The clinical pharmacology of biotechnology products
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MEANINGFUL EVALUATION OF BIOTECHNOLOGY PRODUCTS

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INTRODUCTION

During the last decade national and international regulatory authorities have had to meet the challenge of evaluating medicinal products derived from new biotechnological procedures, mainly through recombination of genetic information from dissimilar organisms (recombinant DNA technique, rDNA) and the fusion of dissimilar cells to form a monoclonal hybridoma that is viable and differentiated *in vitro* over an extended time (monoclonal antibodies).

The innovations caused by medicinal products derived by biotechnological processes comprise a) products of higher purity, b) production of larger quantities, c) modifications of the molecular structure to improve the therapeutic usefulness, including new indications, and d) potential possibility of cheaper production.

Numerous national, international and supranational guidelines have been prepared concerning the production and quality control of these products as well as concerning preclinical animal toxicity testing, e.g. the EC Notes for Guidance (1). However, very few recommendations have appeared pertaining to the clinical evaluation and the final estimate of the benefit/risk ratio (2, 3).

The purpose of this paper is to present a survey of the status of regulatory requirements/evaluation 1990 based upon experience with "old" biological products and "new" biotechnologicals. The products derived by biotechnological procedures shall be considered together, since their evaluation with regard to quality, safety and efficacy is in principle the same. However, some of the actual differences are evidently caused by the different techniques employed in their production: rDNA techniques involving *E. coli* and yeast or transformed cell lines resulting in polypeptides/proteins, which are physiological or modified ("clever proteins"), heterohybridoma techniques involving continuous cell lines or mouse ascitic fluid

resulting in rodent immunoglobulins or the combination of techniques resulting in "designer" or "humanized" antibodies (3, 4, 5).

EXPERIENCE WITH "OLD" BIOLOGICAL PRODUCTS

Parenteral administration of biologicals have been used in human medicine for 3 centuries - the first blood transfusion (lamb to human) being performed in 1667 and the first variolation in 1717 (both experiments in children). However, "The First Therapeutic Revolution" started with the ideas of Pasteur in the second half of the eighteenth century. The first Nobel Prize in medicine in 1901 was awarded Emil von Behring for his work on serum therapy. Since then numerous biologicals derived from extracts of various animal and human organs, body fluids and microorganisms have been and are still being developed and used successfully in the prophylaxis and treatment of several diseases: hormones (e.g. insulin (1922), glucagon and human growth hormone), coagulation factors, vaccines, antisera (antitoxins), albumin, gamma-globulins, anti-digitalis Fab, human anti-D immunoglobulin, plasma, antibiotics, cytostatics, enzymes (hyaluronidase, streptokinase, urokinase, anisoylated plasminogen-streptokinase activator complex) *et cetera*. Many of these products were developed before the existence of regulatory authorities and professional/ethical requirements concerning clinical trials, and the route from idea to clinical use was often very short, the first clinical use frequently arising from compassionate use. These biologicals revolutionized the treatment of numerous infectious diseases, diabetes, haemophilia, acute myocardial infarction *et cetera*. Subsequent improvements of the production, purification and control resulted in medicinal products of a reasonable or high standard, e.g. insulin.

However, the biologicals are not devoid of side effects, a.o. arising from their way of production. We have had to deal with the elimination of pyrogens and microbiological contamination, and among the side effects acute and delayed hypersensitivity reactions have been and are of great concern. An illustration of these problems is, that out of 23 deaths in children reported to the Danish Adverse Reactions Committee 1968-88 eight were attributed to vaccines and 4 to

allergens used in desensitization (Andersen et al., in preparation). Among the wellknown problems are the possible transfer of hepatitis virus, HIV, bovine spongiform encephalopathy and Creutzfeldt-Jakob's disease. Recently we have been faced with the eosinophilia-myalgia syndrome associated with the use of tryptophan probably caused by an impurity from the production involving fermentation using *Bacillus amyloliquefaciens* - despite a purity of more than 99.6 % (6). Some of these recent, unexpected side effects have added to the regulatory concern when dealing with the new biotechnological products.

EXPERIENCE WITH NEW BIOTECHNOLOGICAL PRODUCTS

We have had experience with new biotechnologicals for only one decade, although their development started with the elucidation of the DNA structure by Watson & Crick. During this period a number of products have appeared, some of which are already marketed, others in clinical investigation, e.g. insulin, glucagon, human growth hormone, interferons, interleukines, recombinant tissue plasminogen activator, erythropoietin, granulocyte/macrophage colony stimulating factor, granulocyte colony stimulating factor, hepatitis B vaccine, coagulation factors, murine OKT3, monoclonal antibodies specific for Gram negative bacterial lipopolysaccharide, and monoclonal antibodies alone or conjugated with radionuclides, plant and microbial toxins and oncolytic agents.

The use of these medicinal products comprises single dose administration for diagnostic purpose, short term treatment (bacterial infections, hypoglycaemia, thrombolysis, cancer, myelosuppression), long-term treatment at physiological doses (diabetes mellitus, pituitary nanism) and long-term treatment at supraphysiological doses (Turner's syndrome).

Some of these products are "genuine" human molecules, others are modified ("clever proteins"), and still others are murine antibodies or "humanized" antibodies.

Some products are rather small polypeptides (glucagon with 29 amino acids), others are large (erythropoietin with more than 500 amino acids), and the monoclonal antibodies may be even more complicated.

The products are derived from very different technologies comprising rDNA techniques involving *Escherichia coli*, *Saccharomyces cerevisiae* and transformed cell lines, heterohybridoma continuous cell lines (cell cultures) and mouse ascitic fluid.

The therapeutic benefits from the new biotechnology products have been obvious.The development of rDNA insulin may not be called a revolution, but the haematopoietic growth factors and interleukine-2 are examples of important new drugs. The higher purity with a diminished risk of microbiological contamination is an evident benefit, e.g. rDNA human growth hormone without the risk of transferring Creutzfeldt-Jakob's disease. Products being developed for use in cancer, viral diseases, parasitic diseases, autoimmune diseases and haemophilia may hopefully deserve the designation "The Second Biological Therapy Revolution."

The drugs developed by biotechnological methods are not without side effects, some of which may be potentially serious. However, so far they have mainly been caused by the active molecules and not by unexpected impurities or contaminants from the production.

Allergic/immunological reactions were to be expected when using non-human species specific polypeptides, e.g. murine antibodies. However, the use of monoclonal antibody affinity isolated factor VIII despite the appearance in the final preparation of trace amounts (ng) of mouse antibody leaching from the solid phase support does not result in clinical immunological reactions in the recipients (7). Clinical symptoms related to hypersensitivity or anaphylaxis have not been observed from the use of human peptides developed through rDNA techniques involving *E. coli* or yeast. The previously used rDNA methionyl-human growth hormone gave rise to antibodies, but these were of little or no clinical significance.

Microbiological contamination has not been a clinical problem so far.

Another serious problem is the possibility of an oncogenic potential. At present it cannot be excluded, that there may be a causal relation between the use of human growth hormone (pituitary extract or rDNA synthetized) and the development of leukaemia, although the number of cases reported so far is very small.

Despite this positive experience, all the problems mentioned rightfully are causes for concern.

EVALUATION OF BIOTECHNOLOGY PRODUCTS

Quality

Numerous guidelines exist on the production and quality control of biotechnology products including validation of virus removal and inactivation procedures (1). Evaluation of the quality aspects is important concerning "ordinary" drugs, but is crucial when dealing with biotechnological products, in particular since unwanted side effects caused by impurities and/or microbiological contamination may be very difficult, sometimes impossible to detect in preclinical animal toxicity studies and in short-term human clinical trials.

Potential for mutation drift or genetic alteration of the cloned rDNA sequence, and subtle changes of the host cells during propagation are of concern. One of the consequences may be the production of neoantigens. Evidently a thorough characterization of the final product is crucial. A number of chemical and physical tests provide information on the primary, secondary and tertiary structure of a polypeptide/protein. Although it is still difficult to obtain complete information on the tertiary structure and increasingly problematic, when the size of the protein becomes larger, these tests give reasonable assurance, that any mutant product will not escape detection. The final product furthermore must demonstrate its biological activity in appropriate *in vivo* and *in vitro* bioassays.

Purities of 95 % or more can be achieved. The impurities may be product-related substances, foreign antigens, DNA fragments, pyrogens, "excipients" used during production or in the final product, and contaminating microorganisms.

Eliminating *product-related substances* to ppm levels is difficult and normally not necessary. Individual impurities of the order of 0.1 % may be identified and quantified.

Foreign antigens, e.g. arising from the use of *E. coli* or yeast may be reduced to less than 10 ppm.

The use of mammalian cells for production requires tumour cell lines and viral

vectors. Therefore, the cloned cells contain oncogens and transforming and mitogenic products. *DNA contamination* may be reduced to even lower levels than the antigens. This is of particular importance, since oncogenic effects cannot be excluded following accumulation in the recipient during chronic use. Levels of the order of 0.1 pg of specific (oncogenic) cellular DNA per mg of the drug, however, are assumed to be safe. Using mammalian tumour cells for the production of drugs, the potential risk of contamination of transforming proteins, including oncogene coded products and growth factors, must be considered. Mammalian cell lines require a viral transfecting gene segment as part of the expression vector, which may have the potential to transform cells of the recipient.

Pyrogenic reactions may be caused by pyrogens in the ordinary sense or by an effect of the actual drug substance, e.g. interferon.

"Excipients" used during the production or in the final product in particular comprise human and bovine albumin carrying the risk of viral contamination.

Products developed by biotechnological methods may carry *viral agents* pathogenic for man, which could even be tumourigenic. This problem has been recognized for many years, e.g. concerning hepatitis B and HIV in the "old" biologicals. However, Creutzfeldt-Jakob's disease and bovine spongiform encephalopathy being recognized as "slow virus" diseases were unexpected findings. Other, presently unknown viral agents cannot be excluded. The problem is of particular concern, when continuous mammalian cell lines are used for the production. Certain proteins/polypeptides are produced in mammalian cell lines (e.g. interferon derived from the Namalwa human lymphoblastoid cell line). The regulatory problem is, that some proteins, e.g. human growth hormone, can be produced by rDNA techniques using *E. coli* as well as by mammalian cell lines. The potential risk is greater using the latter technique, and the hormone may be administered for many years to children. So far, most countries as well as WHO consider products derived from continuous mammalian cell lines acceptable from a safety point of view, but the problem is still under debate.

The above mentioned examples of problems arising from the manufacturing process concern the "quality" of the final product. However, the various impurities

mentioned *are* present in the final product, although in infinitesimal quantities, and the potential risk of contamination by hitherto unknown viral agents *cannot* be excluded. The benefit/risk evaluation thus is a toxicological and clinical pharmacological matter, which at present has to be considered case by case. It seems reasonable to assume, that the potential risks are presently overemphasized, but only further clinical experience including postmarketing surveillance may give an answer.

Preclinical animal pharmacology and toxicology

Guidelines on animal pharmacology and toxicology follow the principles known from "ordinary" drugs, however modified due to the nature of species specific proteins developed by biotechnology (1). If the total structure of the products could be definitely identified as identical to the biological molecule, and if impurities did not exist in the final product, animal experiments were not necessary. Since this is not the case, *in vitro* and *in vivo* bioassays as well as pharmacological experiments and limited (acute and subacute) animal toxicity testing are necessary as well as testing for local tolerance and probably also for mutagenicity. These principles evidently apply also to modified molecules and completely new biologicals. The interpretation is often very difficult, since the species specificity may preclude evaluation of pharmacological/toxicological effects, neutralizing antibodies may add to the problems, and immunological reactions may preclude long-term administration, e.g. in normal carcinogenicity testing.

At present the predictive value of these animal experiments is unknown, and the same concerns the *in vitro* tests. However, with the increasing knowledge of particularly immunotoxicology of ordinary drugs and chemicals it seems reasonable to assume, that predictive toxicometrics also comprising biologicals shall improve (8, 9). Immunotoxicological tests (involving a.o. immunohistochemistry) are already requested in the EC guidelines on preclinical toxicity testing of "ordinary" drugs - attention should be paid to possible interference with the immune system in subacute and chronic animal toxicity studies. These tests are relevant also pertaining to drugs developed by biotechnology. Whether testing of non-immunological toxicity in immuno-incompetent animals is possible avoiding the

problems of species specificity, remains to be established. Studies in T-cell deficient athymic animals as well as in Severe Combined Immune Deficiency animals (SCID) might be a solution.

Clinical documentation

The usual pharmacokinetic investigations comprising absorption, distribution and disposition should be performed following single and repeated administration. These studies add to the confirmation of structural identity (e.g. concerning "generic products"), to improved routes of administration and dosage regimens (10) and to the determination of possible changes in kinetics following repeated administration, e.g. increased clearance of rodent antibodies caused by anti-antibodies. The sometimes very low plasma levels of the products cause analytical problems. The use of higher doses is not always feasible, but may sometimes be used, e.g. employing the glucose clamp technique when administering high doses of insulin.

The demonstration of efficacy of biologicals derived from whatever biotechnological technique is as easy/difficult as concerning "ordinary" drugs - most often relying on randomized clinical trials. The relevant reference substance may be difficult to choose, and in particular the duration of the trials may constitute a problem. However, all these problems are wellknown to the clinicians, the clinical pharmacologists and the regulatory authorities.

The final benefit/risk evaluation, which must be performed by the regulatory authorities, as usual involves the documented clinical effects weighed against demonstrated and potential risks. The marketing of interleukine-2 is an example of such an evaluation accepting the documentation of a certain effect in metastatic renal carcinoma, but realizing the incomplete information on dosage regimens and the possible necessity of simultaneous administration of LAK-cells. The acceptance of the indication "Turner's syndrome" concerning human growth hormone is another example. The effect on the final height of the patients is still unknown, but the experience so far justifies the decision.

In some diseases it can be anticipated, that it shall be rather easy to evaluate the benefit/risk ratio - assuming that new biotechnologicals are developed for the

prevention/treatment of diseases like AIDS, malaria, cancer and autoimmune disorders.

Side effects

Potential side effects caused by biotechnological products are of great concern. The side effects wellknown from "ordinary" drugs (renal and hepatic injury, myelosuppression, cardiotoxicity *et cetera*) shall be recognized through clinical trials provided a certain (high) incidence. The three major problems when dealing with biotechnological compounds comprise contamination with "slow viruses" (prions), immunological/autoimmunological reactions and oncogenic potential. Some of these unwanted effects may be very difficult to detect - partly since we may not know what to look for and hence not how to look for it, partly due to the fact, that the side effects may turn up after long-term or even very long-term use of the products and possibly with a low incidence.

The effects of viral contamination may not be observed within years after the administration, as it is the case with Creutzfeldt-Jakob's disease and bovine spongiform encephalopathy. The same problem holds true concerning the development of malignant diseases, as it is wellknown from the experience with secondary malignancies following certain cancer-chemotherapeutics. Both these areas demand postmarketing surveillance.

With regard to the possible immunological/autoimmunological reactions no guidelines exist pointing to a basic "battery" of tests to be recommended during the clinical trials. It seems reasonable to suggest, that at least a number of patients participating in the trials involving repeated administration should be thoroughly investigated with regard to humoral as well as cellular immunological reactions. Circulating antibodies (particularly IgM and IgG) including antibodies to fermentation products or anti-antibodies concerning monoclonal antibodies should be looked for as well as antinuclear antibodies (ANA). The complement system should be studied. The possible development of circulating immune complexes should be investigated. Finally, the number and distribution of B- and T-lymphocytes *et cetera* may be analyzed by means of fluorescence activated cell sorting (FACS). These analyses in combination with a thorough clinical examina-

tion may hopefully detect possible immunological reactions at an early stage of the development of new biotechnological products. So far the clinical experience with the existing products has been positive and has not given rise to particular fears. However, the development of biologicals, which we have not previously had at our disposal, modified molecules/completely new molecules, and the possible use of supraphysiological doses for long periods in large groups of patients with non-malignant diseases, call for attention.

As it has been stated: Today's theory is always at risk from tomorrow's data - leading to the risk of a "biotechnological Chernobyl disaster", i.e. a generalized assault on all biotechnological research and products caused by side effects arising from the use of a single biotechnological medicinal product (2).

POSTMARKETING SURVEILLANCE

As with any new drug there is an increasing need for postmarketing surveillance, in particular for two reasons: The often low incidence of certain side effects and the often delayed onset rendering detection before marketing impossible.

Until now the numerous attempts to establish efficient postmarketing surveillance systems have proved rather unsuccessful. Even large phase IV studies are often too small and suffer from the lack of control groups, short duration (1 year) and an often high drop out rate. Similarly the different systems built up locally, nationally and internationally are probably unsuitable for the detection of the side effects mentioned.

A reasonable approach might be to establish "registers" of some of the patient populations in question, e.g. diabetics, pituitary dwarfs, Turner's syndrome patients, HIV-positive patients *et cetera*, when effective treatment had been established. By modern communication and computer techniques it should be feasible to generate information on several "events", even the rare and delayed types. A major obstacle is the often paranoic aversion by the public and their representatives against registers and computer systems of any kind, which process "personal information." It is to be hoped, that the recently established "Pharmacovigilance Working Party" under the EC Committee for Proprietary Medicinal Products shall be able to

create a postmarketing surveillance system, which can combine data from the 12 European Member States comprising a population of more than 320 million.

CLINICAL TRIALS

Clinical trials concerning biotechnologicals do not in principle differ from trials with other drugs. However, the initial phase I studies with "ordinary" drugs are often performed using small-scale, laboratory batches, and the regulatory requirements concerning quality are limited, which experience seems to justify. When initiating the first clinical trials on biotechnological products, most often involving healthy subjects, it seems reasonable, however, to insist on quality requirements close to those necessary for marketing. This is justified by the potential side effects mentioned previously comprising viral contamination, immunological/autoimmunological reactions and oncogenic potential. At present the requirements differ very much from country to country, which is unacceptable.

VARIATIONS

When dealing with "ordinary" drugs, minor variations of the production process and pharmaceutical formulation normally do not give rise to great regulatory problems. However, concerning biotechnological products, with which we have a limited experience, it seems reasonable - at least for a longer period - to perform a more thorough analysis of the possible consequences of the variations for the properties of the final product. Even minor changes in the biological production process may lead to significant changes in biological effects, purity and nature of impurities as well as risks of microbiological contamination. At the EC level it has been decided, that even minor variations shall be presented to the Committee for Proprietary Medicinal Products for approval according to Council Directive 87/22/EC.

GENERIC EQUIVALENTS

The scientific evaluation of generic products concerning "ordinary" drugs normally does not create problems. However, when dealing with the more complicated polypeptides/proteins and the different ways of biotechnological production

techniques, it is a question, whether a mere demonstration of an acceptable relative bioavailability is sufficient documentation for granting a marketing authorization. At present the different national regulatory authorities seem to agree, that biotechnological "generics" should be investigated in more detail - besides the obvious quality requirements. At least a limited toxicological examination is necessary as well as a bioavailability study and a small scale clinical investigation. Provided, that the clinical documentation is publicly available through publications, repetition of the clinical trials is evidently unnecessary, unethical and represents a waste of resources.

DISCUSSION

The biotechnological evolution/revolution so far has provided us with a few important innovations, but beyond any doubt several new products already in the pipeline shall be of great therapeutic benefit. The assessment of these products by the regulatory authorities has become an unpleasant challenge, since we are dealing with potential risks, with which we have little or no experience. Although the authorities of the US, Japan and the EC endeavour to promote research, development and marketing of these potentially valuable therapeutics, it is understandable, that the requirements concerning quality, safety and efficacy are severe, as it is apparent from the various guidelines. However, it is to be hoped, that the increasing experience with biotechnologicals shall enable more "relaxed" requirements - provided, that the fear of the potential, serious side effects turns out to be unjustified. Every regulatory authority and guideline stress the importance of evaluating the new biotechnologicals case by case adjusting the requirements to the state of the art. However, guidelines have a deplorable tendency to become at least minimum requirements, and they tend to become stationary. The American "Points to Consider" in many respects are preferable to guidelines. One extreme is the first injection (1922) of insulin in a 14 years old boy only half a year after its isolation. The other extreme is the (hopefully) unnecessary delay of the marketing of new biotechnologicals through rigid regulatory requirements. The latter situation shall do more harm than benefit to the patients,

and it shall result in enormous expenses to society. Some of the new biotechnologicals already marketed are extraordinarily expensive, and since it is reasonable to assume, that large patient populations may benefit from some of these drugs, their introduction may result in a great burden on the health budgets of the industrialized countries and the inaccessibility to patients in developing countries.

Cooperation between the regulatory authorities of the EC, US and Japan is necessary to reach harmonized, scientifically justified and reasonable "requirements" for future developments in this field.

SUMMARY

Based upon experience for three centuries with "old" biological products and for a decade with "new" products derived by biotechnological procedures and recognizing the rapid advances in molecular engineering of proteins/polypeptides at the same time as the increase in the knowledge of pathophysiology and immunology, it does not seem unjustified to expect a "Second Biological Therapeutics Revolution" from biotechnologicals in the prophylaxis and treatment of viral and parasitic diseases, cancer and autoimmunological disorders. However, despite increasing knowledge and experience the benefit/risk estimate is still empirical. Present guidelines rightfully use the words "flexibility", "individualized approach", "case by case", "*ad hoc*" *et cetera* to describe the requirements involved in the development and regulatory evaluation of new biotechnology products. The necessity of an individualized evaluation is caused by several factors: Differences between biotechnological production processes (rDNA techniques involving *E. coli*, yeast or cell lines, heterohybridoma techniques involving mouse ascitic fluid or large scale tissue culture, and genetic engineering in combination with hybridoma technique); molecular complexity of the products; dosage regimens (single dose, short/long duration of treatment, physiological/supraphysiological doses); therapeutic indications (severity of disease).

The requirements with regard to quality are and shall continue to be strict (molecular identification, impurities including antigenic contaminants and oncogenic DNA fragments, viral contamination).

The predictive value of animal experiments and *in vitro* tests shall probably increase.

Hopefully, clinical experience shall prove, that the present fears of microbiological, immunological and oncological side effects are unjustified. At present, the clinical investigations of biotechnological products apart from the obvious purpose of demonstrating therapeutic efficacy must concentrate on potential side effects relying on clinical examination, immunological investigations and postmarketing surveillance.

The final benefit/risk assessment must weigh the inadequacies of quality and safety parameters with regard to predictive value against the severity of the diseases to be treated.

Compared to "ordinary" drugs more strict requirements are necessary concerning variations of the production process, generic equivalents and clinical trials of biotechnological products.

Present guidelines should be regarded as Points to Consider and not eternal requirements.

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Discussion - MEANINGFUL EVALUATION OF BIOTECHNOLOGY PRODUCTS

J.A. Galloway

I would like to ask what is the extent of communications between the regulatory agencies within the European Community and also to the FDA and what are the impediments to those communications?

P. Juul

As far as the EEC is concerned, we meet in Brussels at the Committee for Proprietary Medicinal Products eight times per year. We have six working parties which meet normally four to six times per year with representatives of each of the twelve member states discussing particular drugs or particular problems, producing guidelines or notices to applicants etc. With regard to communications with the FDA, I can mention that the European guidelines are sent to the FDA at the same time as they are sent to the industry and the national authorities for comments. So far, there have been one or two informal meetings between the two parties.

J.A. Galloway

What about any communication between the EEC and the Japanese regulatory authorities?

P. Juul

They also started. There have already been two meetings and a third one is planned.

R.G. Werner

Could you elaborate somewhat more about the objections of the EEC against mammalian cell cultures?

P. Juul

They have been raised by only two out of twelve countries. Denmark is one of them but we probably have to agree with the majority. Our concern about the use of mammalian cell lines, in this case for the production of human growth hormone, refers to the possible transferral of oncogenic DNA material to an injectable preparation that will be administered for many years to children. One should not forget that there are two other products at least on the European market produced by methods where we consider

the risk of transfer of oncogenic material, including virusless. Of course, we accept mammalian cell lines; otherwise we would be without some of the more important drugs which can only be produced this way. The problem in this case is that we have a choice.

W.M. Wardell

I'd like to emphasize the subject of international harmonization, because I feel strongly that this is the only way to stop the drug development process from getting increasingly encumbered by the accretion of sometimes idiosyncratic national requirements. I have been to one or two meetings watching regulators talk about harmonization, but my growing feeling is that harmonization is not happening. I see regulators enthusiastically describing their own requirements but I do not see any pressure on them to harmonize.

P. Juul

One could almost say that so far, the EEC harmonization has meant that you add the twelve opinions, which means that the most severe and strict requirements are always the ones being accepted. On the other hand, one should not forget the agreement on the lack of necessity of LD50s, and I think that the European attitude about the longest duration of chronic animal experimentation, limiting it to six months may influence the FDA. At present it is very difficult to suggest changes, but personally I think that the usual type of carcinogenicity testing is in 99 out 100 cases a mere waste of resources, animals and time. This should probably be reviewed but it is difficult to resist asking for such a test since if the product turned out to be carcinogenic in man, we would be the ones to blame.

F. García Alonso

I would like to ask what is your opinion about the necessity to repeat clinical trials in different countries within the EEC, particularly in the case of biotechnology products such as human growth hormone or interferon.

P. Juul

I understand your concerns. Only exceptionally repetition in another EEC country is necessary. It does not make sense, for instance, to evaluate the effects of a new human growth hormone in patients with Turner's syndrome when they have been established with another product in another country. I think that an acute toxicity study

and data from about ten patients switched from one of the preparations to another is all what we should ask.

L. Gauci

Shouldn't we focus more in postmarketing surveillance rather than in new clinical trials? Why hasn't this approach been followed more aggressively? Perhaps a common database of individuals followed several years should be considered.

P. Juul

I think that the main reason why postmarketing surveillance has not been approached more aggressively is that we do not have an exact idea of how to perform it. A database as you suggest could probably be envisaged in the case of some drugs, for instance recombinant human insulins. Hopefully the Pharmacovigilance Working Party shall come up with new ideas within the EEC.