



# R&D Briefing

## *Cause for Concern?*

### Non-clinical Safety Testing of Biotechnology Products

Top 10 issues of concern in the non-clinical testing of biotech products

- 1 Choice and number of species/ identification of pharmacologically relevant animal model.**
- 2 Implications of antibody formation in test animals on the duration of toxicology studies.**
- 3 Conduct of genotoxicity studies.**
- 4 Lack of harmonisation of regulatory requirements between regions.**
- 5 Conduct of reproductive toxicology studies.**
- 6 Nature and extent of pharmacokinetic/ toxicokinetic/distribution studies.**
- 7 Regulatory requirements/lack of regulatory guidance.**
- 8 Use of animal models of disease.**
- 9 Conduct of carcinogenicity studies.**
- 10 Use of homologous proteins in repeated-dose toxicity studies in animals.**

- Despite the substantial increase in the number of products of biotechnology reaching the market in recent years, there is still uncertainty within the pharmaceutical industry regarding the non-clinical safety testing of such products.*
- What are the major issues? Do these relate to the toxicity tests themselves or to regulatory requirements? What information could be collected to help resolve some of the difficulties?*
- The main concerns amongst toxicologists, in 40 of the companies responding to a questionnaire, included the identification of relevant animal species for toxicity testing and the lack of regulatory harmonisation and guidance.*
- Greater interaction between pharmaceutical companies and amongst regulators together with general guidance, not definitive guidelines, from the authorities should help resolve these concerns.*

Figure 1 The main issues of major concern to companies were similar irrespective of area of expertise, and were spread across geographical regions. Regulatory issues effectively top this list since taken together they concerned 50% of companies.

## Perspective

As with all pharmaceuticals, the products of biotechnology must undergo non-clinical safety testing before initiation of clinical trials and for marketing purposes. Although industry experience in this field spans more than 15 years there is still some uncertainty regarding regulatory requirements and expectations.

To throw light on the issues of major concern and to identify the type of information that might be collected to help resolve these difficulties, the Centre for Medicines Research (CMR) conducted a survey of company toxicologists.

## Corporate and Personal Experience

Replies to a concise questionnaire were received from 46 companies. Forty of these (19 US, 14 European and 7 Japanese) have been involved in the non-clinical safety testing of products of biotechnology; their experience is broad. Thus, 70% of the 40 companies have been working in this area for over six years as have 54% of the respondent toxicologists.

Over the past 10 years, 85% of the companies have tested three or more products non-clinically; five companies have tested more than 10 products. The companies are working with many different classes of product; the main areas of expertise are growth factors and monoclonal antibodies.

### Definition

For the purposes of this survey a product of biotechnology was defined as "a naturally occurring or modified protein, DNA or RNA product, produced by expression in cell lines (bacterial, yeast, mammalian, insect or vertebrate) or transgenic animals, and used for therapeutic, prophylactic or diagnostic use in humans".

## Issues of Concern

The issues of most concern, identified from the questionnaire, fall into two main categories: aspects of the tests themselves and regulatory issues. They were spread equally among the regions (Europe, Japan, the USA) in which the toxicity testing takes place; no concern was particular to one region.

### Have companies experienced difficulties arising from differences of opinion between regulatory regions?

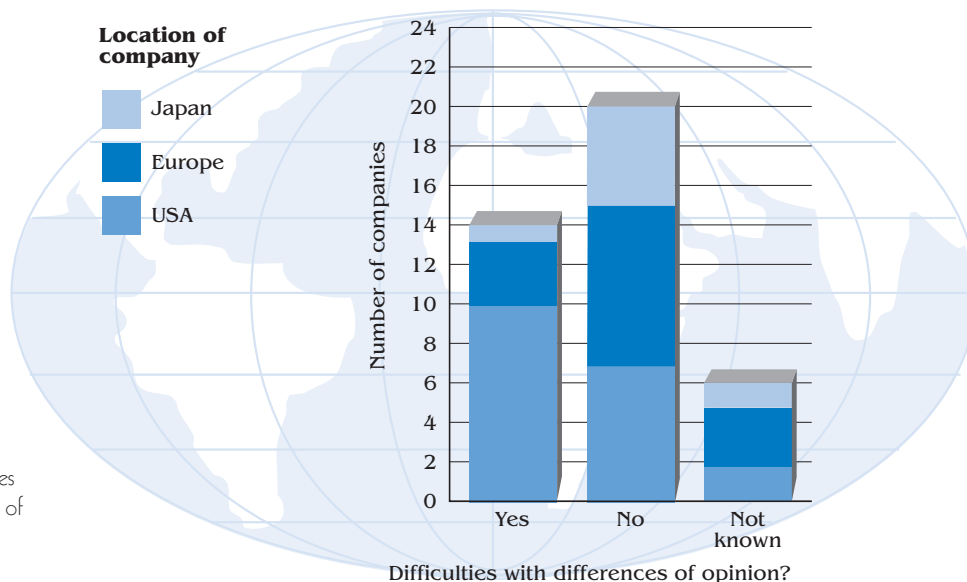


Figure 2  
Although more than one-third of companies reported difficulties arising from differences of regulatory opinion around the world, few provided specific details.

### Aspects of Toxicity Testing

The majority of the top 10 concerns (see Figure 1) relate to the toxicity tests themselves. In particular, the identification of pharmacologically relevant animal models and/or the choice and number of species required for safety testing are of concern to almost half the companies.

Toxicologists also have significant concerns about the implications of antibody formation in test animals - how this affects the duration of toxicity studies, and possible effects on the efficacy and kinetics of protein drugs, through inactivation or a change in clearance.

The relevance of genotoxicity studies concerns 40% of the companies.

### Regulatory Issues

There are two key issues on the regulatory front which together concern 50% of companies (see Figure 1). Firstly, lack of harmonisation around the world and, secondly, the nature of regulatory requirements and lack of guidance.

Over a third (35%) of the companies, the majority being located in the USA, have experienced difficulties arising from differences of opinion between regulatory regions. No such difficulties were reported by 50% (see Figure 2).

Importantly, 24 companies (60%) have been requested by regulatory authorities to conduct toxicity studies which they consider to be inappropriate (see Figure 3). Chief amongst these are genotoxicity tests.

Not all interactions with the regulatory authorities have been unrewarding. Respondents were asked whether different authorities provide sufficient guidance, either published or through informal interaction, on this type of testing. The US Food and Drug Administration (FDA) largely satisfies company needs whereas the Japanese Ministry of Health and Welfare (MHW) fails to do so (see Figure 4). However, the MHW is addressing this problem. Opinions on the European CPMP (Committee for Proprietary Medicinal Products) are divided.

Regulatory requests which were considered inappropriate

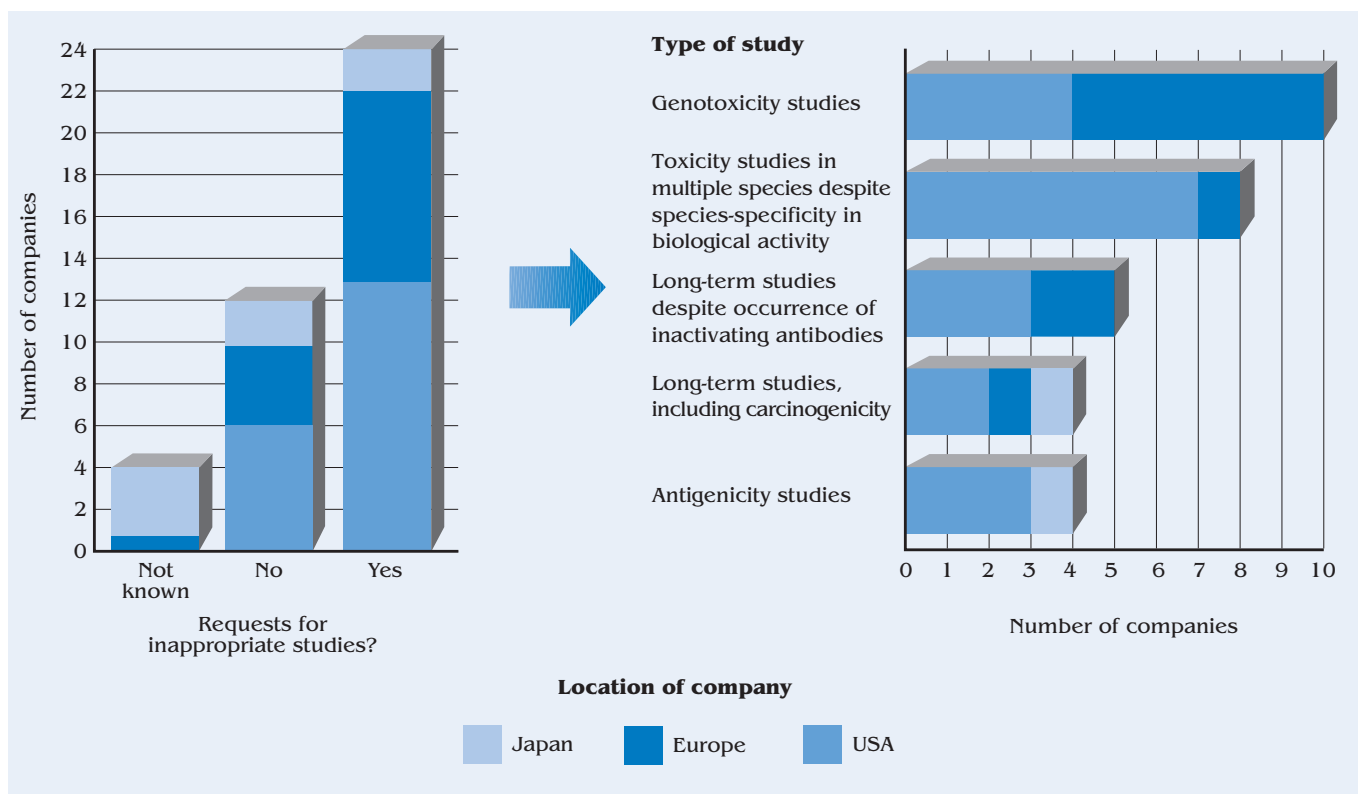


Figure 3 The content of safety testing packages is obviously of prime concern since 60% of respondents had experienced regulatory requests for studies which they considered inappropriate.

## Interaction with regulatory authorities - Is sufficient guidance provided?

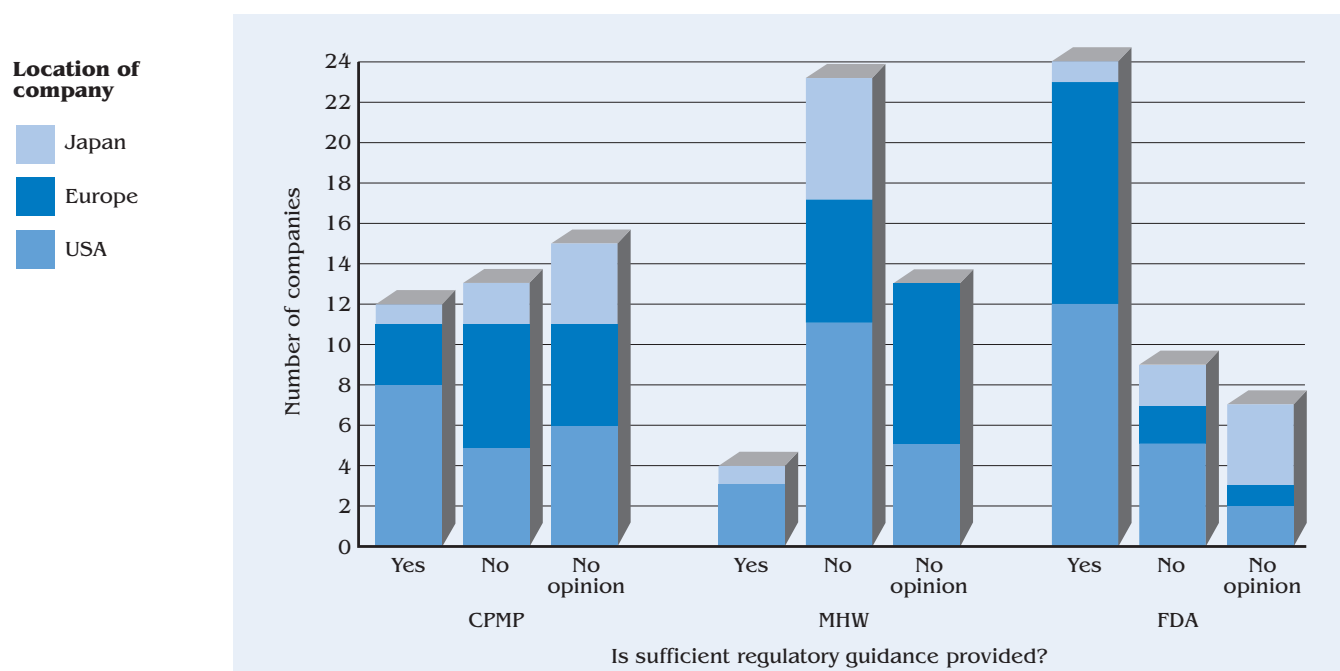


Figure 4 For the majority of companies, the US Food and Drug Administration provides sufficient guidance on the non-clinical safety testing of biotechnology products, but the Japanese Ministry of Health and Welfare fails to do so.

## Potential Solutions

How can these concerns be resolved? Six potential solutions were provided by the survey respondents:

1. More interaction within the pharmaceutical industry to exchange experiences (85%);
2. More interaction amongst regulatory authorities (78%);
3. General guidance (73%);
4. Definitive guidelines from the regulatory authorities (23%). However, 8 of the 9 toxicologists in this group are relatively inexperienced with regard to designing safety studies for products of biotechnology;
5. Identifying the differences between current and ideal toxicity testing strategies (53%);
6. A central database of information, particularly toxicity testing strategies (48%).

Copies of the full report, "Non-clinical Safety Testing of Products of Biotechnology: Issues of Concern" which contains 41 pages, 14 figures and tables, and 2 appendices, can be obtained at a cost per copy of:

Non-sponsoring organisation	£500
Sponsoring pharmaceutical companies	FREE

These can be ordered, quoting reference number CMR95-63R from Shaida Dorabjee, Research Services Manager, at the Centre for Medicines Research.

(All cheques should be made payable to Centre for Medicines Research. Non-UK cheques should be in sterling and drawn on a London bank.)

September 1996



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