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The problems of biologicals

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The licensing system introduced with the Medicines Act of 1968 arose from reaction to the thalidomide disaster and is intended to protect the public from a repetition of such an event. The criteria for licensing any medicinal product are quality, safety and efficacy. Analysts have a role in all three aspects but the pharmaceutical analyst is particularly concerned with regard to quality, quality in relation to safety and to some degree with quality in relation to efficacy. Although this concern applies to all medicinal products, biologicals pose special challenges to the analyst.

Biological medicines fall essentially into two categories: traditional biologicals isolated from or consisting of material of natural origin, and products obtained by genetic engineering (recombinant products). In the former group fall blood and blood products, vaccines, complex hormones and some fermentation products. Into the latter fall some hormones previously only available as isolated products (insulin, growth hormone) and an increasing number of products previously unavailable or available only in amounts too limited for therapeutic use (erythropoietin, cytokines).

With such complex materials obtained by complex processes, it is difficult to perform the necessary tests to confirm quality criteria solely on the final bulk material or dosage form. For many years it has been recognised that an essential component for ensuring quality of biologicals is control over the manufacturing process to guarantee high standards and reproducibility of the product.

The role of the analyst is basically twofold: to detect and control contamination, and to determine content or potency.

Contamination is to be interpreted in the broad sense to include contamination of starting materials, such as the viral contamination of blood; contamination from the process, such as residual cellular components from a fermentation or cell culture process; adventitious contamination, such as bacterial endotoxins or lack of sterility; and contamination of the substance itself by related impurities and non-specific contamination by metals, solvents, reagents and so on.

These contaminants are detected and measured in various ways: by tests to detect the presence of viruses; by immunological methods to measure residual nucleic acid and cellular protein; by in vivo tests to measure pyrogens or in vitro tests to measure endotoxin; and by a battery of tests based on separation techniques and physico-chemical methods to distinguish and quantify impurities.

The measurement of potency historically was based on in vivo assays reflecting as far as possible the desired biological properties of the preparation. More recently in vitro methods have been introduced that can offer similar assurance of potency. For some simpler biologicals, such as small proteins, the specificity and precision of non-biological assays based on HPLC have allowed the replacement of biological assays for routine control.

The range of test methods that an analyst can deploy depends on scientific and technical contributions from different disciplines in biological, physical, chemical and pharmaceutical areas. This spread of disciplines involved is one of the factors that distinguishes biological medicines from other medicines products. Advances in the role that an analyst can play in the control of biologicals are dependent on the progress of science in all these disciplines.

The increasing role of analysts in recent years in examination of biologicals has taken place because of new experimental methods that allow more detailed and specific testing of properties of the test material. Data obtained from such methods has in turn been used to introduce improvements in manufacturing processes. This has resulted in products of higher quality and consistency with benefit to patients and to public health.

The expansion of biological medicine through novel recombinant products offering treatments of some diseases for the first time, novel vaccines for a wider range of infections, and new therapies employing xenotransplantation and gene therapy will present the analyst with greater challenges to ensure that the full potential of these products is achieved.