



BERT SPILKER

## How to win the hearts and minds of regulatory agencies

There is no question that some pharmaceutical companies have an easier time than others in negotiating with regulatory agencies. Knowing how best to approach regulators is essential, says long-time drug development and regulatory affairs expert Bert Spilker.

The level of success that companies have with regulatory agencies often comes down to the way they present their data, and their behaviour towards the regulators themselves. In addition, the “medical need” for a product being developed and how well the company’s product addresses this are also important factors in the success a company will have in its interactions.

### medical need – medical value

Every new chemical entity needs to address a medical need of a specific group of patients. This “need” is the reason why the product is being developed, whether the group targeted represents all patients with a disease or only a small subset. This is the “public health need” for a new product.

The ability of the new product to address the medical need is referred to as its medical value. Simply having a great medical need does not indicate anything about a new drug’s medical value, which is based on clinical data and the determination of how well the drug addresses the medical need.

The medical need for the therapy you are developing and the medical value of your product in addressing that need will influence the regulatory agency’s flexibility in negotiating a mutually acceptable development plan.

The relative safety of your product is another essential factor that will impact the decisions reached on the quantity and type of data required for marketing your product. The greater the medical value of a new product, the greater the desire on the part of the agency to assist the company in achieving its goals.

Consistency of evidence (ie, confirmation of results in two or more separate well-designed and well-controlled trials) is the most convincing type of clinical evidence to present to regulatory agencies. Therefore, each company should determine how it can

provide this type of evidence to regulators.

This may mean that it could conduct two (or more) smaller trials where the same results can be demonstrated. Two smaller trials are usually more convincing than a single larger one. Even supportive data from a single small study (or a meta-analysis) that shows a positive effect is valuable in helping to confirm results of a single large pivotal trial.

### avoiding pet peeves of regulators

Having discussed this topic with several US FDA commissioners and other senior FDA executives, and confirmed that most of these complaints were also true in Europe, I have compiled a “top-ten” list of approaches and attitudes to avoid. However, these are not listed in any order of importance.

1. Do not be defensive, particularly about any of the drug’s problems or issues.
2. Do not try to explain away adverse events. Present a rational plan to study them.
3. Do not try to hide bad data. Rather, be upfront about them and explain what you plan to do to study the problem or potential problem.
4. Do not lecture regulators about a specific approach or scientific point.
5. Do not seek approval for an acute disease, hoping that the drug will be used off-label for a chronic one.
6. Do not seek approval for a minor disease, hoping that the drug will be used off-label for a major one.
7. Do not bring professors with international reputations to impress or lecture the agency.
8. Do not try to schedule spurious meetings or those that are not truly required.
9. Do not have senior executives treat the agency in the manner they would use with investors.

10. Interact with regulatory agencies on a high scientific level, where data are the coin of the realm.

Suggestions and “requirements” from regulators that the company does not agree with and/or wish to pursue must be discussed with them, and a strong rationale presented, assuming that sufficient data to counter the request or requirement are not available.

The company’s goal should be to find a compromise position if the agency does not agree to drop a request. A key point to remember is that regulatory agencies must save face in all negotiations.

Show that your company wants to work collaboratively with regulators. Clearly, there usually remains some degree of an adversarial relationship, but every attempt must be made to minimise this. One of the best ways is to focus discussions on a scientific level using high standards of development, and avoid opinions, wishful thinking and defensive behaviour.

It is critical to avoid making assumptions about the agency’s view on any important issue, as such assumptions often lead to an undesirable situation or problem for the company. One of the times when assumptions are often made occurs after regulatory meetings if the company has not summarised every point of agreement at the end of that meeting.

In such cases one often hears the company professionals discussing at a briefing session (or later) whether or not the agency really agreed with the company’s position or proposal. While some of these uncertain areas may be clearly stated in the meeting minutes this does not always occur and the company is left with uncertainty.

For all important such areas or questions, product development plans and activities should not be based on any assumptions, but a clear answer sought from the regulators.

The use of surrogate endpoints (a subset of biomarkers) is a highly controversial topic, particularly for choosing primary endpoints in a trial.

Regulatory agencies have been burned on several occasions when some biomarkers, particularly biochemical or physiological biomarkers have been accepted as valid surrogate endpoints, and were used to demonstrate clinical efficacy.

As a result regulators are usually reluctant to accept any biomarkers as surrogates that are not fully validated.

This is a standard that few surrogates can meet, and many companies are forced to accept longer and/or more complex clinical trials that employ clinical endpoints that are not surrogates.

The required number of patients to include in a marketing dossier as well as the number of trials required are also important areas to negotiate, as there are often sound reasons why commonly used standards cannot be met (eg, for orphan drugs).

## The principle that two smaller studies confirming efficacy and safety are far better than a single larger study is one to keep in mind in creating development plans

Nonetheless, the principle that two smaller studies confirming efficacy and safety (with statistically significant results) are far better than a single larger study is one to keep in mind in creating development plans. In some cases the confirming study may be a meta-analysis or even an observational study, if a better designed trial raises issues that cannot be easily addressed.

In appealing any negative decision relating to a "shortcut" the company has proposed, it is important to go sequentially up the leadership chain and to copy the regulatory staff with whom the sponsor has previously discussed the issue, unless a specific legal issue is involved and the company can appeal directly to the general counsel of the agency.

These topics and other related issues are discussed in greater detail in "Guide to Drug Development: A Comprehensive Review and Assessment" by Bert Spilker, published by Lippincott, Williams and Wilkins, 2009. Bert Spilker, [www.bertspilker.com](http://www.bertspilker.com), ([bspilker@comcast.net](mailto:bspilker@comcast.net)).

## EC decides against new directive on GMP for excipients

The European Commission has decided not to go ahead with legislation applying Good Manufacturing Practice provisions to certain excipients because of concern that it would lead to an increase in costs without providing any public health benefits.

Instead, it will look into the possibility of taking a risk-based approach to GMP for excipients, based on the quality risk management principles of the International Conference on Harmonisation (ICH). Under the existing pharmaceutical legislation (Directive 2001/83/EC, as amended), the Commission is required to adopt a directive on a list of excipients to which specific GMP conditions should be applied.

This requirement was added at a late stage of negotiations on the 2004 amendments to Directive 2001/83. The reason for doing so, according to an impact assessment report by the consultancy, Europe Economics, was concern over the possible risks of materials contaminated with transmissible spongiform encephalopathies (TSEs), and known cases of excipient mislabelling and mix-ups which had led to numerous deaths in Haiti and Bangladesh. Six product categories had been identified as appropriate for the proposed list because of the potential risk they presented:

- excipients derived from a TSE-relevant animal species (excluding lactose);
- those from human or animal material with potential for viral contamination risk;
- excipients claimed or sold as sterile and used without further sterilisation;
- those at significant risk of endotoxin/pyrogen contamination;
- propylene glycol; and
- glycerol.

A number of options were put forward, including maintenance of the status quo, legislation (GMP requirements), technical guidelines for certain excipients, a risk-based approach, and self-regulation.

Questionnaires were sent to suppliers and users of excipients between March and July 2007, and the results were incorporated into the Europe Economics report.

Published at the beginning of 2008, the report found that both suppliers and users expected prices to rise as a result of any change in the regulations.

Legislation would push up prices the most, followed by guidelines, while self

regulation would increase prices slightly more than the risk-based approach. A significant part of the increases would be absorbed by pharmaceutical manufacturers.

The idea of a directive with a detailed list of excipients found little support, with many favouring a more risk-based approach to applying GMP to excipients, the report says.

It concluded that there was no reason why continuing current policies should significantly increase the risk of unsafe excipients being used in pharmaceutical products, and that the status quo was the best option. However, it did recommend that the existing regulations should be more effectively monitored and enforced, and said that Directive 2001/83 would need to be amended to remove the requirement for a new directive on a list of excipients.

The Commission says that the results of a public consultation conducted by its enterprise directorate have confirmed the concerns raised by stakeholders and experts that the requirement for a list of excipients is too inflexible. The consultation revealed a need for a "balanced approach" to applying selected GMP provisions to excipients, according to the Commission. This, it says, would be justified from both the public health and business perspectives if it was based on internationally agreed concepts and criteria for quality risk management, and involved drug manufacturers in the decision-making process. If such a route were chosen, Directive 2001/83 would have to be amended accordingly.

The Commission has separately published guidance on harmonising the conduct of Good Clinical Practice inspections by the EU member state authorities. The document specifically concerns GCP inspections and co-operation among inspectors and the reference and concerned member states in evaluating the GCP compliance of approval applications in the EU's mutual recognition and decentralised procedures.

It notes that clinical trials conducted both within and outside the European Union/European Economic Area relating to product approvals in the EU/EEA are subject to GCP inspections. Inspections can take place as part of the verification of applications for marketing authorisation or as a follow-up to the granting of an authorisation.

[ian.schofield@informa.com](mailto:ian.schofield@informa.com)