main implications of recent revision of pharmaceutical law on variations?

**Georges** The European Commission hopes to have the text approved for two new regulations in 2003, probably around the middle of the year. This is a key issue because regulatory affairs professionals have to allocate some 50% of their work time to variations. The new regulations provide for three different types of variation in Europe whereas at present we have only two - Type I (minor change) and Type II. In future there will be Type IA, Type IB and Type II. Type II (major change requiring a written authorization to be granted by the competent authority) will remain as it is today. Type IA – quick notification – is a fourteen-day procedure for very simple variations that do not impact the safety or quality of the product. Type IB

variations (implicit approval procedure) will be the same as current Type I variations.

There will be a number of interesting issues in the new text on variations, and procedures have also be somewhat simplified. In particular, in terms of the centralized approval procedure, there will in future be a specific quick annual review of the influenza vaccine. Currently, regulation on variations through the mutual recognition system makes provision for a rapid annual update approval for 'flu vaccines. This was established by the Commission in 1997, and it works perfectly well. However, at that time, only the well known 'classical' 'flu vaccines existed. Now, companies are using new technologies to develop 'flu vaccines in sufficient quantities to meet European and worldwide needs in case of epidemics or emergency situations. Such vaccines would undergo evaluation through the centralized approval procedure, so now a quick annual update is required through the centralized procedure as well.

I should add that the two new regulations are supplemented by Annex 1, which explains the differences between Type IA and Type IB variations and Annex 2, which clarifies what constitutes a line extension and provides a list of line extensions.

**Phacilitate** [What is the position now with regard to mercury-containing preservatives?](#)

**Georges** This is one of the numerous 'safety perceived' issues that the world of vaccines has to take into account. In fact, vaccines are given to healthy people - often to healthy children - and very mild adverse events are considered to be acceptable. It was a huge issue between 1996 and 2000 and led to a strong recommendation by the authorities to withdraw the mercury-containing preservative Thimerosal from vaccines. We enjoyed a very candid and open discussion with the European authorities during this time. When the decision was finally taken to withdraw this agent, it was not because vaccines as such were dangerous, but because of the contribution of vaccines to overall mercury intake. There is a maximum level stipulated by the WHO, and total uptake of mercury during the first two years of life is too high. Most of this mercury originates from food and cannot be controlled. However, it is possible to control the amount of mercury in pharmaceutical products, and this is significant for vaccines in particular because children receive several doses of vaccine in the first year of life. However, the authorities in the USA and in Europe did point out at the time that the risk associated with mercury is less important than the risk from not vaccinating the children. Removing Thimerosal presented manufacturers with some problems because removal of the preservative can modify, for example, parameters such as the stability, antigenicity and immunogenicity of the vaccine. Those properties are susceptible because there may be an interaction between the active molecule in the vaccine and Thimerosal. So it was not an easy situation to resolve, but manufacturers have addressed the issue and it has ceased to be a problem.

**Phacilitate** [What are the main challenges in the adaptation of the Common Technical Document \(CTD\) to a vaccine?](#)

**Georges** I was a representative from the industry at the ICH during the development of the CTD, with particular interest in biologics. We did not actually adapt the CTD to vaccines as such. In fact, when the table-of-contents of the CTD was being developed, it was decided that for each section we should consider specificity for biotech products. This related mainly to sections pertaining to quality issues – the pharmaceutical and biological information – because it has been decided at the level of ICH that there is no real specificity of biological product in preclinical trials in animals and clinical trials. So we now have a specific text for appropriate quality sections. At that time it was not decided whether all biologics, including vaccines and blood-derived products, would be included within the scope of the CTD, but now it has been decided that the CTD will be applicable to all products. So, we do have to follow the format of the CTD but in each section we have to think, for vaccines, what do we have to address in this section.

The FDA is likely to develop a specific guideline for each type of biological product, be it gene therapy product, biotech product, vaccine, blood-derived products or other. But for now, we have to adapt the content section by section. It will be compulsory to conform to the CTD from

July 2003.

**Phacilitate** What barriers remain along the path to harmonization and what are the implications for vaccine supply in the developing world?

**Georges** In Europe, regulatory processes and procedures are harmonized, guidelines are harmonized, the requirements for the dossier are harmonized - almost everything is harmonized. However, one thing is not and it causes quite a problem. As I mentioned before, public health policy and vaccination recommendations remain within the competencies of the member states. Each has different recommendations and different vaccination schemes. And, of course, where there are different vaccination schedules, companies must accommodate all of them within clinical trials. So at the European level, this is one major aspect that is not harmonized.

On a global level, thanks to ICH, most scientific requirements are harmonized. However, although there are specific guidelines on biologicals and biotech products, we do not have specific guidelines on vaccines. Looking at European guidelines and US guidelines there are no major divergences. However, on a world scale it is a little different. The WHO has its own guidelines and recommendations, and many individual countries, in Asia, Latin America or Africa for example, not only follow the WHO requirements - which is logical - but in addition set up their own requirements. And there, as worldwide vaccines manufacturers, we have some concerns. However, the WHO has organized regular expert meetings with regulatory specialists within the authorities of the USA, Europe and Japan, together with representatives from the industry. These groups come together to harmonize the WHO recommendations and this is the first step in a worldwide harmonization process that is specific to vaccines.

At the level of ICH, but not specific to vaccines, there is a new group working on global harmonization in which includes the ICH partners plus WHO.

Lack of world harmonization has a major impact. To give an example, the law, in the EU and in most countries in the world require a batch release to be granted by the relevant authorities for each individual batch of vaccine. A company can obtain a batch release in Europe and then other countries may accept that European certificate or they may want to repeat the testing operations. However, every laboratory is different, equipment is different the test animals may be different or the lab team may not be familiar with the test procedures. The risk is that the subsequent test results may not agree with the original test results, and so the company must enter into discussions, which may be very time consuming. This additional effort takes time, costs money, and finally, when the authorization to import the vaccine batch is granted, the company may have only 1-1.5 years left before the batch expiry, given that discussions may have taken 6-12 months.

**Phacilitate** What major trends can expect to emerge in the next five years?

**Georges** In the European Union, the review of the pharmaceutical legislation that is currently underway will provide an overall update across all pharmaceutical products, including vaccines, and will have a significant impact. One example from the vaccine perspective is the creation of the Vaccine Antigen Master File (VAMF). Under this new system, for each variation to combined vaccines, a company will be required to submit a dossier to the CPMP only (centralized procedure). This is a major advance. At present, each manufacturer prepares combined vaccines, but different combined vaccines can contain common antigens. Some of those vaccines are approved at the national level, some are approved via mutual recognition and others have been approved through the centralized procedure. So, when a company modifies any aspects of the manufacturing process or quality control operations of one of its antigens, a dossier shall be submitted through all of the procedures for a single variation. It is a nightmare for us and it is a nightmare for the authorities. Under the new system, a company will receive a certificate of approval from the CPMP that is valid also at the national level. We have calculated that a variation to a diphtheria antigen requires some 63 assessments under the current system. So the new approach enables us to replace 63 assessments with a single

assessment, which is wonderful. The VAMF system has not yet been adopted, but the attitude of the authorities has been very positive and we will all benefit from this change.

Another advance that has been proposed in the new law relates to 'generic' versions of biological products. Biologics are very sensitive to the process of manufacture and it is not at all appropriate to simply regard so-called generic versions of such agents in the same way that generics are regarded in conventional pharmaceuticals. Currently, for conventional generics, a company is required to submit only the part of the registration dossier, i.e. the CMC data, (the quality data, pharmaceutical, biological, etc) plus the data on bioavailability and bioequivalence. This is not sufficient in the area of biologics and, in future, manufacturers claiming that they have developed a biogeneric will have to submit preclinical and clinical data also. Demonstrating the similarity of two biologics is not so simple! This is a very welcome advance.

Finally, I hope that we will see advantageous treatment of vaccines in the new clinical trial directive. Currently, a company is required to submit a dossier to the regulatory authority. For a conventional pharmaceutical product, after a period of 60 days, if there has been no communication to the contrary, the investigational product is approved for clinical trials. However, for biological products the authorities in the different member states can require a company to wait for written approval.

How long will such a procedure take in the respective member states? The directive shall be implemented in the individual, national Law in 2003 and a lack of harmonization in this respect is likely to occur, each member state remaining free to require or not a written authorization to be needed for biologics.... which will be a serious issue when organizing multi-state clinical trials in the EU.

Dr Georges is a member of Phacilitate's vaccines advisory board.

---

© *Phacilitate Ltd, 2003*