J. Pharm. Pharmacol. 1994, 46: 697

Editorial—Harmonization and Back to Basics

"A foolish consistency is the hobgoblin of little minds."

I must admit a liking for this quotation from the American essayist, Ralph Waldo Emerson. It can be applied to all those silly situations where the needs of bureaucracy appear to overwhelm any considerations or intentions of the user or provider of a particular commodity. Something over thirty years ago there was a bizarre dispute between a United States government department and a chemical supplies company. As I recall, the government department had laid down rules on how the suppliers should present their goods for sale and this involved the catalogues of the suppliers being fitted into some sort of dossier, leading to a requirement for a particular page size for the catalogues of their suppliers. The implication was therefore that the chemical supplies company had to redesign its catalogue, to look like all the others presumably, if it wished to be considered for government contracts. I think Emerson would have approved of the supply company's outrage. Unfortunately, I cannot recall the eventual outcome (although both the chemical supplier and the United States government are still in business!), but there is some irony in the fact that the United States is one of the few countries that does not seem to have accepted A4 paper as the standard for general office use.

This is not to say that there are no situations where consistency is not a worthwhile goal. The rules and regulations governing the introduction of new drugs may be considered to have had their biggest impetus following the thalidomide disaster of the early 1960s. Most countries began to introduce strict controls on the testing of new chemical entities at this time, but not unnaturally, the different countries applied different criteria to deal with the problem as they perceived it. Scientific tests have never been wholly rational and are bound to depend to a large extent on the materials and expertise available, and on the current thinking. Thus the new regulations tended to be developed with distinctive national flavours, and when a drug was developed in one country, it would not necessarily have been subjected to all the tests required by another.

This difficulty could be accommodated in the early days of drug regulation. If the drug was intended for a local market, the testing would be directed at the market's requirements; if the market was slightly wider, the relatively restricted tests required could be repeated as needed. Some multinational companies even found it was reasonable to set up development laboratories in different countries, purely for carrying out all the development trials required by the local authority even if this meant repeating work already done elsewhere in the organization. However, as pharmaceutical research became more and more directed to compounds which would have world-wide application, and as testing became more sophisticated and demanding, and hence more expensive, such an approach became less acceptable. The research companies began to seek ways of structuring the development process to produce a drug dossier that would cover the requirements of all the various authorities that would be involved. Ideally, the work involved in producing such a dossier ought to have been less than the sum of the work that would be required in the separate countries.

Unfortunately, however, it was not the drug industry which made the rules on testing, but the separate government authorities. Although many tests may appear to be essentially the same, it was often the case that the detail was sufficiently different to require slightly different tests, although the outcome of the tests would be barely distinguishable. A chronic toxicity test in the same species might be crucially different in the time or frequency of dosing required by different authorities and even for those countries 'separated by the same language' there could be disagreement on the exact definition of a rodent.

Naturally, many countries attempted to introduce reciprocal agreements, but again the complete acceptance of a drug registered in another country could never be so straightforward, and such reciprocal arrangements could only be partial. However, such agreements were the foundation of the International Conferences on Harmonization, the first of which was held in Brussels in 1991, and included in its sponsors representatives of industry and government. The key word here is 'harmonisation' or 'harmonization' to comply with the convention of this Journal (another case of foolish consistency, perhaps?), with its implications of putting together existing practices, so they can co-exist without too much conflict between them.

A strong influence in recent years for dossiers that would cross national borders has been in the development of European unity. As the countries of Europe become closer with common laws and even common citizenship, there is now a legal imperative to have common drug regulation. This requires something more than harmonization of the existing codes.

A phrase that has had some popularity in the United Kingdom over the last year or so has been 'back to basics.' Perhaps it is a back-to-basics approach that is needed to begin to redesign the protocols for testing new medicines, a design that need not confine itself to the European scene. Now would seem to be a good time to make critical evaluations of both the tests required for the safety testing of new compounds and the amount of detail in the information provided in the safety applications. As an example of the former, we should ask if some toxicity testing, involving thousands of animals, is justified on scientific or ethical grounds, as an example of the latter, whether such detail as evaluation of analytical methodology for determination of purity or identity of active compound and excipients is really part of this document.

I do not underestimate the enormous effort that would be needed to construct this new regulatory edifice from scratch, but I am confident that the able scientists in the regulatory authorities can salvage the relevant material from the old structure to ensure firm foundations for a system that will be both efficient and efficacious in developing the medicines of the twenty-first century.

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