SWISS PHARMA

Proceedings
Quality of Drugs
in the Year 2000
Symposium
Swiss Federal Institute of
Technology Zurich (ETH)
October 25, 1991

12a/1991
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Swiss Review for the Pharmaceutical Industry
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Rivista svizzera per l'industria farmaceutica
Revista suiza para la industria farmacéutica
Schweizerische Zeitschrift für die pharmazeutische Industrie

Im Mai 1992 erscheint

DIE SCHWEIZER CHEMIE

Bildberichte, Ansprachen usw. der Generalversammlungen der Schweizerischen Gesellschaft für Chemische Industrie (SGCI) von 1979 bis 1991
Mit einem Editorial von Dr. Andres F. Leuenberger (Basel), Präsident der SGCI

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SWISS PHARMA *13* (1991) No 12a

12a/91

TABLE OF CONTENTS

SWISS PHARMA

ISSN 0251-1673

Swiss Review for the Pharmaceutical Industry
Revue suisse pour l'industrie pharmaceutique
Rivista svizzera per l'industria farmaceutica
Revista suiza para la industria farmacéutica
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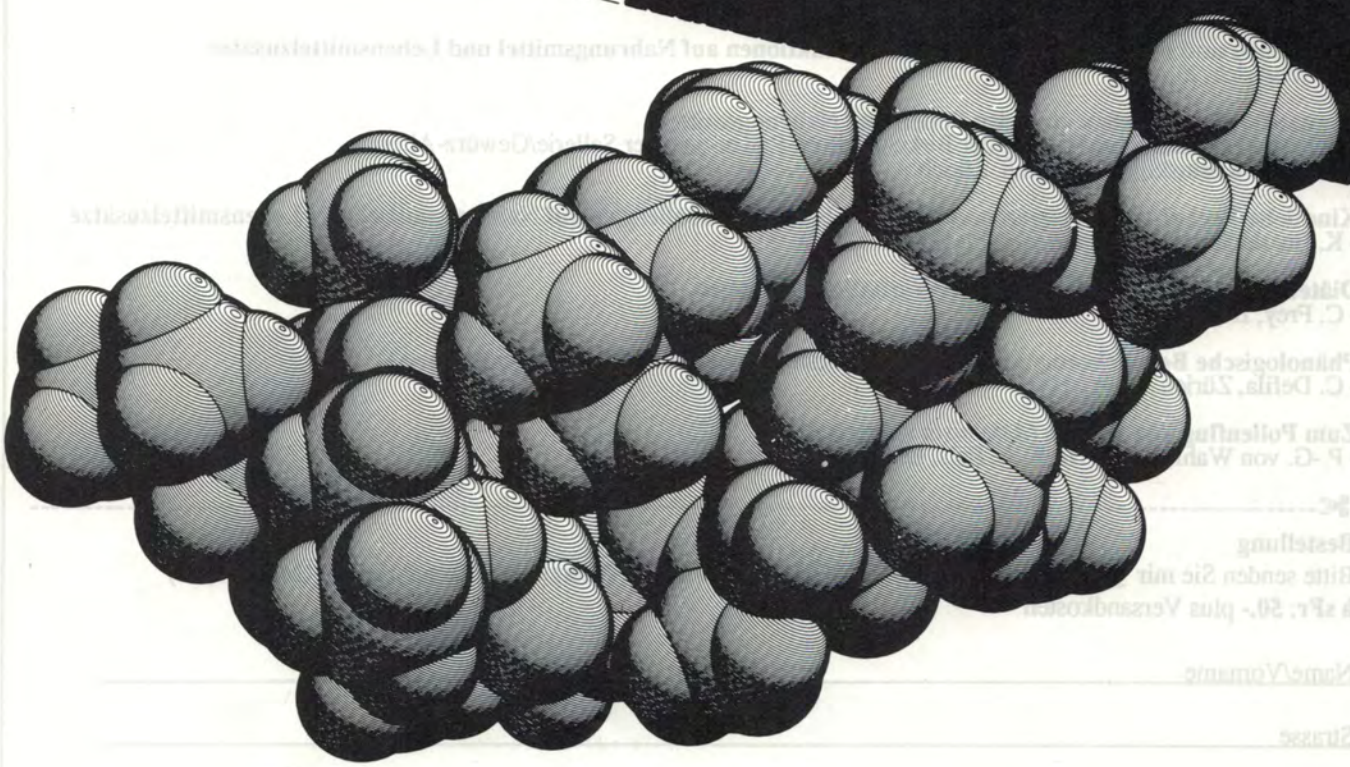

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Swiss Federal Institute of Technology Zurich (ETH), Symposium «Quality of Drugs in the Year 2000», October 25, 1991

Pharmaceutical Quality Assurance

A Challenge of the Future

PD Dr. Hans W. Schmid, Department of Pharmacy, Swiss Federal Institute of Technology (ETH), CH-8092 Zurich, and Pharmaceutical Faculty, University of Basle, CH-4051 Basle, Switzerland

Quality Assurance — A Postgraduate Seminar

Quality assurance for pharmaceuticals has moved to a completely new dimension in the last two decades and we will see an ongoing development in this discipline in the future. In view of the complexity and the time span of pharmaceutical issues, trends and tendencies have to be evaluated early and measures for adaptation have to be taken years in advance.

This is the reason why the pharmaceutical departments of the ETH Zurich and the University of Basle took action to set up a postgraduate seminar for Pharmaceutical Quality Assurance (first implementation during the winter semester 1991/92). The objectives of this seminar can be defined as follows:

- *Study projects of pharmaceutical quality assurance with special regard to quality management, quality planning, quality steering and quality control;*
- *Determine critical issues and elaborate solutions in view of international quality requirements;*
- *Promote cooperation between universities, authorities and industries in the area of quality assurance.*

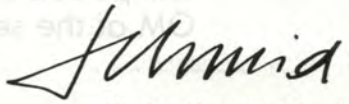
Quality Assurance — A Top Management Issue

What has changed in the scope and volume of quality assurance is not only regulations, requirements and standards such as Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP) guidelines, but rather the philosophy to position and integrate quality assurance in top management thinking. The quality circle thinking, the «quality is free» philosophy and the quality institutes in various companies have created a new way of positioning and practising quality assurance from the top downwards. These changes happened gradually with the development of quality expectations on the user level — the doctors and patients. Universities, authorities and especially the pharmaceutical industry have been challenged to cope with these expectations.

The user of drugs is basically not interested in why a product has an adverse reaction, why a product can cause interactions, why the stability is limited or why it works only in a special application. The user expects primarily QUALITY — SAFETY and EFFICACY. Our responsibility is to make every effort in quality management, quality planning, quality steering and quality control to achieve the best quality, complete safety and maximum efficacy.

The Challenge of the Future

Expectations will continue to change and requirements to increase. We will, especially in the European environment, see changes in the registration process, we have to introduce harmonized procedures in the preclinical and clinical studies, we will progress with the mutual recognition of pharmaceutical plant inspections, we have to define quality standards for new products and technologies in the development and production of pharmaceutical products and we have to comply with the legal requirements and the harmonization process of a large European pharmaceutical market. All these aspects are covered in the papers of the symposium «Quality of Drugs in the Year 2000» published in this issue of SWISS PHARMA 13 (1991) No 12a.



PD Dr. Hans W. Schmid

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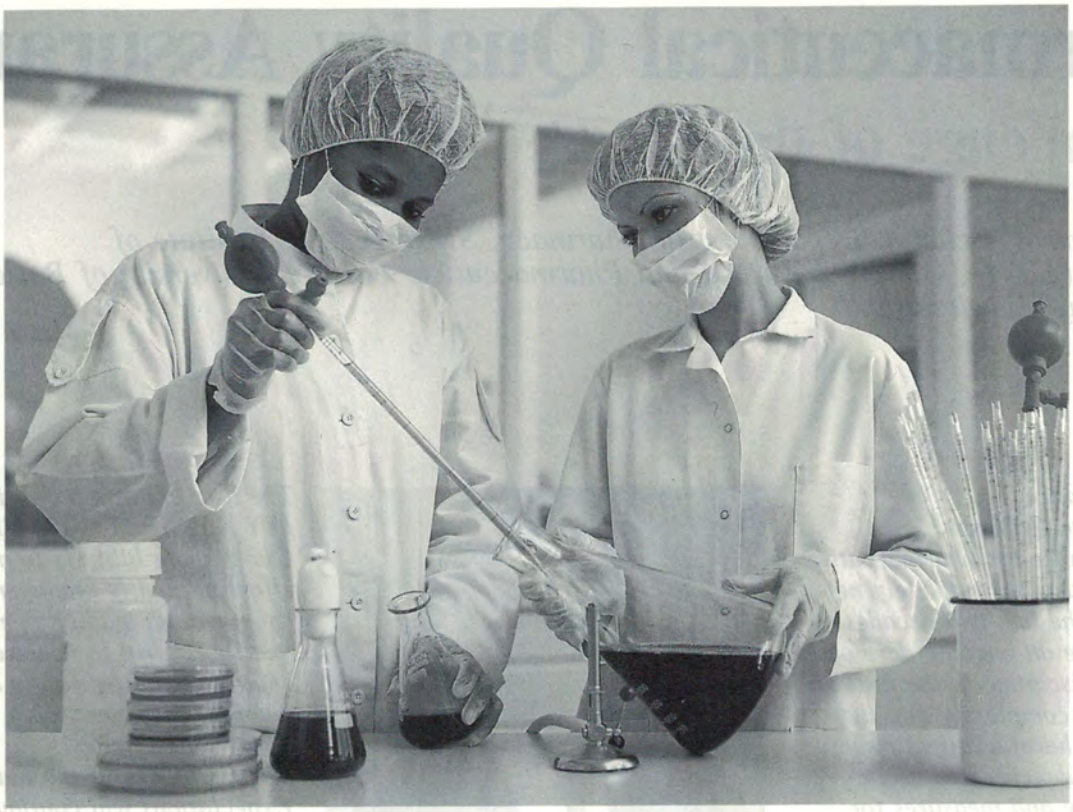

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Swiss Federal Institute of Technology Zurich (ETH), Symposium «Quality of Drugs in the Year 2000», October 25, 1991

Quality Guidance in Preclinical and Clinical Studies

Prof. Dr. R. Bass, Institute for Drugs, Federal Health Administration (BGA), Seestrasse 10, D-1000 Berlin 65, Germany

The objective of this symposium is to position the term «quality of pharmaceuticals» in a new dimension regarding preclinical safety, clinical safety and clinical efficacy. Quality has to be built into a product during the long research and development phase and cannot simply be controlled at the end of production. Major emphasis will be put on preclinical development, whereas in some cases clinical development will also be covered.

Professor Rolf Bass MD is Head of Toxicology, Director and Professor at the Institute for Drugs of the Federal Health Administration (BGA) in Berlin. Since 1984 he has been Adjunct Professor of Pharmacology and Toxicology at the Free University, Berlin. His research interests are in reproduction and short-term tests in toxicology. From 1984 until 1991 he was chairman of the Safety Working Party of the Committee for Proprietary Medicinal Products (CPMP) of the European Communities.

The Harmonizing Work is Going on . . .

The various issues to be considered in *preclinical development* are summarized in *Figure 1* «Quality Guidance in Preclinical Development». The peculiarity of these various issues is that they may be classified differently in national and EC regulations. For example, although Good Laboratory Practice (GLP) is in Germany regulated under the Chemicals Act, it is not compulsory for it to be so in the European Community. It will take some time before harmonization is achieved. There are also some differences in the guidance of local and national inspection of Good Laboratory Practice. Expectations of the regulatory authorities and the pharmaceutical industry still have to be harmonized. Changes are also to be expected in the future with regard to the Pharmaceutical Evaluation Report (PER), where mutual recognition already exists to some extent. In the area of animal protection there exist Council Directives of the European Community that are European law. There are, however, also national guidelines in many areas and further harmonization is necessary.

The situation in the *clinical area* is quite similar to the situation in the preclinical area, although there are some major differences *(Fig. 2)*. A very important issue is the Declaration of Helsinki, which emphasizes the «ethical» importance of carrying out clinical studies. The Declaration of Helsinki has also changed and has been adapted over time to recent needs and requirements. The European Community has set up guidelines for Good Clinical Practice (GCP), but some nations also have their own national guidelines relating to specific issues of GCP. There is, of course, also a large

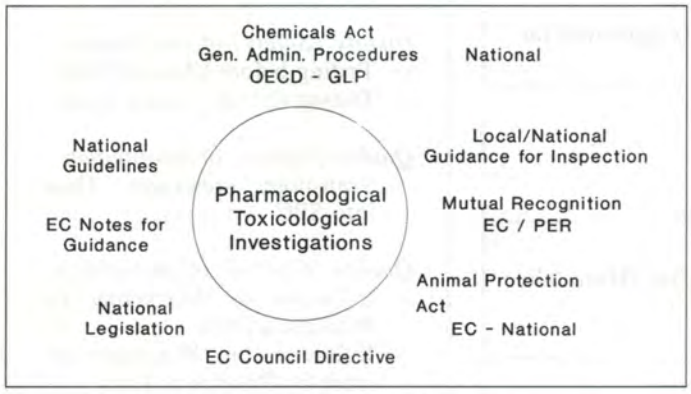
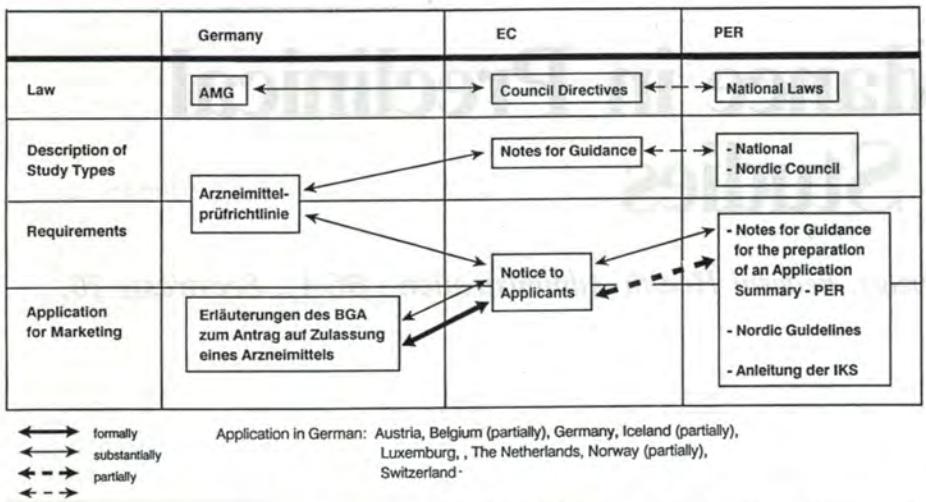


Fig. 1: Quality Guidance in Preclinical Development.

Fig. 2: Quality Guidance in Clinical Development.

Table 1: Comparison of Rules and Regulations; Guidance: EC-Germany-German Speaking Countries.



variety of guidelines e. g. WHO, FDA, EC, oriented towards a certain group of patients or indications to be described in the clinical studies. Such guidelines focus on efficacy and clinical safety. As in the preclinical area, mutual recognition is also practised in the clinical area.

The aim of all harmonization work is to create a common European drug registration system for the member states of the European Community. During this process, common criteria for decision-making must be determined. This will enable the authorities to take harmonized single decisions in the future.

It is interesting to compare the rules, regulations, requirements and recommendations of the various countries. In *Table 1*, the rules and regulations of Germany are compared to the EC and the Pharmaceutical Evaluation Report (PER scheme), participating countries, originally EFTA countries such as Switzerland. It is interesting to note that EC countries like Germany also apply the PER scheme. European and national law are not yet completely harmonized and in case of dissent European law would always take priority. Differences still exist, especially in the degree of detail of description of the study types and in local/national requirements for marketing application. In practice, the Notice to Applicants in the European Community still differs, for example, from the more comprehensive German system defined in the «Arzneimittelprüfrichtlinie». Differences such as these will have to be eliminated step by step in the future.

Preclinical and Clinical Quality Aspects

In *Table 2* four crucial quality aspects are summarized:

- the quality of the product before and after approval;
- the quality of the information;
- the quality of availability;
- the quality of pricing.

As Europe has developed into a large pharmaceutical market such quality requirements are becoming increasingly important and must be harmonized. Special emphasis must be put on the reproduction of the quality of the *«model medicinal product»* after launch, once the product has been approved for marketing.

With the exception of quality of the product for approval, harmonization has not been achieved to a sufficient extent. The common basis of quality information, both with respect to the European countries and to the different addressees of the information is the *Summary of Product Characteristics (SPC)*. The complete harmonization of the layout, structure and content throughout the EC still needs to be achieved. The same is true for the quality of availability; the quality of pricing is not the subject of this article.

With respect to preclinical viewpoints, the crucial quality aspects are summarized in *Table 3*, listing pharmacodynamics, pharmaco-/toxicokinetics, toxicology and a grey zone called «other information», as areas to be investigated experimentally. Special emphasis is placed on the quality of preclinical data before any clinical trials can commence. Furthermore, it is important to take into consideration increases in knowledge and the results of ongoing preclinical studies during the clinical trial phase. All new preclinical data also has to be transposed into the Summary of Product Characteristics (SPC). This sort of data also has an influence on the marketing conditions and the pharmacovigilance, and has to be built in to the information on availability.

Table 2: Quality Medicinal Products. Goal of the European Community.

Quality (Safety) of the Product Approval for Marketing of a «Model Medicinal Product» – Pharmaceutical, Chemical, Biological, Biotechnological Quality – Preclinical Quality (Safety) – Clinical Quality (Safety) – Efficacy Reproduction of the Quality of the «Model Medicinal Product» approved for Marketing after Launch
Quality (Safety) of the Information – Information for the Patient – Information for Health Professionals – Summary of Product Characteristics of the EC (SPC)
Quality (Control) of Availability – General Sale, Pharmacy only, Prescription only, Special Uses (Hospitals, Specialists etc.) – Pharmacovigilance
Quality of Pricing

Table 3: Quality Medicinal Products. Preclinical Viewpoints.

– Pharmacodynamics – Pharmaco-/Toxicokinetics – Toxicology – Other Information
Quality (Safety) of the Product – Testing before Clinical Trials – Testing during Clinical Trials *Qaulity (Safety) of Information* – Transpose «relevant» Data into SPC *Quality (Control) of Availability* – Influence on Marketing by Preclinical Data – Influence on Pharmacovigilance by Preclinical Data

Table 4: Quality Medicinal Products. Clinical Viewpoint.

Clinical Pharmacology
- Pharmacodynamics
- Pharmacokinetics

Clinical Experience
- Clinical Trials (Efficacy, Safety)
- Postmarketing Experience
- Unpublished Experience

Other Information (e. g. unpublished experience)

Quality (Safety) of the Product
- Testing during Clinical Trials

Quality (Safety) of Information
- Transpose «relevant» Data into SPC

Quality (Control) of Availability
- Influence on Marketing by Clinical Data
- Influence on Pharmacovigilance

Similarly, the clinical viewpoint has been summarized in *Table 4*. The areas of investigation are clinical pharmacology and clinical experience and, similarly to the preclinical viewpoint, a grey zone called «other information». The results will then have to be transposed during clinical trials and after marketing. This is the way in which the European Community categorizes the procedure. Quality and safety aspects of a new product are focused particularly on two issues, i. e. testing during clinical trials and the transposition of the relevant data into the Summary of Product Characteristics (SPC).

Table 5: Quality Medicinal Products. Quality Data – Quality Review: Preclinical/Clinical Viewpoints.

Material/Data available
- Expert Report (Expert Report; Tabulated Study Reports; Textual Summary)
- Study Reports
- «Raw» Data

Quality Availability of Material/Data

Review of Material/Data submitted
- Drug Law/Council Directives
- Arzneimittelprüfrichtlinien/Notes for Guidance
- Erläut. BGA/Notice to Applicants
- Assessment Reports, Conclusions, Decisions
- Committees

In *Table 5* some major aspects of a model application for marketing of a medicinal product are summarized and some ideas on the structure of a review in the future are defined. An important document today and also in the future will be the expert report, containing tabulated study reports and usually also a textual summary and other information. All available data is documented in study reports and furthermore a lot of «raw» data is available. In the review process of all this data, in the future possibly electronically documented, a better system of reporting and evaluation has to be developed within the EC. Although some guidance exists as described in the national drug laws and Council Directives, further harmonization is still necessary, when we look at the assessment reports containing the quality description of the decision made by one member state.

Some major issues of the expert report are given for the preclinical area *(Table 6)*. No critical opinion can be completely neutral, but it has to be based on the best judgment of the expert. In the area of Good Laboratory Practice (GLP), updated scientific knowledge, based on the most relevant literature, has to be given. Correlation also has to be made to other parts of the expert report: for example, to the possibility of the appearance of impurities and stereoisomers. Whether such impurities or stereoisomers can influence the preclinical studies or clinical studies is of key importance. Furthermore, any omission of studies has to be justified. Benefits and advantages recognized from pharmacology and toxicology have to be explained and recommendations based on pharmacological and toxicological studies have to be evaluated. The expert report also contains comments on studies on animals and man and on the transition phase. In addition, we are looking for comments on pregnancy and lactation, carcinogenicity, mutagenicity and on other irreversible effects. For example, irreversible damage to the liver would have to be commented on in the preclinical investigations and be reported in the SPC. Less emphasis is placed on the lethal dosage from acute and toxicity studies.

Cultural Differences

Table 7 summarizes some major issues in preclinical work. There still exist different approaches between the development of chemicals and medicinal products in the OECD, Europe, Japan and the USA. We are also confronted by differing requirements before and during

Table 6: Quality of Expert Report (e. g. Preclinical).

- Critical Opinion/Judgment
- Good Laboratory Practice (GLP)
- Relevant Literature (to be) considered
- Correlation to Parts II and IV to be given (Impurities, Stereoisomers)
- Omission of studies to be justified
- Referencing Systems to be applied
- Benefits/Advantages as seen from Pharm/Tox to be explained
- Recommendation as seen from Pharm/Tox for the SPC to be given

- Comments Animal/Man
- Comments on Pregnancy/Lactation
- Comments on Carcinogenicity
- Comments on Mutagenicity
- Comments on other Irreversible Effects

Table 7: Some Major Issues in Preclinical Work.

- Different Development for Chemicals (OECD) and Medicinal Products (Europe, Japan, USA)
- Different Requirements before and during Clinical Trials and for Approval for Marketing
- Different Requirements in Europe, Japan, USA
- Mutual Recognition depends on Implementation of GLP
- Coverage of GLP
- Influence of Animal Protection

Are these Differences in Quality?

Table 8: Some Major Issues in Clinical Work.

- Different Requirements during Clinical Trials (Dose Selection; Placebo versus Standard Therapy as Control)
- Different Requirements for Approval for Marketing (Europe, Japan, USA)
- Mutual Recognition depends on Implementation of Good Clinical Practice (GCP) (Safety – Efficacy; Pharmacodynamics – Pharmacokinetics)

Are these Differences in Quality?

Table 9: Quality of Application as a Measure: Preclinical and Clinical Quality.

Formal Quality of Application
- EC Standard Format
- Additional National Peculiarities

Quality of Content of Application
Reason and Reasoning concerning:
- Study Selection
- Study performance
- Study Reporting
- Study Evaluation
- Quality of Data

preclinical and clinical trials, as well as approval for marketing. The opinion that the same degree of protection should be granted during the clinical trial as applied after marketing of a product is now gaining general acceptance. Requirements in Europe will be steadily harmonized, but there are still differences between Europe, Japan and the USA. The smoothening of mutual recognition within the European Community also depends a lot on the implementation of Good Laboratory Practice (GLP). There are also still considerable discrepancies in the animal protection area.

Some major issues in clinical work are summarized in *Table 8*. The different cultures of the countries and continents, as well as religious differences, have a big impact on the requirements during clinical trials. We know that the first, or at least the subsequent doses of a medicinal product to be given in the US are substantially larger than in Japan. There are similar discrepancies in the planning and execution of clinical trials. It is generally known that there are still differing requirements for approval existing in Europe, Japan and US and that mutual recognition depends to a large extent on the implementation of Good Clinical Practice. Finally, the question is raised whether the same quality standards should be applied in all the continents, or whether we should continue to accept some differences in «quality» from continent to continent, or even from country to country.

Some issues concerning formal guidance for the application in the EC are summarized in *Table 9*. One major problem for the introduction of such a formal guide is the various languages and national peculiarities in the European countries. In the quality of content of application, the study selection, the study performance, the study reporting, the study evaluation and the quality of data

Table 10: Application Form for Marketing Authorization (front page).

Name of company	NATIONAL APPLICATION NUMBER	
Name of finished product		
Name of active ingredient		

APPLICATION FOR A MARKETING AUTHORIZATION OF A MEDICINAL PRODUCT IN A MEMBER STATE OF THE EC

This application concerns a:
- ○ *National Application:* number, if available, country:
- ○ *EC application* according to Directive *83/570/EEC* (multistate application) rapporteur:
- ○ *EC application* according to Directive *87/22/EEC* (concertation procedure) rapporteur:
  - ○ *List A*
  - ○ *List B*

  Date of acceptance as a List B product by CPMP:

Part I A: Administrative Data

1. *Proposed name* of the medicinal product in the concerned member state: If different names in different member states are proposed in a Community Product, these should be mentioned:

1.1 *Name of the active ingredient(s)* (INN, Ph. Eur., National Pharmacopoeia, trivial name or chemical description)

1.2 *Pharmacotherapeutic classification* (use ATC classification system, WHO Collaborating Centre for Drug Statistics Methodology)

should also be considered. This would include both preclinical and clinical areas.

In *Table 10* a new form for harmonized application has been developed. The objective is to use electronic data transmission and to use this form for European as well as for national applications throughout Europe (Note for Guidance, 1991).

The Role of Good Laboratory Practice and Good Clinical Practice

As outlined in *Table 11* it is important to know the concept of and reason for the preclinical studies before any clinical studies are initiated. During the preclinical phase the data necessary for the marketing authorisation should be assembled and evaluated. Good Laboratory Practice (GLP) has to be applied in the performance of all such studies, as well as in reporting. Good Laboratory Practice *(Table 12)* covers the quality of the laboratory, performance of the studies, reporting and archiving, as well as the internal quality assurance programme applied.

The rationale for applying and implementing GLP *(Table 13)* was originally

Table 11: Quality of Content of Application: Preclinical Development.

Study Selection
- «Preclinical» before Clinical Studies
- «Preclinical» during Clinical Studies
- «Preclinical» for Marketing Authorization
- «Preclinical» for Pharmacovigilance

«Troubleshooting»

Good Laboratory Practice (GLP)
- Study Performance
- Study Reporting

Quality of Data

to prevent fraud and is now to create the right environment. Full transparency of the data and unlimited availability are crucial (see *Table 14*, which is the introduction to the Tabulated Study Report Formats of the EC). As outlined in *Table 15*, the quality of content of an application for marketing concerning clinical development needs guidance, both on study selection and perfor-

Table 12: Quality of Preclinical Data: Good Laboratory Practice (GLP).

Quality of Laboratory
- Building
- Equipment
- Materials
- Personnel

Performance of Studies
- Test and Reference Substances
- Experimental Systems
- Standard Operating Procedures (SOP)
- Study Plans

Reporting and Archiving
- Study Reporting
- Archiving of Documents
- Archiving of Probes/Materials

Quality Assurance Programme (QA)

Table 13: Reasons for Creating and Implementing GLP.

- To prevent Fraud
- To create an «Environment» where Data/Results from «Safety» Studies become available anywhere for Review at any Place
- EC-Tabulated Study Report Format

Table 14: Survey Form for Preclinical Studies.

Name of company	APPENDIX to Expert Report Part IC2	
Name of finished product		
Name of active ingredient		
Application date: Survey on Tabulated Study Reports	Addendum to application no.:	
		Page number of Tabulated Study Reports: from page . . . to page . . .
III.A. Single dose toxicity		|.....|.....
III.B. Repeated dose toxicity		|.....|.....
III.C. Reproduction toxicity		|.....|.....
III.D. Mutagenic potential		|.....|.....
III.E. Oncogenic/carcinogenic potential		|.....|.....
III.F. Pharmacodynamics		|.....|.....
III.G. Pharmacokinetics		|.....|.....
III.H. Local tolerance (toxicity) studies		|.....|.....
III.Q. Special toxicity studies (e. g. immunostimulation)		|.....|.....

mance, and on issues described in the EC Good Clinical Practice (GCP). On study selection and performance *«Principles for the Proper Conduct of Clinical Drug Trials»* were published in 1989 in English (Drugs made in Germany 32, 21–23) from the German original in Bundesanzeiger 243, 16617 ff. (1987). The reasons for creating and implementing GCP are similar to those described for GLP *(Table 13)* and to protect trial subjects.

At the interphase between clinical and preclinical development it will have to be determined at each step which are the preclinical studies necessary to precede and to support the different types of clinical investigation. A thorough analysis of all data available before decision-making and evaluation of the degree of risk that would be encountered in a clinical situation followed by the decision on a suspicion requiring clarification finally lead to the consequence on the use in humans, and on the need for particular preclinical studies.

Expectations in the Year 2000

Expectations of the quality model for the year 2000 are summarized in *Table 16* for

Table 15: Quality of Content of Application: Clinical Development.

Study Selection and Performance
- Planning of Clinical Trials
- Study Conduct
- Analysis of Data (e. g. Adverse Events during Clinical Trials)

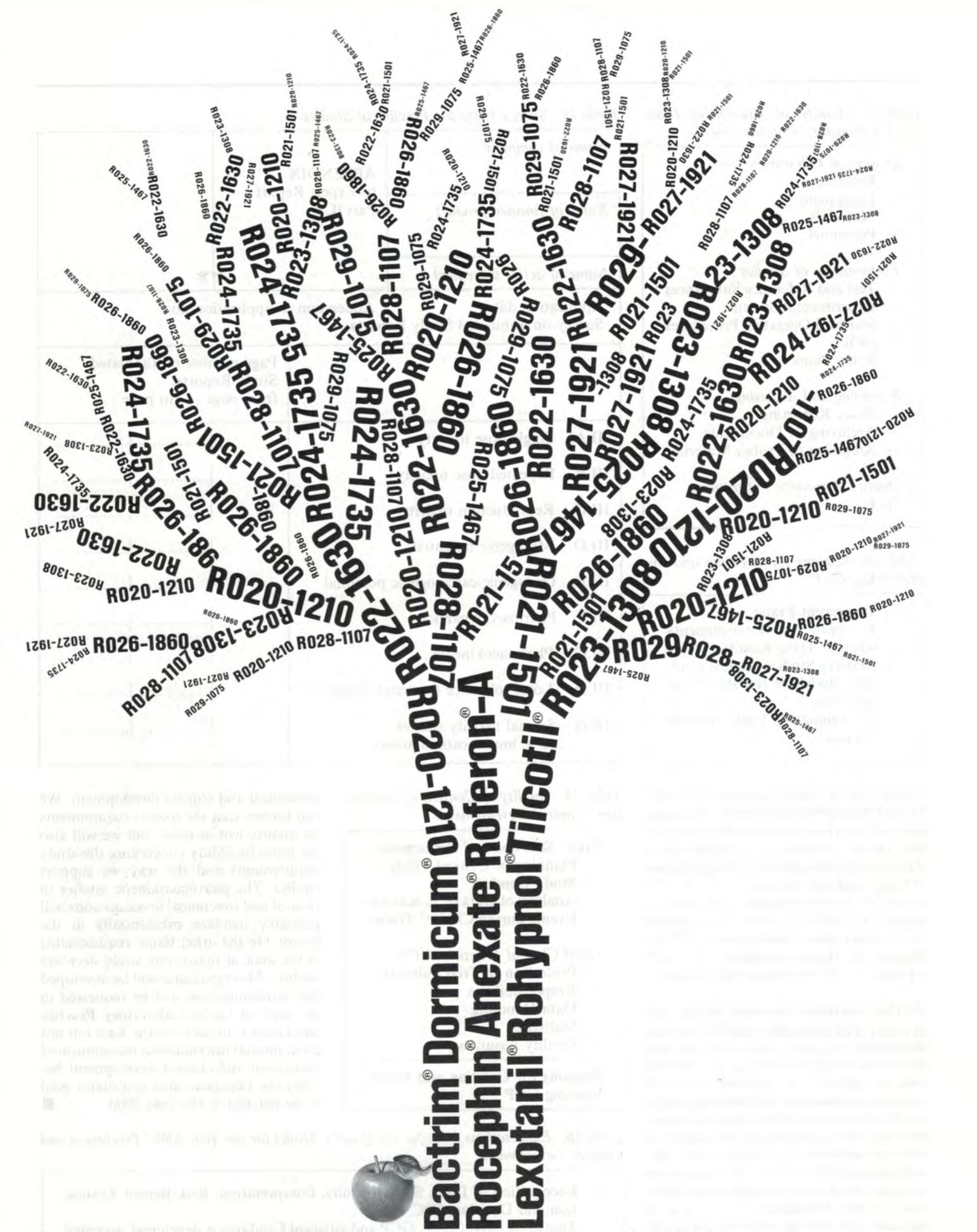
Good Clinical Practice (GCP)
- Protection of Trial Subjects
- Responsibilities
- Data Handling
- Statistics
- Quality Assurance

Reasons for Creating and Implementing GCP

preclinical and clinical development. We can foresee that the formal requirements on quality will increase, but we will also see more flexibility concerning the study requirements and the way we support studies. The pharmacokinetic studies in clinical and preclinical investigations will probably increase substantially in the future. On the other hand, requirements in the area of toxicology could decrease slightly. More guidance will be developed and harmonization will be requested in the area of Good Laboratory Practice and Good Clinical Practice. Last but not least, mutual international recognition of preclinical and clinical development beyond the European area is a major goal to be reached in the year 2000. ■

Table 16: Expectations from/for the Quality Model for the Year 2000? Preclinical and Clinical Development.

- Recognition of Data, Study Results, Interpretation, Risk-Benefit Evaluation and Decision, SPC
- Thinkable only if GLP, GCP and adjacent Guidance is developed, accepted and followed
- Mutual International Recognition of Preclinical and Clinical Development beyond the European Example (EC/EFTA) is the Major Quality Goal for 2000



Die Frucht Ihrer Verschreibung von heute ist das Präparat von morgen.

Roche

F. Hoffmann-La Roche AG, Basel,
Pharma Schweiz

Swiss Federal Institute of Technology Zurich (ETH), Symposium «Quality of Drugs in the Year 2000», October 25, 1991

Future Standards for Manufacturing Authorization and Inspection of Manufacturers in the European Community

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The Pharmaceutical Industry in EEC Member States maintains high standards of Quality Assurance in the development, manufacture and control of medicinal products. A system of Marketing Authorizations issued by Member States ensures that all medicinal products are assessed by a Competent Authority to ensure compliance with the contemporary standards of safety, quality and efficacy. A system of Manufacturing Authorizations ensures that the licensed products are only manufactured by licensed manufacturers, whose activities are regularly inspected by the Competent Authorities. Manufacturing Authorizations are required by all pharmaceutical manufacturers in EEC whether the products are sold in EEC or exported.

Philippe Meyer is a pharmacist, he holds two postgraduate diplomas, one in Environmental Sciences and another in Pharmaceutical Technology and Industrial production. Appointed Inspector, he has been working for twelve years for the Belgian Ministry of Health. In 1987 he was asked by the Commission of the European Communities to coordinate the editing of the Community Guide to Good Manufacturing Practice (GMP). He is now responsible, in the Unit «Pharmaceuticals», for the coordination of different activities related to harmonization of GMP, inspection and control of medicinal products, the quality of medicinal products and pharmacovigilance.

The Historical Background

The foundation stone of the European Community was laid down by Robert Schuman, the French Minister of Foreign Affairs, on 9 May 1950, when he made his Declaration at a press conference in Paris. The objectives of his plan, prepared with Jean Monnet, should not be sought only in the first Treaty on European Coal and Steel Community, but also in the other Treaties on Atomic Energy and Economic Community, as well as in the Single Act adopted in 1986 and in the present developments of the Community.

It was clear, from the very beginning of this historic initiative, that the Community should be built step by step, by concrete achievements which first create a de facto solidarity. Reinforcement of peace, integration of all European citizens in a single economic space, social cohesion and progress towards a real political union are the basic principles underpinning the European Community.

Although they covered different fields, the three Communities created since 1951 shared in fact the same final objectives. The merging of their institutions was completed in 1967, by a Treaty establishing a single Council and a single Commission. This approach was supported by the European Parliament which in 1978 adopted a resolution proposing that the three Communities should be designated «the European Community».

The Institutions of the Community

The Community is a new form of relationship between states, and four institutions have been set up to ensure this role *(Table 1)*:

Table 1: The Institutions of the Community.

- *Commission:* 17 Commissioners (1 President)
- *Council:* 12 Representatives of the Governments
- *Parliament:* 518 Members in Political Groups
- *Court of Justice:* 13 Judges

Ancillary Institutions:
- Economic and Social Committee
- European Investment Bank
- Court of Auditors
- etc.

Table 2: The Commission.

- Represents Community Interests
- Presents Proposals for Legislation
- Is the Guardian of Treaties
- Is an Executive Body
  1 President
  6 Vice-Presidents
  10 Members

- The *Commission (Table 2)* must serve interests of the Community only, being neutral by definition. It has the right (and the duty) of initiative, in presenting the proposals for Community legislation. All legislative proposals have to be put forward by the Commission, which is also responsible for seeing to it that the measures adopted are properly implemented. It is also, to a limited extent, an executive body.
- The *Council (Table 3)* is made up of twelve representatives of the Member States. Its composition varies according to the matters to be discussed (Ministers of Foreign Affairs or others). The Council is the supreme legislative body adopting the proposals made by the Commission. Since the adoption of the Single Act in 1986, most decisions may be taken by *Qualified majority*, a procedure which considerably improved the decision-making process.
- The *Parliament (Table 4)* and its role are slightly different from national parliaments. It is consulted on all important matters, but the outcome of the consultations is not binding. In short, if the Parliament disagrees with a proposal, it may still be adopted by the Council if there is a unanimous vote, which represents the unanimous wish of the Member States.
- The *Court of Justice* is the fourth institution, and its role is to supervise the interpretation of Community legislation.

Table 3: The Council.

Supreme Legislative Body
12 Representatives of the Governments of the Member States
- Matters requiring Unanimity:
  (Taxation, Social Security of Workers, etc)

or
- Qualified Majority (54 Votes out of 76)

Weighting of Votes

FR	10	SP	8	BE	5
FRG	10	PO	5	DK	3
IT	10	GR	5	IR	3
UK	10	NL	5	LUX	2

Table 4: The Parliament.

518 Members, in Political Groups, regardless of Nationality
- Has Supervision of the Commission (annual report)
- Budgetary Powers
- Consulted on all Important Matters
- Cooperation Procedure (two Readings)

The Legal Instruments of the Community

The legal instruments developed by the Community to work on national legal systems or on specific addressees can be either binding or non-binding.

Three *binding legal acts* are used in the EEC:
- *Regulations* apply in full in all Member States. Member States are bound directly.
- *Directives* require that Member States take adequate measures to achieve the objectives desired by the Community. In other words, directives have to be transposed into the legislation of Member States, and there is some possibility for them to take account of, for example, the existing regulatory framework.
- *Decisions* are measures intended to bind individual firms or Member States.

Two *non-binding* measures – *recommendations* and *opinions* – enable the Community institutions to express their views to Member States or individual citizens, and their real significance is more moral and political.

In the field of medicinal products, besides these legal measures provided for by the treaties, *notes for guidance* are very often used to give additional technical information on requirements from Competent Authorities. These guidelines are not legally binding, they are issued by the Commission after adoption by different committees and thorough consultation of interested parties.

In the field of medicinal products, measures adopted up to the present have taken the form of directives, decisions, and guidelines. A regulation concerning a future system of free circulation of medicinal products in the Community has been proposed by the Commission and is under consideration by the Council.

Harmonization of the Pharmaceutical Legislation

The Pharmaceutical Industry in Europe accounts for 60% of total world pharmaceutical exports. Although there had been a slight decrease in the recent past, this industry is still responsible for 40% of all new medicinal products discovered in the world. These very good results are obtained by 2000 companies employing around 400 000 persons.

The economic importance of this industry, as well as the very important public health and social security aspects, is at the origin of an important harmonization process within the Community. *Table 5* includes only the major dates in the evolution of pharmaceutical legislation concerning authorizations for marketing or for manufacturing. It does not include legislation on prices nor proposals concerning the rational use of medicinal products.

Table 5: Landmarks in the EC Harmonization of Pharmaceutical Legislation.

1965	Marketing Authorization: Quality, Safety, Efficacy
1975	Harmonization of Test Requirements Manufacturing Authorization CPMP – First Community Registration Procedure
1983	Current Multistate Procedure
1987	Biotech and High Tech Concertation Procedure
1989	Council GMP Directive and Extension Directives 89/342/EEC – 89/343/EEC – 89/381/EEC
1990	Proposal for: – European Medicines Evaluation Agency – Binding EC Registration Procedures
1991	GMP: Commission Directive

Manufacturing and Marketing Authorizations

Applicants for *marketing* authorization have to prove that the manufacturer of the medicinal product is authorized in his own country to manufacture medicinal products. However, it is not clear whether or not a manufacturer should be inspected in relation with the relevant manufacture before the authorization for marketing is granted. The manufacture of the product in question may be inspected but this is not *presently* common practice in most Member States. However, there is a clear indication that the manufacturing process takes on a more and more important part in the application dossier, as it appears from *Table 6*.

Inspectors feel also that these data should be controlled by inspections on site before a marketing authorization is granted. Collaboration between inspectors and the Quality Working Party of the Committee for Proprietary Medicinal Products is developing. For the first time, two guidelines have been drafted in close collaboration between these groups: these guidelines address the question of ionizing irradiation in the manufacture of medicinal products, from both the GMP and marketing authorization application points of view. One could expect further guidelines, concerning validations for example, to be prepared in the future.

Manufacturing Authorization and Good Manufacturing Practice

Directive 75/319/EEC is the basis for harmonization of manufacturing authorizations. This directive requires Competent Authorities to grant manufacturing authorizations after an inquiry carried out by their agents has proven that sufficient and suitable premises and equipment are available. This directive also addresses the release of batches by a «qualified person», the recognition of releases performed in the Community according to Community legislation, and the exchange of information between Member States as is appropriate to guarantee that the requirements for the authorization are fulfilled.

These provisions have been completed by another Directive adopted in 1989 (89/341/EEC), which enters into force on 1 January 1992.

This directive requires the compliance of manufacturers with the principles of EEC Good Manufacturing Practice, adopted since then by the Commission in the form of a directive, including products intended for export outside the Community. It also provides that detailed guidance in line with these principles should be prepared and published by the Commission, that repeated inspections must be carried out and inspection reports prepared by the officials and, finally, that these reports must be brought to the knowledge of manufacturers and transmitted upon reasoned request to other Competent Authorities.

In fact, a drafting group of inspectors had begun drafting detailed guidelines even before the adoption of the GMP directive, and the EEC guide to GMP was published in January 1989, after thorough consultation with Industry and EFTA countries, including the Pharmaceutical Inspection Convention (PIC). Several supplementary annexes were adopted in January 1991 or will be adopted very soon. This guide is in no way an additional guide, but a document intended to replace the national guides of Member States. The PIC countries decided to adopt the same text, and most of the draft WHO guide is based on the EEC guide.

As provided for by Directive 89/341/EEC, the Commission adopted a directive laying down the principles of GMP in June 1991 (91/356/EEC). For the interpretation of these principles, this directive refers to the guide and its annexes.

As regards the manufacture of *starting materials*, a preliminary discussion in the group of inspectors led to the conclusion that there was no evidence that a complete system of manufacturing authorization would be useful or possible and that, when necessary, manufacture of starting materials could be inspected according to either the PIC annex on GMP for active ingredients, or CEN 29 000 standards. This point should be considered in relation to the European Drug Master File Procedure adopted in 1990 (vol III addendum of our collection). According to this procedure, a manufacturer of active ingredients may submit some data which are essential for the protection of its know-how directly to the licensing authorities.

As discussed above, the problem of inspection of these active ingredients manufacturers is not yet resolved, and it is expected that they *would* be at least audited by the applicant for the marketing authorization.

Also in relation to starting materials, the European Pharmacopoeia is preparing a system of certification of the adequacy of the monograph to control active ingredients. According to this system, active ingredients manufacturers could transmit to the Commission of the European Pharmacopoeia a description of their manufacturing process and samples of products and request the Commission

Table 6: Relationships between Marketing Application Dossier and Manufacturing Authorization/Inspections.

Directive 65/65/EEC – Authorization for Marketing: Brief Description of Method of Preparation
Directive 75/318/EEC – Synopsis of the Manufacturing Operations, including Various Stages of Manufacture Precautions for Homogeneity Manufacturing Formula In-process Controls
Directive 87/19/EEC – Validation of Manufacturing process (incl. Equipment and Environment)
Directive 75/318/EEC modified by 91/507/EEC – Details of Sterilization Process/Aseptic Preparation

to certify that the product and its manufacturing process are properly controlled by the monograph. Again, these manufacturers should be audited by the applicant for the marketing authorization, but one can expect inspections to be carried out in some cases.
Inspection reports in the Community have been discussed by the EC group of inspectors, and it appears that the format proposed by the PIC would be acceptable in the Community. The principle of having a comprehensive description of the premises prepared by the manufacturer itself led to the agreement of the site master file concept. After verification by inspectors, this site master file would be a part of the inspection report.

Harmonization of inspection procedures is also in progress, with a view to ensure a good mutual recognition of inspections carried out in all Member States. In this respect, associate inspectors activities such as action in case of non compliance and analytical monitoring of marketed products are also under consideration. In case of quality defect, products should be withdrawn from the market, and in order to ensure a rapid withdrawal of these products from all national markets, a system of rapid alert was set up by the Commission. This system uses a standardized fax form and a network of contact points in the Member States. A system of classification of these alerts is in preparation.

Conclusion

This too long, and still not exhaustive, overview of the recent and future developments in marketing authorization systems and in inspection in the Community has shown that manufacturing operations are more and more closely looked at during registration.
It has also shown that there is now a legal basis for repeated GMP inspection of pharmaceutical manufacturers and that the resulting information should be exchanged between competent authorities where necessary. Inspection procedures are being harmonized, and PIC countries are involved in this process.
There is an agreement between licensing authorities (mainly those assessors involved in quality) and inspectorates to develop their collaboration during the registration process.
All these developments go towards a reinforcement of quality of medicinal products manufactured in Europe. This quality assurance is vital for ensuring a high level of protection of patients, within and outside Europe, together with a real free circulation of medicinal products.

Note: The documents referred to in this presentation are available in the series «The rules governing medicinal products in the European Community», references of which are given in *Table 7.* ■

Table 7: The Rules Governing Medicinal Products in the European Community.

Volume I Binding rules CB – 55 – 89 – 706 – EN – C – New Edition (in press)
Volume II Notice to applicants for marketing authorizations CB – 55 – 89 – 293 – EN – C
Volume III Guidelines on the Quality, Safety and Efficacy CB – 55 – 89 – 843 – EN – C Addendum (July 1990) CB – 59 – 90 – 936 – EN – C
Volume IV Guide to Good Manufacturing Practice CB – 55 – 89 – 722 – EN – C New Edition (in press)
Volume V The rules governing medicinal products for veterinary use CB – 55 – 89 – 972 – EN – C
Office for Official Publications of the European Communities 2, rue Mercier L-2985 Luxembourg Tel. (352) 499281/Telex. PUBOF 1324 b

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Quality Standards for Pharmaceutical Development and Production

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Progress towards the quality standards of the year 2000, may be compared to a journey on an uphill road. To predict where this road will lead us, we must first know where we stand today, and to fully understand our present position, we need to be aware of the events that led us here. Before looking to the future, we should therefore first take a look at the recent past.

R. Stuart Heir, Head of Quality Assurance International Sandoz Pharma Ltd., Basel, a British citizen, graduated as Member of the Royal Society of Chemistry at Portsmouth polytechnic in 1965. He worked in a variety of technical functions with Wyeth and then Cyanamid of Great Britain, joining Sandoz UK as QA manager in 1969. He was subsequently transferred for three years to Sandoz Canada, also as QA manager. In 1980, he returned to Sandoz UK in the dual function of QA manager and Technical Auditor/ Consultant to the parent company in Basel. In 1986 he moved to Sandoz Pharma Basel to take up his present position, with responsibility for technical support and supervision of the Quality Assurance units in the affiliated companies with particular emphasis on the development of GMP standards and GMP compliance auditing.

Development of Regulatory Control

Public health is, and always has been a highly emotive and political issue, and legislation to protect the public interest has a long history.

In the case of pharmaceuticals, control of starting materials and preparations via pharmacopoeial monographs, has been progressively supplemented by layer upon layer of government legislation and guidelines designed to ensure the safety, efficacy and quality of pharmaceutical products.

These controls extend far beyond the Quality Standards pioneered by the Pharmacopoeias, as they address practically every aspect of development, safety, efficacy, manufacture, and control.

The reason for this is that practically no other product is taken so completely on trust as a pharmaceutical. Modern drugs and dosage forms have brought with them enormous benefits to health and the quality of life, but they are often highly potent, and can be dangerous if mis-used, badly manufactured, or contaminated. End product testing cannot by itself assure the quality and safety of every dosage unit. For a sterile product with a one-in-a-million chance of non-sterility, who would wish to be the one-in-a-million patient?

Even very low levels of defective units can present a high potential hazard, and the patient is unlikely to recognise the problem until it is too late.

The quality of pharmaceutical products is therefore highly dependent on the conditions and control of the manufacturing process, and for this reason, quality standards in the industry have not only been developed on the basis of end product testing, but also to give the required assurance of quality, on the so-called «Good Manufacturing Practices» or GMPs.

If we take a look at the history of regulatory control, we see there have been other factors however *(Table 1)*.

In 1937 in the *United States,* 107 people died after taking an elixir of Sulphanilamide which contained diethylene glycol, instead of propylene glycol. In 1938 the *Federal Food, Drug and Cosmetic Act* introduced a registration system for new drugs, and a factory inspection system.

Table 1: Development of Regulatory Control.

– Sulphanilamide Elixir Tragedy (USA)	1937
– Food, Drug and Cosmetic Act (USA)	1938
– Thalidomide Tragedy (Europe)	1959
– Kefauver-Harris Amendments GMP regulations (CFR 21)	1962
– PIA GMP guidelines	1968
– WHO GMP guidelines	1969
– PIC convention	1970
– Development of National GMPs in Europe	1970-onwards
– EC Guide to GMP for Medicinal Products	1989

In *Europe,* the Thalidomide tragedy of 1959 resulted in much tighter controls on new drug substances and presentations, but it was only some years later that GMP concepts were actively developed.
In *North America,* the concept of GMP had taken hold much earlier than in Europe, and the first official publication was the Canadian document *«Manufacture, control and distribution of drugs»* issued in 1957. This document did not specifically use the term «Good Manufacturing Practice», but clearly addressed this subject.
The phrase «Good Manufacturing Practice» was first mentioned in the 1962 *Kefauver-Harris Amendment* to the US Food, Drug and Cosmetic Act. At that time, the *Food and Drug Administration (FDA)* had already been in existence for almost thirty-five years, and it was well prepared to take up the cause of GMPs. In fact, the FDA has been the pioneer in drug regulations and control, and is arguably the most powerful and influential regulatory authority worldwide.
One of the first initiatives in *Europe* was taken by the *European Pharmaceutical Industries Association (PIA),* which published its voluntary GMP guidelines in 1968.
The *World Health Organization (WHO)* were also active and in 1969 published their GMP guidelines which provided a basic outline of GMPs for worldwide use, and laid the basis for the *WHO Certification Scheme for Essential Drugs.*
In October 1970, *The Pharmaceutical Inspection Convention (PIC)* was published by the European Free Trade Association, with the objectives:

- To protect interests of public health by ensuring appropriate standards in manufacture of medicines.
- Effective quality control of manufacture.
- To set up effective systems of national inspection and testing of pharmaceutical products in member countries.
- To facilitate international trade on a wider scale through the recognition of inspections made by national health authorities.

This was a major step on the road to harmonisation, and the PIC in its 21 years of operation has published several important documents including Basic Standards of GMP, and several supplementary guidelines. Current membership is fifteen countries, with six more under application.
The early 1970s and 1980s saw the development of further *national GMP guidelines in Europe,* culminating in the publication of the EC GMP guidelines in January 1989.
Before leaving the subject of regulatory development it is perhaps appropriate to remind ourselves of the recent deaths of at least 109 children in Nigeria. In this case, a supplier mislabelled ethylene glycol as propylene glycol, and the manufacturer of the dosage form failed to check the mislabelled containers. As in 1937 – quality has to be produced, it cannot be assured by regulatory control alone.

Technological Developments

In parallel with the developments in regulatory standards, the Pharmaceutical Industry has seen unprecedented technological advances both in the production of pharmaceuticals, and in their testing and control. The availability of more advanced technology and the ability to measure quality parameters that were not measurable before, has transformed quality standards in the industry.
Today's dosage form requirements for specific assay of the intact drug substance with narrow release limits, the quantitative determination of low levels of degradation products, requirements for dosage uniformity and in-vitro dissolution, the requirements for rigorous validation of test procedures and the production process itself, were in most cases simply not possible a few years ago.

Table 2: Recently Issued GMPs.

– GMP Regulations of Japan	1988
– EEC Guide to GMPs for medicinal products	1989
– PIC Guide to GMP for Pharmaceutical Products	1990
– WHO – Draft PHARM/90 129/REV3	1991
– FDA Guide to the inspection of Bulk Pharmaceutical Chemicals	1991

These developments have been incorporated into pharmacopoeial and regulatory requirements to the point where each new development tends to set the state of the art, and the availability of new technology has often seemed to provide the rationale for the adoption of higher, and of course more costly quality standards.
The concept of GMP, as we know it today, and the corresponding expectations for product quality have therefore been shaped by the pharmaceutical industry itself, by the advancing technology, by the regulatory authorities and pharmacopoeias, and unfortunately by incidents, with the inevitable public pressure for more regulation of the industry.
These are the events which led us to where we are today, and continue to exert a strong influence on the developing situation in quality standards and GMPs.

The Situation Today

If we take a look at recent events in the field of quality and GMP, and compare with the past, we see a sharp increase in rules, regulations, and the corresponding standards expected of the industry *(Table 2).*
The current GMP regulations tell part of the story, as the past three years have seen a much increased activity in this area.
In 1988 the Ministry of Health and Welfare in *Japan* issued the third edition of the GMP regulations. In this edition, GMP regulations for medical devices, for diagnostics, and oriental medicine formulations were included. Significantly, the text of the US GMP regulations was added as a reference.
Publication of the *EC* guide to GMPs in 1989 marked yet another step on the road to harmonisation, with comprehensive and well written GMPs. These were subsequently adopted by the PIC which produced its updated guidelines in 1990, and also form the basis for the WHO Draft of GMPs 1991.
The WHO draft also contains a section on Bulk Pharmaceutical Chemical manufacture, similar to the 1987 PIC guidelines.
Regulatory authorities do not normally inspect bulk pharmaceutical chemical plants, although the sites and methods of manufacture are controlled through the

registration process. The FDA, however, is actively interested in such manufacture, and the Mid Atlantic region issued a new inspection guide in March 1991. This guide introduces new environmental, processing, and quality standards, with particular emphasis on quality assurance, record review and approvals, validation, water quality, cleaning procedures, and written procedures.

The accelerating pace of regulatory requirements, and the moves towards harmonisation of GMP standards and requirements, are however, an evolutionary process. For revolution, we must look once again to the *United States.*

In 1988, the discovery of fraud in the applications of some generics companies, resulted in a fundamental re-appraisal of the FDA's role, and a significant expansion in the agency's inspection targets and techniques. The FDA's enforcement powers were also put under review, and a decision taken to expand its staff by the addition of a large number of what has been described as «criminally trained experts». This focus on enforcement, was demonstrated by the introduction in 1990 by the FDA's Mid Atlantic region of the *Pre-Approval Inspection Programme,* whereby GMP compliance is directly linked to *New Drug Application (NDA)* approval.

The objectives of this programme were stated as follows:

- Evaluation of the establishment's compliance with Current Good Manufacturing Practice (CGMP) requirements, including coverage of the specific batches used to demonstrate bioequivalence.
- Evaluation as to whether the establishment has adequate facilities, equipment, procedures and controls to manufacture the product in conformance with application commitments.
- Audit of the accuracy of the biobatch manufacturing and testing information submitted with the application.
- Collection of a sample of the biobatch from the bioequivalence test laboratory.

Such inspections had been occasionally conducted in the past, but not so rigorously. Unlike the usual GMP plant inspection, the pre-approval inspection focuses on the specific production process described in the NDA, to ensure integrity of the biobatch and manufacturing process. Evaluation of bulk chemical suppliers, contract testing laboratories, and contract packagers is also included, as is a review of all development, clinical supply or stability batch documentation, with the requirement that they are complete, and in commercial production format. Current GMP standards have also been applied to clinical batches made several years previously. If the data is not to the FDA's satisfaction, then the Company's NDAs may be withheld until such time as appropriate corrective measures are taken.

Direct linkage of the approval process with a GMP compliance inspection is therefore an extremely powerful tool which as the FDA has already demonstrated, it is quite willing to use, both in the United States, and in connection with overseas inspections.

Although the regulatory climate is becoming more difficult, there are at the same time, very positive moves to harmonise quality standards in pharmacopoeial, and in registration requirements. The four major pharmacopoeias, namely the United States, the British, the European and the Japanese, are now actively moving towards the goal of compendial uniformity for excipients, and a joint conference was held in Orlando, Florida in January 1991. A further development is the First International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals For Human Use to be held in Brussels in November 1991. The conference is jointly sponsored by the regulatory authorities and industry associations of Europe, Japan and the United States.

The steering committee have issued the following statement:

«This Conference will provide a unique opportunity for regulators and industry to reach consensus on the steps needed to achieve greater harmonisation of technical requirements and to set out practical and realistic targets for such harmonisation where significant obstacles to drug development and the regulatory process have been identified. The Conference will not only look at existing issues but will, based on past experience, seek to minimise future divergences of new registration requirements as a consequence of technical progress.»

Moves towards the harmonisation of GMP regulations, registration requirements and pharmacopoeial standards are of vital importance to the industry, operating as it does on a worldwide basis, and faced with a multiplicity of standards and requirements in international markets. Compliance with these ever changing requirements is very difficult, expensive, and brings no tangible benefit to the consumer.

The present position in the pharmaceutical industry is therefore one of transition. The regulatory basis for change has already been set by the recent flood of new guidelines and regulations. The implementation of these new requirements will be driven by the integration process in Europe and certainly by emerging events in the United States.

The moves towards harmonisation have come just in time.

Future Trends

In Europe, regulatory authorities face a difficult task in applying consistent standards of GMP across all community member states.

The inspection authorities vary considerably in resources, and in their approach to regulatory compliance and although the EC GMP directive becomes effective in 1992, it may well be some years before uniform inspection standards are reached. Nevetheless, implementation of the GMP directive, and harmonisation of registration requirements will bring compliance and quality issues into much sharper focus than before, and the regulatory pressure on industry is likely to increase.

In the United States there is only one regulatory authority, which is already well established, but the present developments in the role of the FDA, and the means by which the regulations are enforced, have not yet run their course, and there may be surprises to come. The impact of the Pre-Approval Inspection Programme should not be underestimated, as it is extremely effective, and other regulatory authorities are likely to move in the same direction.

Harmonisation of standards is a process of mutual benefit to the regulatory authorities, as well as to industry, and in removing some of the problems of compliance with multiple standards, will allow more focus on quality parameters relevant to the consumer.

Harmonisation of GMP requirements is already taking place to a certain extent, but interpretation and enforcement vary considerably. By the year 2000, a third major player, namely Japan, will have joined in. It remains to be seen how GMP compliance and quality standards are developed, as there seems to be an imbalance between the Japanese GMPs, and the standards set by leading manufacturers, who in some respects, are well ahead. Will we see competition via GMPs? – Perhaps!

Progress in harmonisation of standards, and the continued development of realistic regulatory requirements can only come from an open-minded cooperation between the authorities, the industry, and the health care professions. But quality has to be produced, and the challenge of higher quality standards must be met by the manufacturer.

It is an uphill road, but with opportunities as well as problems, as the following examples illustrate.

Quality of Raw Materials
Much more emphasis is likely to be placed on the quality of raw material supplies. It is clearly a waste of time and resources to validate a manufacturing process only to find that the quality of the raw materials is not properly controlled by the manufacturer. Higher quality standards for the products must lead to much more attention being paid to the quality of raw materials, and the industry should be prepared to take advantage of national certification schemes for suppliers, based on ISO 9000 for example.
It is possible that harmonisation of pharmacopoeial requirements may simplify the supply situation and lead to a greater willingness on the part of raw material suppliers to meet the requirements of the industry. If this does not occur, then the quality of the raw material supplies will increasingly be the limiting factor in the improvement of product quality.

Validation
The concept of validation is now well established, and integrated into the overall concepts of GMP. In Europe, it has received rather less attention by the regulatory authorities than in the United States, but it has not been ignored, and is likely to be targeted in future.
Qualification of plant and equipment, and the systematic validation of production processes are essential pre-requisites for the efficient production of consistently high quality products. Validation concepts will therefore continue to be developed for pharmaceutical production processes.
More attention will also be focused on the validation of cleaning procedures, both microbiologically and chemically, and particularly on computer systems.

Manufacturing Environment Standards
Environmental Standards will be further developed for sterile, as well as non-sterile products, with more emphasis on product containment to exclude contamination. Factory design has changed, but will be further developed around the concept of cleanliness zoning, probably following the trends set by the newest factories in Japan, but also by the new European «high technology» factories resulting from production rationalisation in the industry after 1992.

Documentation Systems
The requirements of documentation and records are well specified by the various GMPs, but continue to be a source of regulatory problems in the industry. As the FDA's Pre-Approval Inspection Programme has demonstrated, documentation standards in development will come under increasing scrutiny.
Computerisation of documentation systems may improve compliance, but it brings problems of complication, and lack of transparency for the operator. The issues of validation and change control also present problems, but nevertheless, the race towards the paperless factory will of course continue.

Computerisation
The computerisation of all areas of pharmaceutical manufacture and control will continue its advance, with more convergence of systems than we see today. More sophisticated processing techniques for raw data in the laboratory, the generation of product quality data from the manufacturing equipment itself, the increased use of statistical process control methods, with continuous analysis of trends in process performance and product quality, are already a reality, and will of course be further developed in future, so raising attainable quality standards still higher.
The increasing complexity of such systems will present new challenges for validation and regulatory control, and will certainly have an influence on the development and concept of Good Manufacturing Practice.
This is an area requiring very close cooperation between industry and the regulatory authorities.

End Product Testing
Despite better product design, higher quality raw materials, and exhaustive process validation, end product testing is still likely to be around in the year 2000. Nevertheless, on-line quality monitoring systems are already in use for tablet or capsule inspection and particulates and hairline cracks in ampoules for example. Advances in sensor technology will extend the range of applications.

End product specifications will continue to be raised in line with process or test capability, the demands of the regulatory authorities, and consumer expectations of high quality.

The narrowing of release limits, the trend to ever lower limits for impurities, by-products and degradation products, stricter microbiological control of non-sterile dosage forms, will all place increasing demands on the production process, the manufacturing environment, the test laboratories, and not least, on the quality systems.

Bulk Pharmaceutical Chemical Production
Bulk pharmaceutical chemical production has so far received relatively little attention with respect to Good Manufacturing Practice guidelines, but this is already changing. By the year 2000, it is likely that GMP standards comparable in their scope to those used for galenical manufacture will be established, and enforced by regulatory inspection. The FDA's inspection guidelines of March 1991 give some indications of the changes to come.

ISO 9000 and Quality Management
Finally, we should consider the relevance of ISO 9000 to the development and maintenance of quality standards in the production of pharmaceuticals.
If quality could be determined solely by end product testing, then quality standards would depend on manufacturing and test technology. But this is not the case. The development and maintenance of high quality standards is also an organisational matter, and this is increasingly becoming the limiting factor. The availability of sophisticated technology, state of the art production facilities, and the existence of clear and comprehensive regulatory guidelines, will come to nothing if not integrated by the manufacturer into an organisational matrix focussed on the goal of quality. People cannot be «validated», and the increasingly complex technical and regulatory environment therefore makes organisational development for quality, increasingly urgent.
The *ISO 9000 series* is a set of generic quality system standards *(Table 3)*, applicable to practically any industry, and certification bodies have already been

Table 3: ISO 9000 Series.

- *ISO 9000 Quality management and quality assurance standards:* Guideline for selection and use
- *ISO 9001 Quality systems:* Model for quality assurance in design/development, production, installation and service
- *ISO 9002 Quality systems:* Model for quality assurance in production and installation
- *ISO 9003 Quality systems:* Model for quality assurance in final inspection and test
- *ISO 9004 Part I – Quality management and quality system elements:* Guidelines

established in many countries, particularly in Europe.

Submission to yet more inspection and controls in order to gain ISO 9000 certification is not justified for a pharmaceutical manufacturer, as the GMP regulations together with other regulatory requirements do cover the standards required. However, the quality system structures described in the standards have much to offer, as they provide a clear organisational framework for quality.

ISO 9000 does not provide all the answers, but the basic principles and the concepts of quality management are being increasingly taken up by pharmaceutical manufacturers. By the year 2000, these developments in «organisational technology» will be an essential part of the development of higher product quality standards in the industry.

Conclusions

The year 2000 could well see «GMP watchers» in the *United States* anxiously studying the trends set by the European Regulatory Authorities, or rather, Authority. But the chances are that they will also look in the other direction, to *Japan*. The Japanese pharmaceutical industry was a late starter, but is advancing rapidly, and the effect of Japanese consumer-led quality standards is already visible. Japanese hospitals dominate the prescription drug market with their demands for convenience in use, and unblemished quality. Japanese consumers are probably the most quality conscious in the world, as any exporter to Japan will confirm, and the demands of this large market for quality and even higher quality are certain to be reflected in the developing regulatory requirements and the «state of the art».

It should not be forgotten that in the past, the road to high quality standards has led Japanese industry to increased competitiveness, and success.

We must also follow that road in the future. ■

Swiss Federal Institute of Technology Zurich (ETH), Symposium «Quality of Drugs in the Year 2000», October 25, 1991

Legal Requirements and Issues with Regard to the Completion of the EC and Prospectives for the Year 2000

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When lawyers set out to explain a complex subject from a legal point of view, there is always a danger that scientists will show little interest, since they feel that legal problems bear no relevance to their scientific work. But no one involved in the development and marketing of pharmaceuticals can afford to ignore the basic legal issues, for example in connection with registration, or in particular regarding the liability risks in this field. This article provides a basic review of the key legal issues of the pharmaceuticals business, without excess detail. In the first part it deals with the position of a planned European registration authority — to be called the European Medicines Agency (EMA) — with regard to the future registration procedures in the EC. It analyzes the problems concerned in reporting adverse drug reaction, and describes the authority of the planned EMA with regard to implementing measures for control of risks. As the problems of so-called pharmacovigilance and risk management cannot be dealt with by the authorities and the industry without considering the fundamentals of liability law, the basic principles of liability laws are explained, with respect to the marketing of pharmaceutical products.

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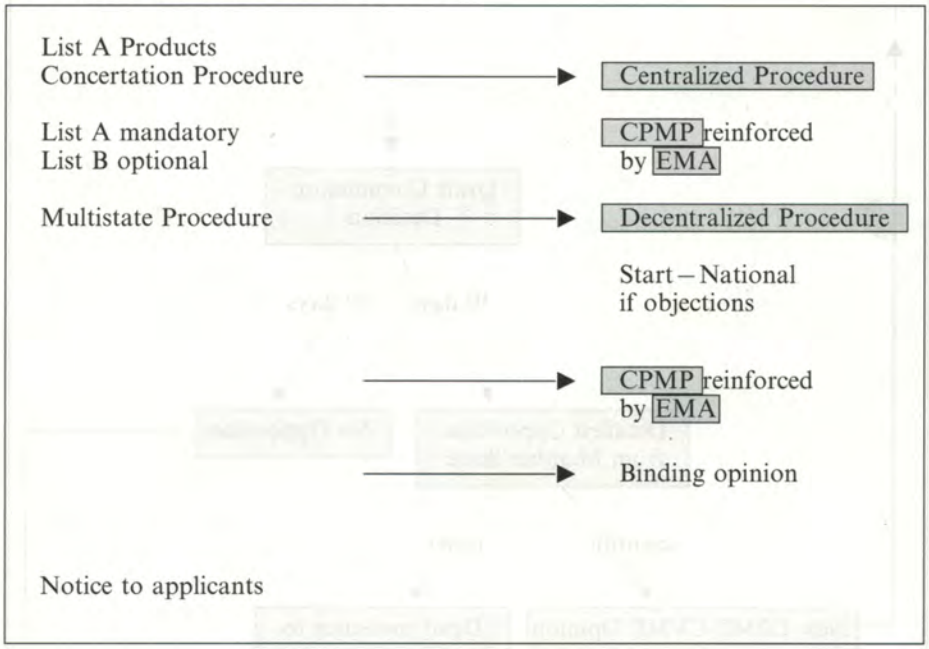
Future EC Registration System

The EC directives and regulations on the creation of a future registration system have not yet been finally approved, so that the following comments on this subject are based on existing drafts and are therefore necessarily of a provisional nature. The Member States of the EC are still involved in heated discussions regarding the role, tasks and powers of the European Medicines Agency (EMA). Nevertheless, the major points contained in the proposals under consideration will most likely come into effect, since the primary question currently being de-

Table 1: Future EC Registration System (1st draft June, July 1990), (CPMP = Committee for Proprietary Medicinal Products).



bated concerns the method by which the evaluation procedure of the EC can be carried out within the individual Member States. The decision-making process at EC level has obviously already met with wide approval among the Member States. *Table 1* shows a comparison of the existing and future procedures. The new procedures are basically unchanged, and are a continuation of recent progress achieved with the existing procedures.

It is necessary to differentiate between the concertation procedure, which will be termed *«centralized procedure»* in the future, and the multistate procedure, which will be called *«decentralized procedure»*. The first type, the concertation procedure, is compulsory for all pharmaceutical products included in List A of the relevant EC guidelines, and concerns those products produced by genetic engineering. Pharmaceutical companies are also allowed to use this procedure, however, on a voluntary basis for new pharmaceuticals with a promise of special

Table 2: Centralized Procedure I (CPMP = Committee for Proprietary Medicinal Products; CVMP = Committee for Veterinary Medicinal Products).

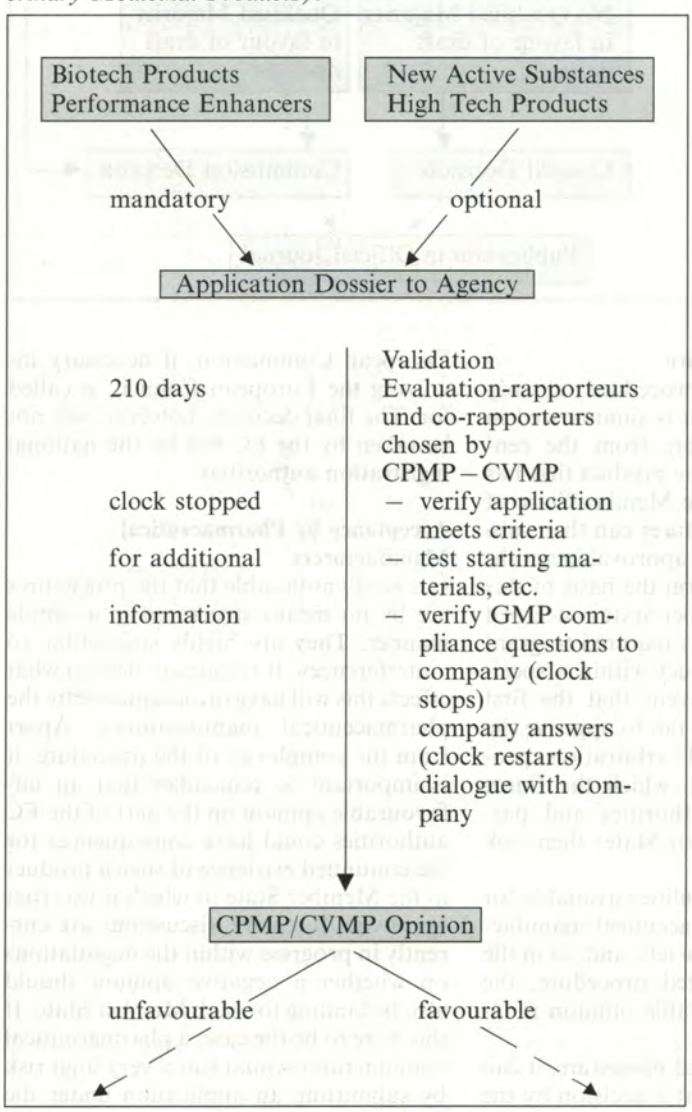
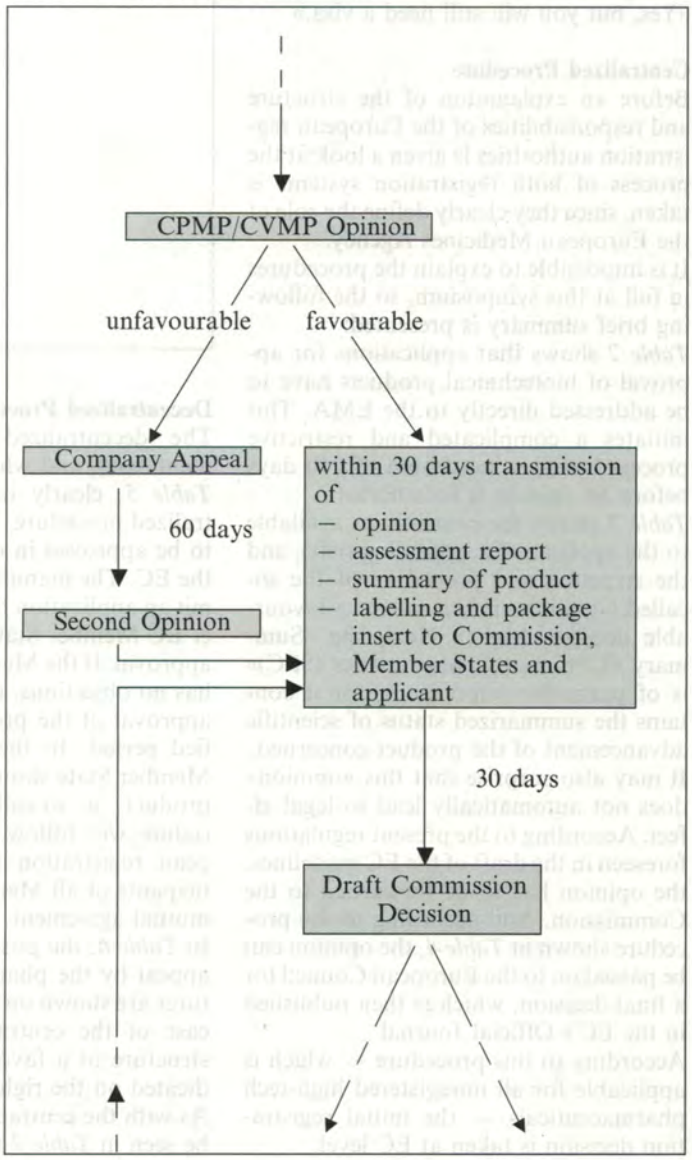


Table 3: Centralized Procedure II.



therapeutic progress, or which are at least defined as new chemical compounds. Before such innovative products can be approved by the Member States, a recommendation by the CPMP is required.

This procedure is clearly different from the so-called «multistate» procedure, according to which a pharmaceutical product must have already been approved in one Member State, with approval in the other Member States subsequently being given on the basis of this initial registration. It may come as a surprise that existing and future registration procedures in the EC do not provide for the automatic mutual recognition of already existing approvals. It is expressly required that each Member State decides whether it approves a product accepted by another Member State. Fernand Sauer, head of unit DGIII C2 of the European Commission, has very aptly described the types of procedure in his reply to the question whether the future registration system would be equivalent to «a passport to Europe». His reply was: «Yes, but you will still need a visa.»

Centralized Procedure

Before an explanation of the structure and responsibilities of the European registration authorities is given a look at the process of both registration systems is taken, since they clearly define the role of the European Medicines Agency.

It is impossible to explain the procedures in full at this symposium, so the following brief summary is presented:

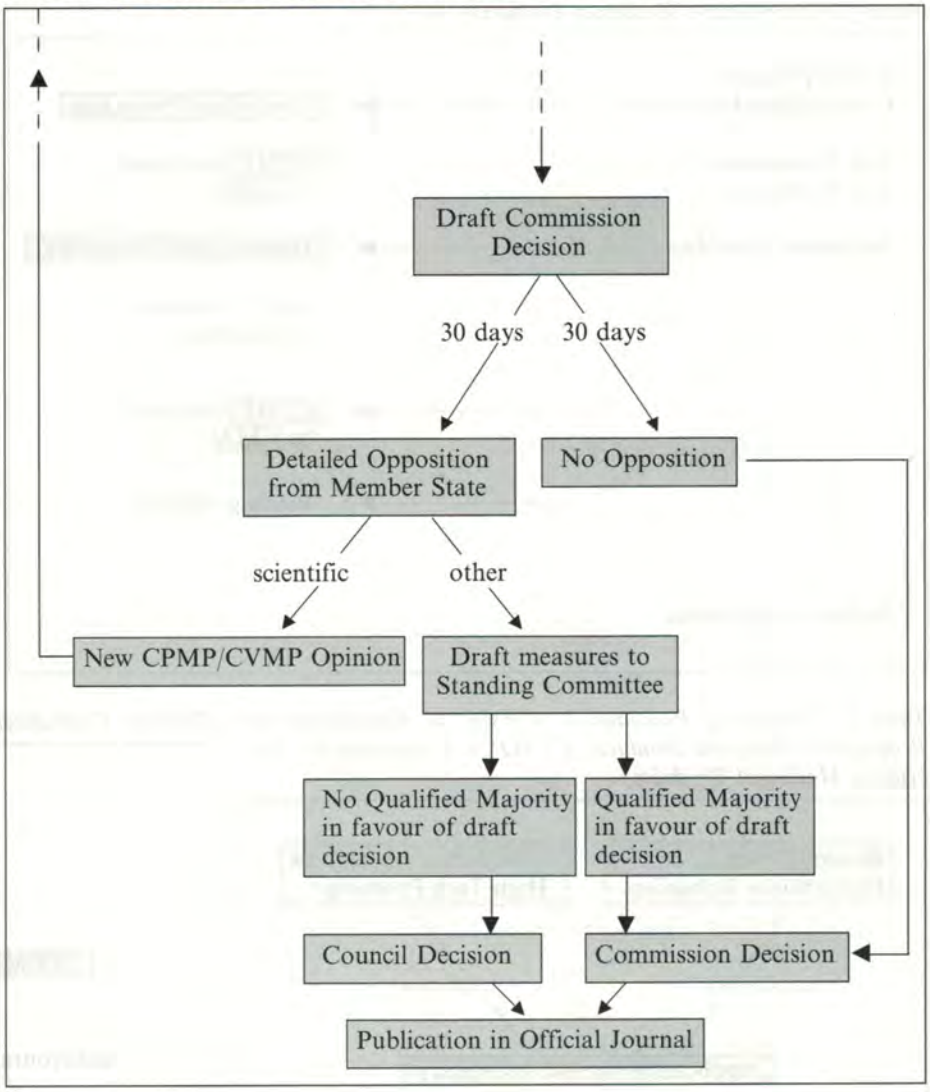
Table 2 shows that applications for approval of biotechnical products have to be addressed directly to the EMA. This initiates a complicated and restrictive process lasting a maximum of 210 days before an opinion is formulated.

Table 3 shows the possibilities available to the applicant for appealing (left), and the structure and procedure of the so-called «opinion» in the case of a favourable decision (right). Here, the «Summary of Product Characteristics (SPC)» is of particular importance, for it contains the summarized status of scientific advancement of the product concerned.

It may also surprise that this «opinion» does not automatically lead to legal effect. According to the present regulations foreseen in the draft of the EC guidelines, the opinion has to be forwarded to the Commission. And according to the procedure shown in *Table 4*, the opinion can be passed on to the European Council for a final decision, which is then published in the EC's Official Journal.

According to this procedure – which is applicable for all unregistered high-tech pharmaceuticals – the initial registration decision is taken at EC level.

Table 4: Centralized Procedure III (Source: EC Commission).



Decentralized Procedure

The decentralized procedure already mentioned, and which is summarized in *Table 5*, clearly differs from the centralized procedure. The product first has to be approved in one Member State of the EC. The manufacturer can then submit an application for approval in another EC Member State on the basis of this approval. If the Member State concerned has no objections, it is required to grant approval of the product within a specified period. In the event that the first Member State should fail to approve the product, a so-called arbitration procedure will follow, in which the European registration authorities and participants of all Member States then seek mutual agreement.

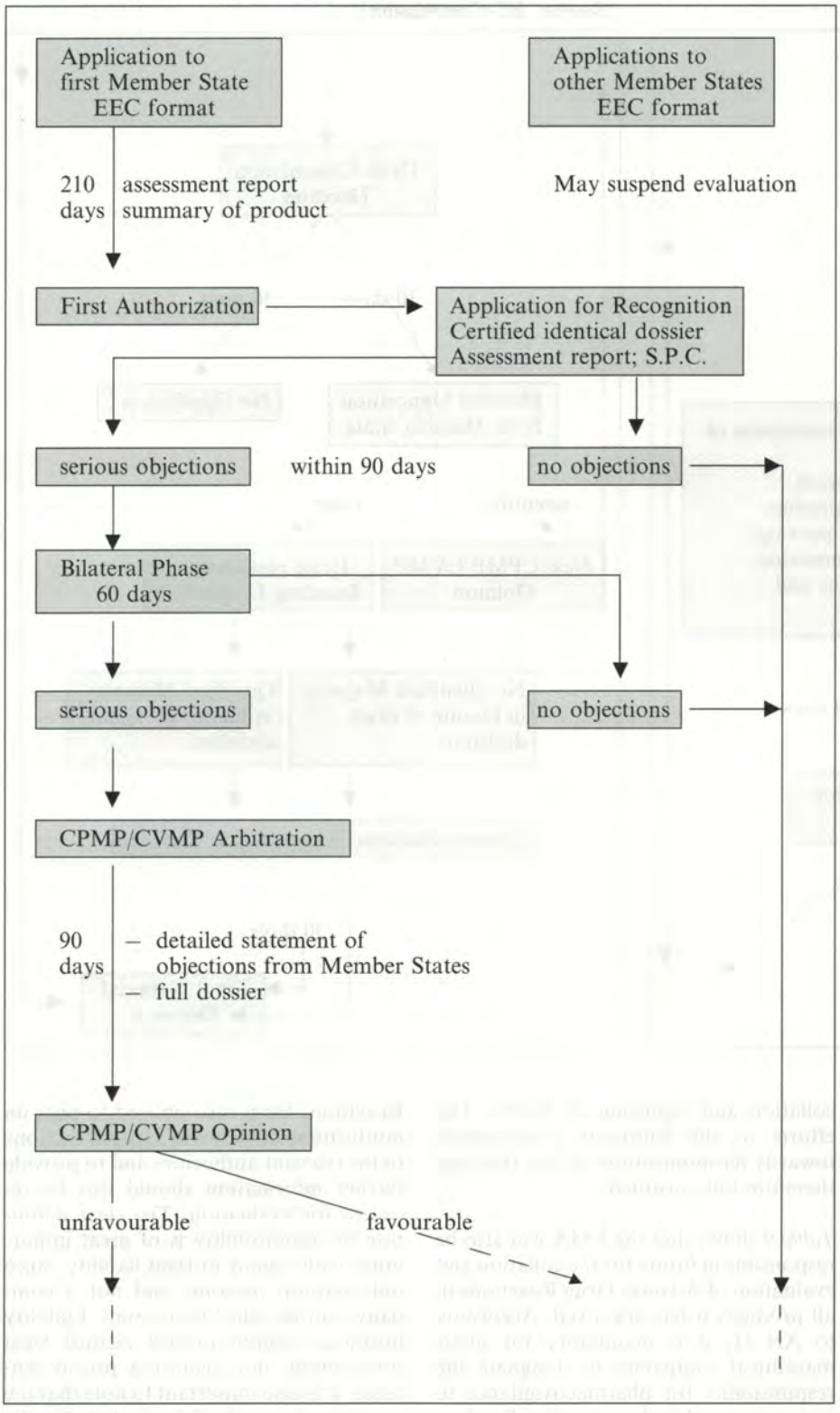
In *Table 6*, the possibilities available for appeal by the pharmaceutical manufacturer are shown on the left, and, as in the case of the centralized procedure, the structure of a favourable opinion is indicated on the right.

As with the centralized procedure, it can be seen in *Table 7* that a decision by the European Commission, if necessary involving the European Council, is called for. The final decision, however, will not be taken by the EC but by the national registration authorities.

Acceptance by Pharmaceutical Manufacturers

It is easily noticeable that the procedures are by no means structured in a simple manner. They are highly susceptible to «interference». It remains to be seen what effects this will have on acceptance by the pharmaceutical manufacturers. Apart from the complexity of the procedure, it is important to remember that an unfavourable opinion on the part of the EC authorities could have consequences for the continued existence of such a product in the Member State in which it was first approved. Intensive discussions are currently in progress within the negotiations on whether a negative opinion should also be binding for each Member State. If this were to be the case, a pharmaceutical manufacturer would run a very high risk by submitting an application under the

Table 5: Proposed Decentralized Procedure I (Source: EC Commission).



decentralized procedure, for he would not only fail to achieve his objective of expanding his product into other EC Member States, but could also be forced to withdraw the product from an already existing market. Even if a manufacturer were not obliged to withdraw an approved product from a market, a negative decision on the part of the EC authorities would obviously have repercussions on the existing markets. This characteristic of the procedure will have a negative effect on its acceptance.

On the other hand, it is also conceivable that this procedure will function. It is generally known that health authorities all over the world are faced with an enormous workload in the form of the evaluation of pharmaceutical products. The administrative capacity and actual administrative management of most authorities are inadequate for dealing with the number of registration applications. We already have to expect an extreme prolongation of the registration period of up to five or even six years. The same fate awaits the EC procedures in spite of their planned deadlines, since these are unrealistic. There is already a notable prolongation of official deadlines in the present concertation and multistate procedures. The above-mentioned risks for the pharmaceutical manufacturer could therefore give rise to cautious utilization and thus permit the future system to function more efficiently.

Structure and Responsibilities of the European Medicines Agency (EMA)

Table 8 shows the structure of the planned authority. Of key importance are the *Committee for Proprietary Medicinal Products (CPMP)*, and the *Committee for Veterinary Medicinal Products (CVMP)*. Members of these committees are representatives of the national registration authorities, and they have a major influence on the opinion of the EMA. The Executive Director and the administrative and technical secretariats are responsible for preparing the decision process. It is currently being debated whether this technical staff of the authorities should strictly fulfill the function of a service, or whether they should be allowed to carry out their own evaluations. As is to be expected, the Member States favour the service concept, whereas the EC Commission prefers the second option. There is no end to this discussion in sight. Germany, France and Italy still insist that the members of the CPMP should continue to act on the instructions of the national registration authorities, and that the EMA should only be responsible for providing the technical and administrative prerequisites for the smooth handling of the harmonization of the decision process.

Based on the experience of the past, and the political pressure of a decision to be made in 1993, we can expect a compromise solution aimed at satisfying the interests of the various Member States as far as possible.

If the European Commission is to make the final decision, it must be clarified whether it is to act as the «rubber stamp» of the EMA, or is able to carry out its own evaluations. It is possible that the Standing Committee, an organisation of the Commission, would adopt this function. Representatives of the EMA and the Member States take a very critical view of this potential power centre, and are querying somewhat ironically whether the Standing Committee would not in fact make the establishment of an EMA superfluous.

Table 6: Proposed Decentralized Procedure II (Source: EC Commission).

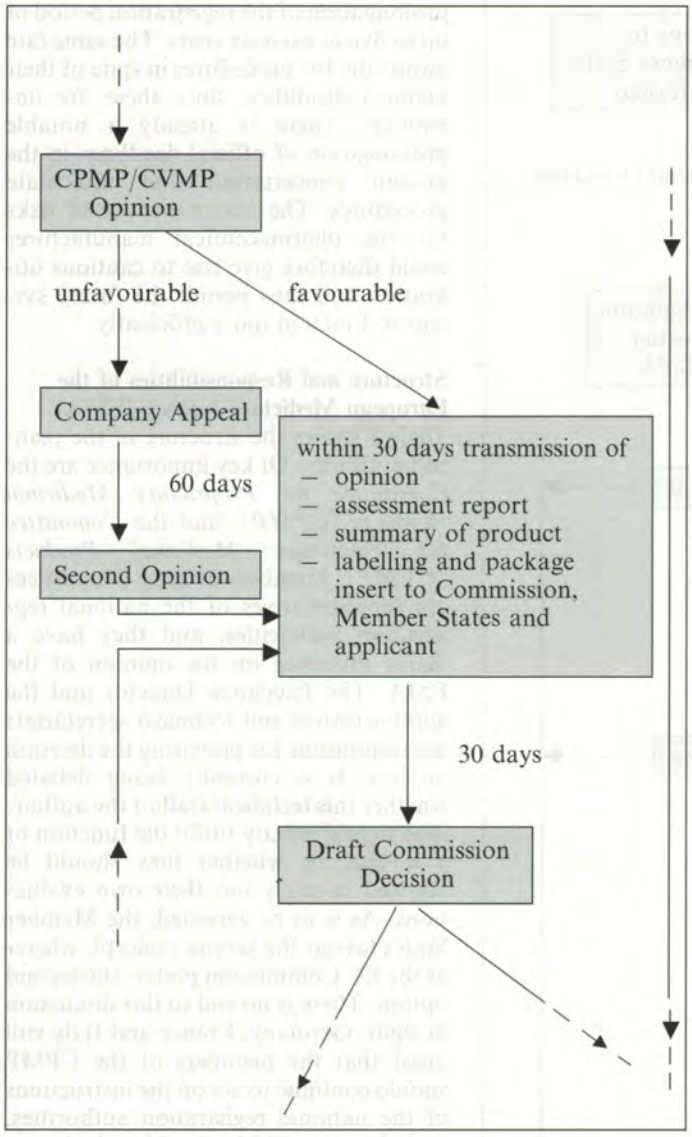
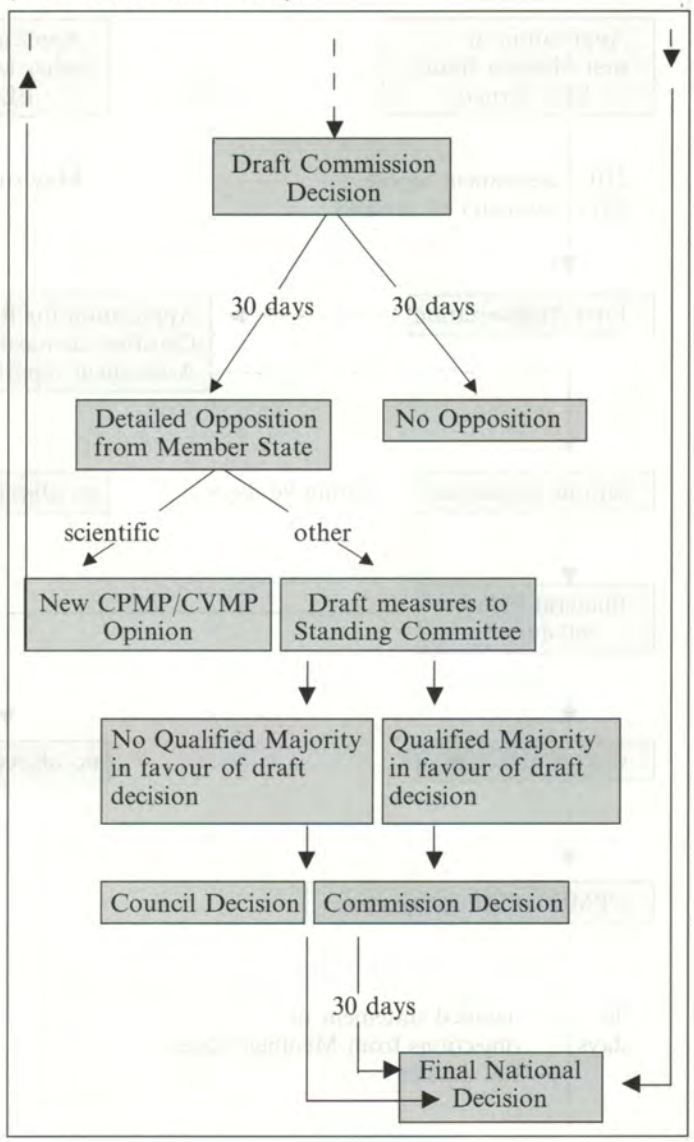


Table 7: Proposed Decentralized Procedure III (Source: EC-Commission).



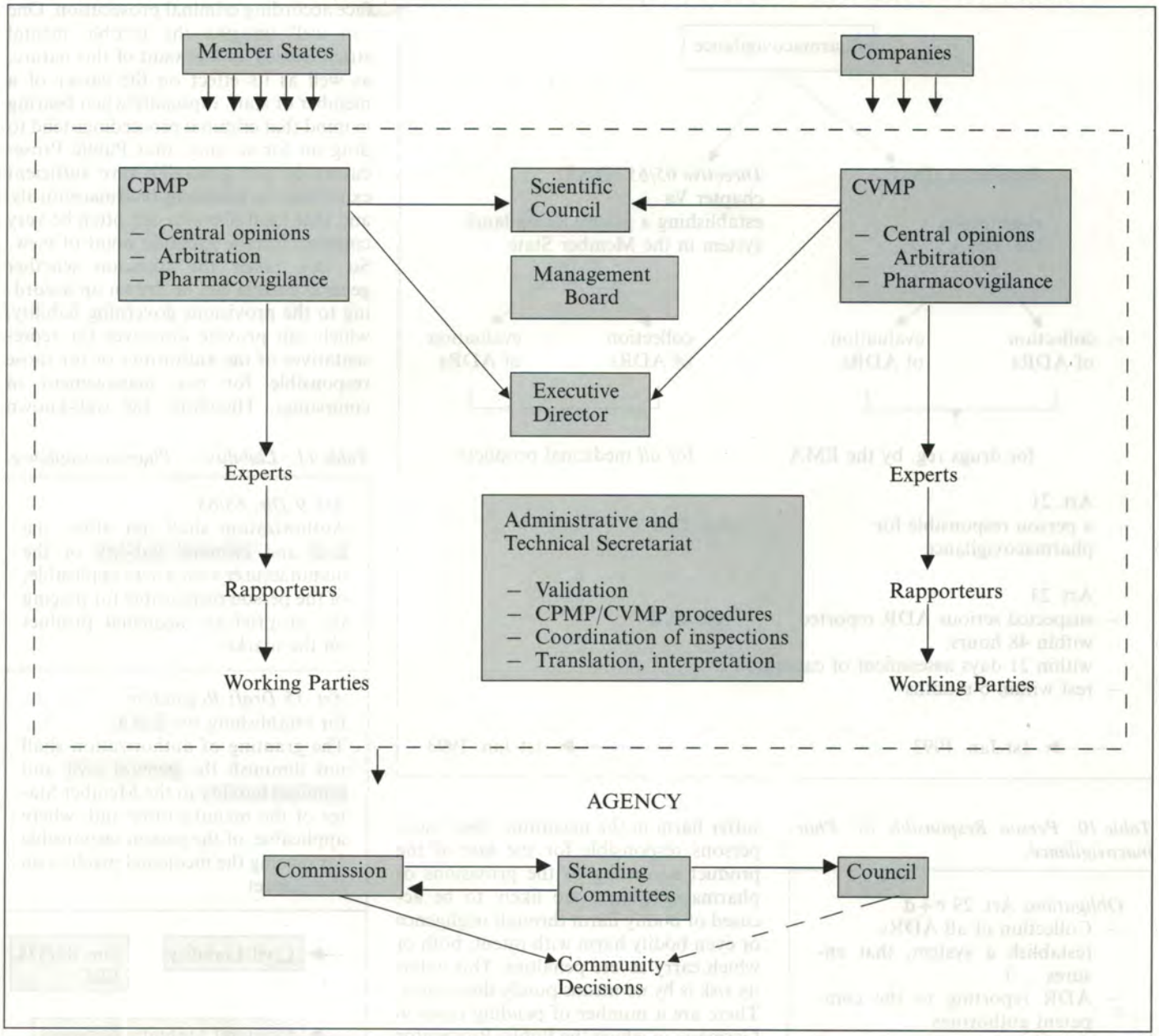
It should also be mentioned here that the original intention of bringing these new procedures into force in 1993 has already been abandoned. According to recent information, it will only be possible to introduce these by 1995 at the earliest, with further interim deadlines for establishing the decentralized procedure as a mandatory one: mandatory in the sense that a pharmaceutical company has to use the procedure after obtaining an initial registration in one of the member states.

Pharmacovigilance in the EC

As *Table 8* demonstrates, the EMA is also responsible for pharmacovigilance. I would therefore like to briefly outline the planned regulations regarding the reduction of the risk of *Adverse Drug Reactions (ADRs)*. Due to the analysis of the EC Commission of the current status of the EC procedures regarding pharmacovigilance, there is a certain inconsistency with regard to the legal status, collation and reporting of ADRs. The efforts of the European Commission towards harmonization in this field are therefore fully justified.

Table 9 shows that the EMA will also be responsible in future for the collation and evaluation of Adverse Drug Reactions in all products it has approved. According to Art. 21, it is mandatory for pharmaceutical companies to designate the responsibility for pharmacovigilance to one person within the company. Furthermore, it is planned to establish a compulsory reporting procedure for ADRs on a daily and hourly basis. Of special significance is the mandatory designation of one person in the company to be responsible for pharmacovigilance *(Table 10)*. This designation already exists in Germany, where one person, the *«Stufenplanbeauftragter»*, is in charge of all action concerning the comprehensive reporting and collation of Adverse Drug Reactions. He is also obliged to pass on notification of Adverse Drug Reactions to the relevant authorities and to provide further information should this be required for evaluation. The clear definition of responsibility is of great importance with regard to legal liability, since only natural persons, and not a company, can be called to account. Liability insurance cannot protect against legal prosecution, nor against a prison sentence. It is also important to note that the possible approval of a product by the European authorities does not influence civil and criminal liability in any way. This is clearly stated in Art. 9 of Directive 65/65, as well as in Art. 15 of the draft of the new regulations. *Table 11* depicts the wording of these clauses. This means that the sale of potentially unsafe pharmaceutical products cannot be justified by the fact that they have been approved for registration by an authority.

Table 8: The European Medicines Agency (EMA) for the Evaluation of Medicinal Products (Source: EC Commission).



Liability in the Future Registration System

Since the registration of a product does not exclude prosecution, it is especially important for the management and staff of a company, as well as for representatives of the authorities, to be familiar with the fundamentals of the liability law. *Table 12* gives a basic breakdown of product liability in Germany, which generally speaking is essentially the same as that of most other Member States. As it has already been pointed out, it is necessary to differentiate between *civil* and *criminal* liability.

There are two types of civil liability:
- strict liability, i. e. liability without fault, and liability in tort;
- negligence liability.

German law governing strict liability in the field of distribution of pharmaceutical products is very stringent, but liability is limited to DM 200 million. The payment of compensation is excluded. Should the company be found to be at fault, however, it will also be ordered to pay compensation for personal suffering. Fierce struggles regarding compensation for personal suffering are a common occurrence in such liability proceedings. Companies are advised not to agree to pay compensation for personal suffering as part of a settlement, since by doing so they would be tacitly conceding that they were at fault. An admission of fault automatically gives rise to the question of criminal liability, however, which would mean that the Public Prosecutor would be in a position to use such a tacit admission in order to bring charges against the management of the company or one of its members of staff.

There are two types of criminal liability, too; one is based on *pharmaceuticals* laws, the other on *criminal* law. According to the German pharmaceuticals law, the sale of a potentially unsafe pharmaceuticals is classed as an offence, even if no harm is caused to the patient. The legislative intent here is to reduce risk by means of preventive measures. But should bodily harm or even the death of a patient result, then the general provisions of criminal law apply. As a general rule, it is the question of timely action which forms the subject of criminal proceedings following withdrawal of a pharmaceutical from the market. Should a pharmaceutical be recalled too late and a person

Table 9: Pharmacovigilance in the Framework of the Future System.

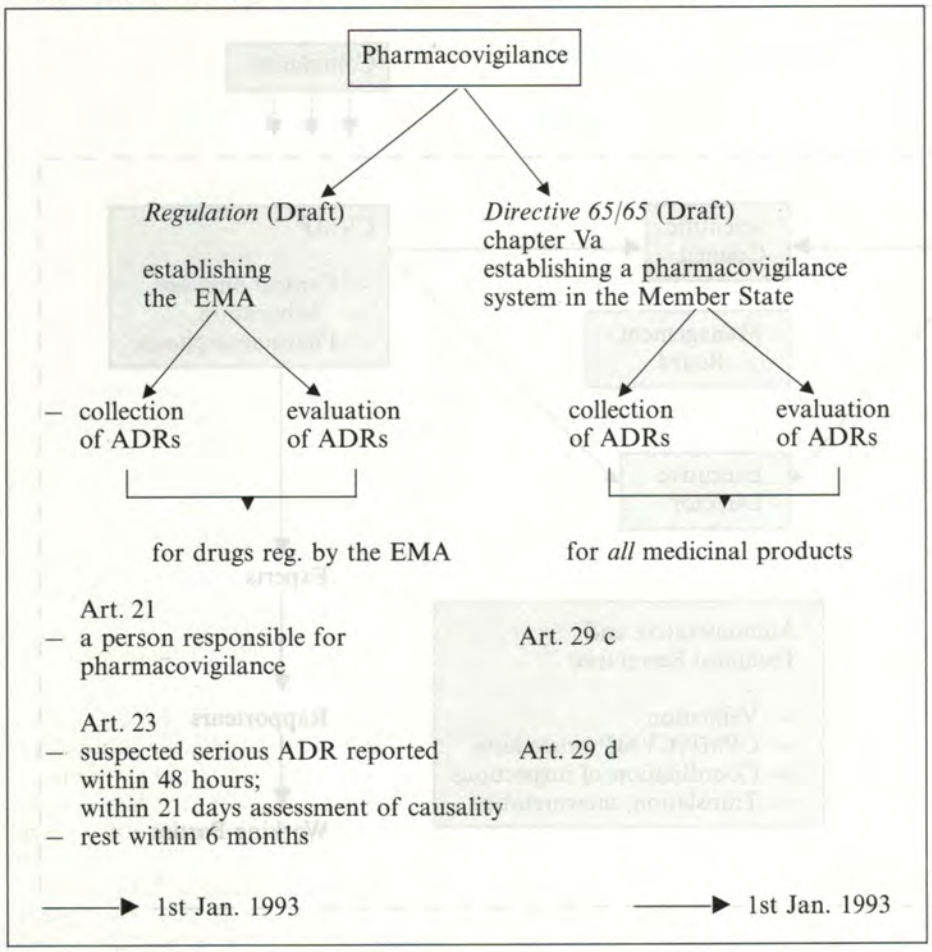
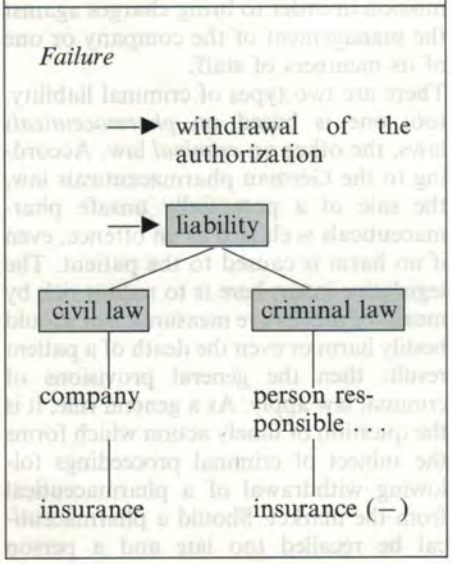


Table 10: Person Responsible for Pharmacovigilance.

Obligations Art. 29 c+d
- Collection of all ADRs (establish a system, that ensures . . .)
- ADR reporting to the competent authorities
- Additional information if necessary for evaluation



suffer harm in the meantime, then those persons responsible for the sale of the product according to the provisions of pharmacovigilance are likely to be accused of bodily harm through negligence or even bodily harm with intent, both of which carry severe penalties. This liability risk is by no means purely theoretical. There are a number of pending cases in Germany in which the Public Prosecutor is investigating whether representatives of the authorities or of companies are to face according criminal prosecution. One can well imagine the terrible mental strain caused by a lawsuit of this nature, as well as its effect on the career of a member of staff, especially when bearing in mind that criminal proceedings tend to drag on for so long, that Public Prosecutors do not generally have sufficient experience in assessing pharmaceuticals, and that legal disputes can often be very complex from a scientific point of view. So this raises the question whether general criteria can be drawn up according to the provisions governing liability, which can provide directives for representatives of the authorities or for those responsible for risk management in companies. Therefore, the well-known

Table 11: Liability – Pharmacovigilance.

Art. 9 Dir. 65/65
Authorization shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the person responsible for placing the proprietory medicinal product on the market

Art. 15 Draft Regulation
for establishing the EMA
The granting of authorization shall not diminish the general civil and criminal liability in the Member States of the manufacturer and, where applicable, of the person responsible for placing the medicinal product on the market

→ Civil Liability — Dir. 85/374 EEC

→ Criminal Liability — National

Table 12: Product Liability in Germany.

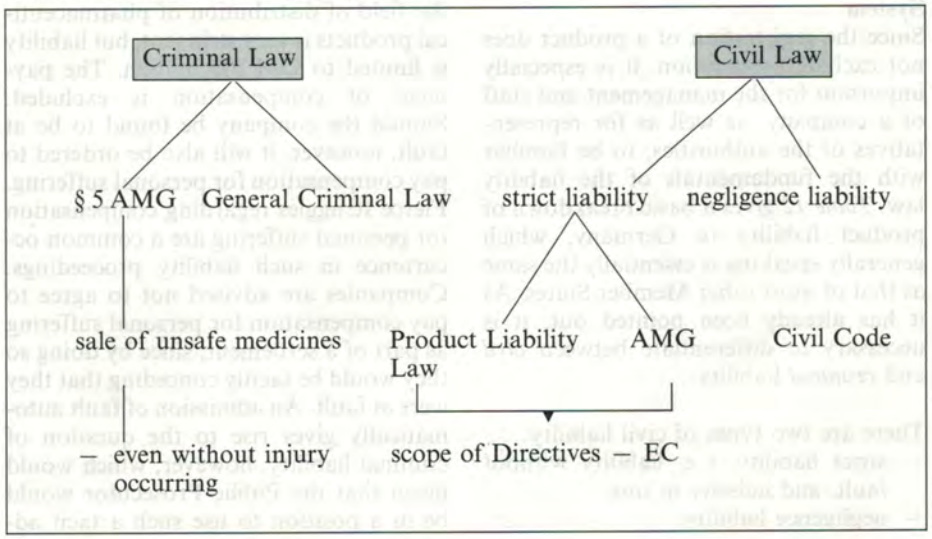


Table 13: Civil Court Aachen – thalidomide.

Criminal proceedings for causing death and severe bodily injuries – One area of dispute was whether fault was involved, especially the point at which the state of knowledge meant that the sale and marketing of thalidomide was negligent.
At what stage in the realisation of the causal relationship ought the manufacturer to have halted sales and marketing? → Criteria for evaluating the causal relationship between treatment with the product and physical injury → Criteria for evaluating the justifiability of risks

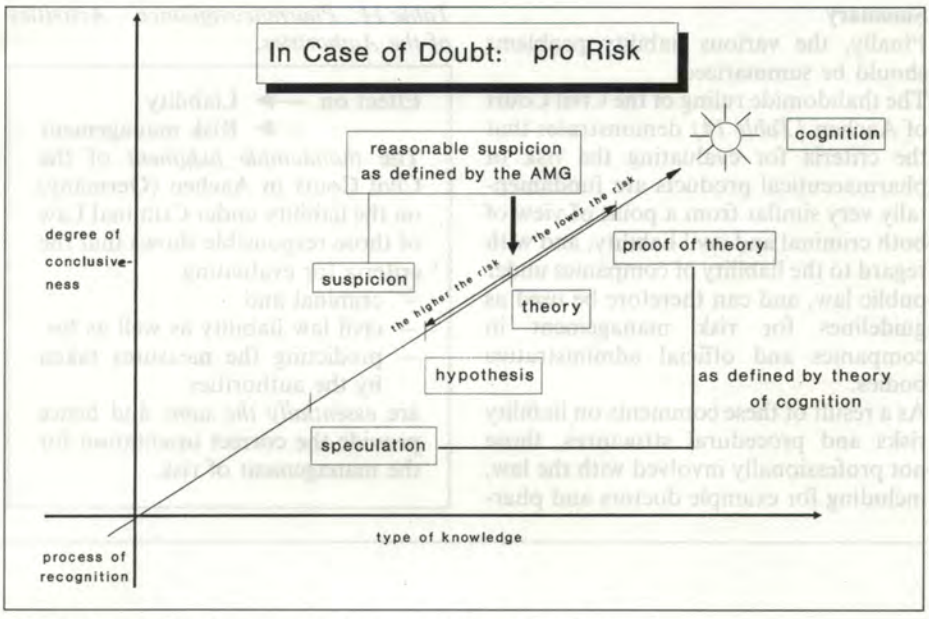


Fig. 1: Causality Assessment: In Case of Doubt pro Risk.

ruling on *thalidomide* by the Landgericht (Civil Court) of Aachen should be cited, in which significant criteria were drawn up which have subsequently been included in the legislation *(Table 13)*. The Civil Court of Aachen found that the responsible members of staff of a company act in a negligent manner if there exists a reasonable suspicion of unacceptable side effects of a medicament of which the sale is not stopped. It is not acceptable to wait until a side effect has been officially established. If a patient should suffer harm in the meantime, then the responsible person or persons can be accused of negligence.

This fundamental principle, derived from the general provisions of the law governing negligence, raises the question of which criteria can be developed for the evaluation of a causal connection between treatment and the occurrence of harm. In the following it is attempted to carry out a *causality evaluation* which can be applied generally and which could function as a directive and a preventive measure against liability risks *(Fig. 1, 2)*. Scientists are in a position to explain to the lawyers in clear terms how the present status of scientific knowledge regarding the causality of medicament risks can be assessed. But the question of when an authority or a company should take action, can no longer be judged on the basis of scientific criteria. Here it is the law, respectively jurisdiction governing fault, which is decisive. In Germany, this takes the form of the term *«reasonable suspicion»*. In order to find a first guideline, we can take the stage of formation of a theory as reasonable suspicion and thus as a first obligation to take action. Jurisdiction governing the right of technical security and protection against hazards has drawn up the following principle: the higher the risk, the lower the demands on the probability of occurrence. This means that when the risks are extremely high, the obligation to take action applies sooner, and when the risks are low, more time can be taken for evaluation and investigation.

If on this basis a reasonable suspicion of causality can be affirmed, then this is merely a first step in the process of full evaluation. An evaluation of the benefit and effectivity of the product must now be carried out, following which both factors have to be brought into proportion to one another. *Figure 2* shows that for the evaluation of a product's benefits, precisely the opposite principle applies. The higher the risk of a pharmaceutical product, the greater the demands on the evidence and extent of benefit of that product, in order to achieve a compensatory effect in the overall evaluation.

A mistake often repeated by medical experts, not only observed in Germany, is that they prove quite plausibly on the basis of scientific criteria that there is no evidence of causality. The conclusion they then tend to make is that there is no obligation to take action. The boundaries between legal and scientific criteria are intermingled to some extent here. The registration authorities can subsequently use such an opinion to the detriment of a pharmaceutical product or a company without contradicting the scientific evaluation of the expert concerned. The expert then suddenly finds himself in the unenviable position of key witness for the prosecution.

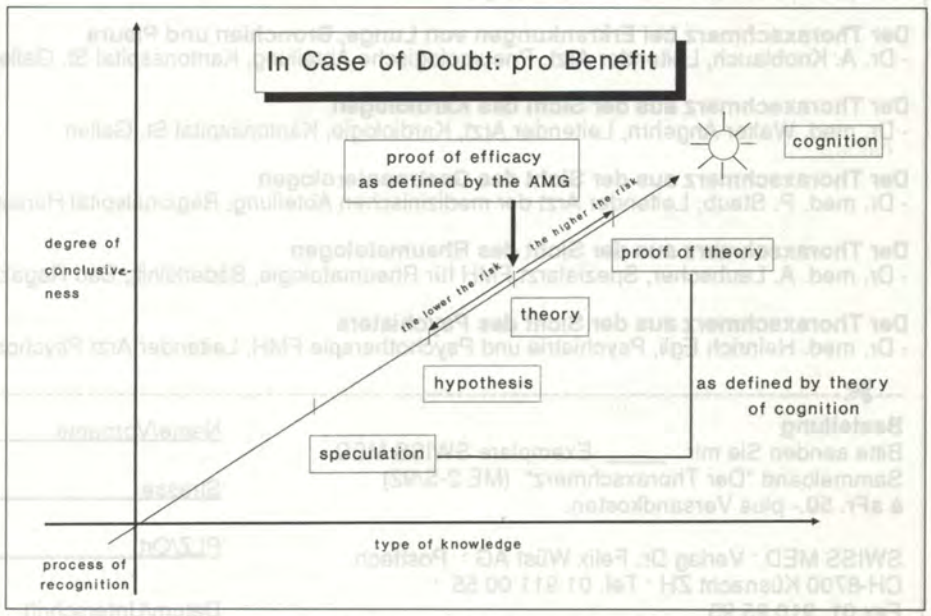


Fig. 2: Causality Assessment: In Case of Doubt pro Benefit.

Summary
Finally, the various liability problems should be summarized:
The thalidomide ruling of the Civil Court of Aachen *(Table 14)* demonstrates that the criteria for evaluating the risk of pharmaceutical products are fundamentally very similar from a point of view of both criminal and civil liability, and with regard to the liability of companies under public law, and can therefore be used as guidelines for risk management in companies and official administrative bodies.
As a result of these comments on liability risks and procedural structures, those not professionally involved with the law, including for example doctors and pharmacists, could well form the impression that the actual purpose of medical activity is being neglected: i. e. the well-being of the patient. It must therefore been emphasized that current liability provisions and jurisdiction have evolved from proceedings in which dissatisfied patients have claimed compensation, and this jurisdiction was the initiator for legislation concerning the registration of pharmaceutical products.
So it clearly must be the legitimate and important demands of the patient for optimum treatment at minimum risk, which are the decisive factors for deeds carried out on the part of doctors and the pharmaceutical industry, and that, of course, includes legal aspects. ■

Table 14: Pharmacovigilance Activities of the Authorities.

Effect on —▶ Liability
—▶ Risk management

The *thalidomide judgment* of the Civil Court in Aachen (Germany) on the liability under Criminal Law of those responsible shows that the criteria for evaluating
- criminal and
- civil law liability as well as for
- predicting the measures taken by the authorities

are *essentially the same* and hence provide the correct orientation for the management of risk.

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Editorial

Gen- und Biotechnologie beim Nutztier: Eine Informationstagung der Gesellschaft Schweizerischer Tierärzte (GST) für die Mitglieder des Schweizer Klubs der Wissenschaftsjournalisten
- J.-P. Siegfried, Arlesheim BL

Beiträge

Zur Entwicklung der Molekularbiologie: Ein Überblick aus veterinärmedizinischer Sicht
- H. Frey, Bern/Liebefeld BE

Allgemeine Einführung in die Gentechnolgie
- U. Hübscher, Zürich

Molekularbiologische Methoden in der Tierzucht
- G. Stranzinger, Zürich

Einsatz des DNA-Fingerprintings in der Tierzucht
- C. Gaillard, Bern

Zur Entwicklung des Gentransfers beim Nutztier
- G. Brem, München (D)

Biotechnologie, speziell Gentechnologie, in der Endokrinologie: Bedeutung für die Milch- und Mastleistung
- J. Blum, Bern

Gen- und Biotechnologie beim Nutztier: Gentechnologisch hergestellte Vakzinen
- M. Ackermann, Basel

Embryotransfer beim Nutztier
- K. Zerobin, Zürich

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