Journal of Pharmaceutical & Biomedical Analysis
Vol. 7, No. 2, pp. 267–269, 1989
Printed in Great Britain

0731–7085/89 $3.00 + 0.00
Pergamon Press plc

Report

Panel discussion: comparative evaluation of biological and chemical methods for the quality control of biomolecules used as drugs*

MARIE L. RABOUHANS

British Pharmacopoeia Commission Secretariat, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, UK

A Panel Discussion was held after Session 3 on Thursday 5 May 1988. The Panel, chaired by Derek Calam, consisted of Derek Bangham, Alan Dinner, Christopher Rhodes and Ingvar Sjöholm.

The discussion, initiated by the Panel members and with participation from the floor, centred on general issues concerning the analysis of biomolecules and the factors that influence the choice of analytical methods. In particular the Panel discussed the relative merits of biological and chemical methods. Drawing upon examples from papers presented during the Symposium, the transition from a need for biological test methods to reliance on physico-chemical techniques was explored. If one accepted the definition of a biological material as one that could not be characterized and controlled adequately by physico-chemical means, the boundary between biological and chemical material was one that shifted with time. For example, biological methods had once been considered essential for vitamins, steroids and for all antibiotics; in 1988 this was no longer the case. Implicit in this definition was the view that materials originally derived from natural sources, but now produced by chemical synthesis or by recombinant DNA techniques, might still be considered as biological materials.

An underlying theme throughout the discussion and, indeed, throughout the Symposium, was that the choice of method depended on the purpose for which it was intended. The degree and type of control would be influenced by many factors relating to the nature and intended use of the substance. These included whether the substance was established in clinical use or novel, the size and frequency of the dose, the route and time course of administration and whether it was likely to be acute or chronic; and the age, sex and health status of the target group for whom the substance was intended. The amount of information required for a biomolecule would depend on whether it was a well established entity about which much was already known, for example insulin, or whether it was a material that had not previously been available as a therapeutic agent, for example erythropoietin.

*Informal synopsis of Panel Discussion held at the Symposium on "Biomolecules — Analytical Options", May 1988, Sollentuna, Sweden.

Both the Panel members and contributors from the audience emphasized that a further factor in determining the degree and type of control was the organization for whom it was required. The quality control requirements of manufacturers, licensing and pharmacopoeial authorities would make different demands and dictate different priorities. A licensing authority reviewed and judged a manufacturer's product-specific data in the context of a broad framework of policy and requirements (laid down for example in European Community Directives and associated guidelines); the ultimate result was the granting or refusal of a product licence. All communciation was confidential between the licensing authority and the manufacturer. A pharmacopoeial authority, on the other hand, developed a detailed specification based on manufacturers' proposals and on independent practical evaluation of material from as many sources as were known to be available; the result was a detailed specification that provided not only the criteria of acceptance (limits) but also the methods by which compliance should be determined in cases of doubt or dispute. This specification was made publicly available. Some of the differences in the scope for action are summarized in Table 1. While it was appreciated that registration and pharmacopoeial authorities were, of necessity, cautious it was agreed that they should be prepared to consider change when presented with appropriate evidence.

Certain prerequisites for accepting physico-chemical control of a material that currently required analysis by biological methods were identified as follows: (i) reliable and consistent manufacture; (ii) absolute identity of the substance; (iii) knowledge of the effect on stability and shelf-life of any modification that might occur.

Attention was also drawn to the need to consider the possible presence of potentially immunogenic impurities. It was important to demonstrate that a substance produced by recombinant DNA techniques or by synthesis, possessed not only the primary and secondary, but also the tertiary and even quaternary structure of the natural material, since these were often critical to the physiological/pharmacological action. Provided that the necessary data had been generated during product development and in the initial validation of the manufacturing procedures, a manufacturer might then be able to rely on much simpler techniques such as UV spectroscopy or nitrogen determination for the purposes of in-process and some routine batch control.

Table 1
Some distinctions between licensing and pharmacopoeial authorities

Licensing authority	Pharmacopoeial authority
In possession of full data Source Process In-process controls	Cannot make assumptions based on Source Process In-process controls
Concerned with Release specification	Concerned with Check specification
Has power to Inspect Obtain material (at all stages of manufacture)	Has need to Demonstrate that bulk material is of appropriate quality Restrict testing to reasonable likely sample available Provide methods that can be upheld in a court of law

It was emphasized that consistent production of biomolecules of acceptable quality relied on the use of validated methods of manufacture. These in turn depended on the availability of validated methods of analysis. In order to demonstrate that a method was appropriate to, and adequate for, a particular purpose, it was necessary to consider some or all of the following parameters: accuracy, precision, sensitivity, specificity, intra-laboratory and inter-laboratory reproducibility (the latter being sometimes referred to as "transferability"). In addition, if a method were being considered as a replacement for, or an alternative to, an established official method, validation should include an assessment of comparability with the official method.

In summing up the discussion, the Panel Chairman laid emphasis on the need for the exchange of views and information between manufacturers, the registration authorities and pharmacopoeial authorities. The broad degree of consensus emerging from the Symposium provided a foundation for constructive discussion on specific issues concerning the analytical basis of the control of biomolecules used as drugs.

[*Received for review 26 August 1988*]