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"ASPECTS OF REGULATORY REQUIREMENTS IN INDUSTRIALIZED COUNTRIES"

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Abstract

Compliance with regulatory requirements of major foreign markets for health registration of pharmaceutical products is a continuing challenge for the multinational pharmaceutical company operating from the United States. Highligths of four sample countries, France, Germany and the U.K. are reviewed.

The topic "Aspects of Regulatory Requirements in Industrialized Countries" would be a good theme for a seminar of 3 or 4 days length. Certainly, there are enough issues, comparisons and contrasts to cover some 20 or more countries which might be dealt with in a meaningful way over the course of several days. First, one has to consider the subjective concept of which are the industrialized countries. Virtually all of Europe can be considered industrialized. Collectively, Europe is the largest pharmaceutical market. In South America, there are several countries that should be

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considered industrialized with a different regulatory atmosphere from Europe. In the East, Japan is second only to the U.S. as a pharmaceutical market and I'm sure no one would question that Japan is world unto itself in terms of regulatory atmosphere and unique concepts about protectionism of its domestic pharmaceutical industry. So for today's presentation, I have choosen to restrict the subject to few European countries - the UK, France, Sweden and Germany. France, Germnay and the UK are members of the common market or EEC (European Economic Community). While Sweden is not a member of the EEC, it has been influenced by EEC decisions, particularly through its trading relationship with EEC members such as Denmark. In fact, Sweden and Denmark as members of the Nordic council on Medicines have agreed to harmonize requirements, and thus Sweden is indirectly committed to EEC directives.

Since the conference is dedicated to manufacturing, quality control and pharmaceutical development, I'm sure you would be most interested in what is boardly termed chemistry/pharmacy requirements. Other disciplines involved in the business of complying with regulatory requirements are, of course, toxicology, pharmacology and the medical/clinical disciplines. Now that the topic is somewhat better defined, the following are my thoughts on the most important aspects of technical regulatory requirements, using the four countries cited as examples.

OVERVIEW

In stepping back from the day to day operations of multi-national pharmaceutical company based in the

U.S., it is obvious that successful execution of health registrations or marketing authorization abroad is a critical milestone in the development of new pharmaceutical products. (Health registrations or marketing authorizations are the international equivalent of U.S. NDAs). As evidenced by the growth of specialists in the industry who deal full-time with government relations or regulatory affairs, the process of achieving health registration is complex and growing more so every year. Compliance with regulatory requirements, especially for the multi-national pharmaceutical company is something that can not be left to chance. Indeed a vital aspect of the management of international pharmaceutical operations is the planning and successful execution of these health registration applications overseas.

Successful planning for health registration must begin in parallel with development of the new drug entity or new dose form in order to insure that regulatory requirements are met during the chemical and pharmaceutical development programs. The work considered technically adequate by the scientists in chemical process development, analytical labs, and pharmaceutical sciences may not be deemed adequate by the regulatory agencies. Planning for compliance with regulatory requirements should, as one of its goals, guarantee that the development program is conducted once to meet fundamental scientific as well as regulatory requirements. The ultimate goal of the regulatory planning process is efficient and timely health registration followed by introduction of the new product at the earliest prossible date. Failure to conduct this planning exercise in today's international regulatory environment represents a hap-hazzard

approach that will result in chaotic, uncertain product introduction schedules and inefficient product development, with the R&D group repeating some of the development work years after the initial program. Of course, this inefficiency is likely to be viewed by senior management as lost sales due to delayed introductions and the wasteful use of resources in repeating development work.

The cornerstone of the regulatory planning activity is knowledge of requirements in markets where product introductions are proposed. This knowledge is on two levels. First, the written requirements of each country are available as published regulations, decrees and guidelines. On a second level, there are certain unwritten or customary requirements that inevitably develop as extensions of broadly written, general regulations or guidelines. Of course, both the written and customary requirements differ from country to country, from one type of dose form to another. For the purposes of illustration, one or two examples of what is meant by customary requirements would be in order. The consolidated Nordic Guidelines published in November of 1983 covering the four Scandinavian markets, including Sweden, have only 3 sentences regarding data required for sterile parenteral products. Yet Sweden has a long standing history of regulatory opposition to sterile-filtered, aseptically filled parenteral drugs. The unwritten, customary requirement for Sweden is either terminally sterilize the product or include a thorough justification in your health registration application as to why the product can not be terminally sterilized. The justification must be more than a theoretical dissertation. It must include either documentation in the form of publica-

tions describing the effects of the means of terminaly sterilizing, such as autoclaving or gamma irradiation, or development work on the product should include an examination of the effects of these methods of sterilization on the dose form. Consistent with my earlier comments, this is the type of information to be included in planning for the development of a new product if you hope to avoid registration delays and a second round of development work.

A second example is from the United Kingdom, where there are excellent guidelines to the applicant. The guidelines instruct the applicant for a product license to report on impurities found with the drug substance. The guidelines define impurities and require that different methods of analysis for impurities be attempted. They do not tell you how many batches to test or report, or how many different methods of analysis to attempt. Most important, they don't tell you what point needs to be demonstrated by the report on impurities. Namely, it must be demonstrated that the synthetic process for the new drug is well under control and that there is a consistent pattern of impurities, or lack of impurities across a reasonable time period during which a reasonable number of full-scale batches have been made. In practice, impurity results should include an absolute minimum of three batches; five to ten batches are typically required to make a convincing case. Thus even in the UK with extensive guidelines, the minimum standards for registration are established in a dialogue between the applicant and regulatory agency.

Legal Basis

It was stated that the cornerstone for regulatory planning is knowledge of the regulations and guidelines

in the target markets; these represent minimum requirements that are supplemented over time by customary requirements. The legislative basis of these regulations in the four sample markets is presented below.

Legislative Basis
of Drug Regulation

U.K.	France	Germany	Sweden	EEC
Medicines Act 1968	P.H. Codes 1959 1967 1972	1976 Drug Reform Law	Drug ordinance 1962	1965 Directiv 65/65

What does this mean to the applicant for health registration? The current UK drug law has been in effect for sixteen years. The ground rules in terms of both written guidelines and customary requirements are well established. By contrast at the other end of the spectrum, there is a less settled situation in Germany. The reform law enacted in 1976, which took effect in 1978, greatly expanded the registration requirements in Germany, once considered a liberal country with respect to drug registration procedures. The staff of the regulatory agency in Germany, the BGA, has been expanded by more than 33%. Many of the new BGA staff people had no experience in either the pharmaceutical industry or pharmaceutical regulation. A new format with a 16 page application form serving as an index was instituted for applications. The BGA declined to issue guidelines until it could gain experience in dealing with the scientific issues resulting from the new law and regulations. Today, six years after the law took

effect, industry is still awaiting guidelines. In short, a period of trial and error followed from 1978 and the requirements for Germany are yet in a state of transition. In the meantime, fine tuning of the customary requirements continues on a trial and error basis.

For the countries cited, perhaps the legislation with the greatest potential impact was the EEC directive 65/65. The intent of this legislation was to eliminate barriers to trade in pharmaceuticals and cosmetics between EEC members. The legislation identified the major barrier as, and I quote the directive "...trade in proprietary medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products...". Some twenty years after this directive, the barriers still exist although they may have been eroded or in some cases cracked, by the political commitment of member states to the EEC. The real impact of directive 65/65 has been to set a minimum standard for drug registration to which all member states must adhere. Several directives followed 65/65 with respect to requirements for drug registration. In 1975 directive 75/318 established standards of physico-chemical testing for drugs and biologicals. While member countries were obliged to adopt these directives, they have had the effect of establishing a lowest common denominator for drug registration. In fact, in a country such as the UK, no substantive change in regulations were required since the minimum standards were already met. The barriers that currently exist are in the form of additional requirements that each member imposes and, in fact, there are numerous

disparities in these additional requirements, a few of which I will mention this morning. What the EEC wanted to achieve, but has yet failed to do is harmonize requirements. At best, harmonization is a goal that EEC members hope to work towards.

At the heart of this issue is the reluctance of local agencies to yield their judgement and authority to the EEC. Legislation went so far as to establish a supra-national agency, the Committee for Proprietary Medicinal Products (CPMP), to review applications from member states for general H.R. approval within the EEC. Since the directive establishing the CPMP in 1975, only a hand-full of applications have been processed (about 30 at last count) compared to the thousands handled by individual regulatory bodies. To quote Dr. Dukes of the Nederlands, a member of the CPMP "Mutual recognition means that a state abandons all control over its own drug market and follows blindly decisions taken by foreign agencies who may be dealing with different situations and have different interpretations of laws and guidelines." With a statement like this, it's understandable why member countries have failed to participate in a functional mechanism for the free exchange of pharmaceuticals across national borders within the EEC. In brief, EEC legislation had tremendous potential impact on the regulatory process in Europe, however, its actual impact has been measured in setting minimal standards in terms of drug manufacture, quality control and health registration.

GUIDELINES

Drug legislation is very broad in its language and provides little specific guidance concerning exact

requirements of the regulatory agencies. The applicant must rely on either published regulations having the effect of law, as found for example in the U.S. in the CFR, or guidelines which may not be the legal equivalent of regulations, but in practice are binding on the applicant. Lets take a look at the type of guidelines available from the countries I have selected.

Without question, the most specific guidance to applicants is provided by the DHSS in the U.K. These guidelines are available as a series of Medicines Act Leaflets or MALs. These cover subjects ranging from general explanation of the licensing system to specific guidance on packaging and labeling.

Three of the MALS of general interest are:

MAL-1 Guidelines to the Licensing Systems (1976)
MAL-2 Notes on Application for Product License (1971-1983)
MAL-41 Additional Notes for Guidance - Biological Medicianl products (1982)

Antibiotics are considered biologicals in the UK and are covered in MAL-41. Note that MAL-2 was first issued in 1971, a mere three years after the Medicines Act of 1968; it has been reissued about every two years, the current version issued in 1983. MAL-2 provides an item by item listing of required information, and explanation for each item and a commentary. These are the headings covered under chemistry/pharmacy requirements:

U.K. (MAL-2)

Part II - Pharmaceutical Data on Dosage Form

1.1 Description
1.2 Complete Formula
1.2.1 Active Constituents
1.2.2 Other Constituents
1.2.3 Overage
1.3 Containers
1.4 Formulations Used in Clinical Trials

2.1 Manufacturing Formula
2.2 Manufacturing Process
2.3 Assembling Process

3.1 Specifications of Constituents
3.1.1 Constituents Complying with Pharmacopoeial Monographs
3.1.2 Constituents Not in a Pharmacopoeia
3.1.3 Suppliers of Active Ingredients
3.2 In-Process Controls
3.3 Finished Product Specifications
3.3.1 Tests and Limits Applied
3.3.2 Analytical Methods

4.1 Formulation Studies
4.2 Analytical Development
4.3 Analytical Results
4.4 Availability Studies
In Vitro
In Vivo

(Continued)

U.K. (MAL-2) Cont'd

Stability

5.1 Batches Examined
5.2 Conditions of Storage
5.3 Containers
5.4 Results
5.5 Analytical Methods
5.6 Summary of Results
5.7 Proposed Shelf-Life
5.8 Label Storage Recommendation
5.9 Continuing Studies

6.1 Type of Container
6.2 Packaging Inclusions
6.2.1 Description and Composition
6.2.2 Duration of Performance
6.2.3 Instructions to Users of Products (Active)

7.1 Nomenclature
7.2 Description

8.1 Synthetic Route
8.2 Description of Process
8.3 Q.C. During Synthesis
8.3.1 Starting Materials

9.1 Evidence of Chemical Structure
9.2 Physico-Chemical Characteristics
9.3 Analytical Development

10.1 Impurities
10.2 Analytical Methods

(Continued)

U.K. (MAL-2) Cont'd

11.1 Tests and Limits
11.2 Analytical Methods
11.3 Reference Standard

12.1 Laboratory Reports
12.2 Discussion of Results

13.1 Stability of Active-Batches Examined
13.2 Conditions of Storage
13.3 Analytical Methods
13.4 Results Obtained

14.1 Metabolic Pathways
14.2 Measurement of Plasma Levels of Drug or Metabolites
14.3 Synthesis of Labelled Compounds

MAL-2 is unique as far as guidelines available in Europe. It is obviously thorough; twenty-one pages are dedicated to details of chemistry/pharmacy requirements and it has equally detailed guidance on toxicology, pharmacology, clinical and administrative matters. MAL-2 is useful as a planning guide or checklist when development of new compounds begin. Since it represents a highest common denominator for regulatory requirements in Europe, its very useful as a starting point for planning world-wide health registration.

Guidelines elsewhere in Europe are less explicit in describing the details of what should be contained in the application. For example, the guidelines for France are found in a Decree issued in September of 1978 covering general information and chemistry/phar-

macy requirements. In contrast to the UK, it provides a format and minimal guidance in terms of details required. Because of this, customary requirements play a major role in the French regulatory scene.

The format specified for chemistry/pharmacy dossier is divided into three sections:

"Partie Pharmacotechnique"

I Scientific Dossier
Properties of Bulk Drug
Galenical Section - Finished Product
Analytical Justification

II Technical Dossier ("Dossier Fabricant")
Manufacturing and Quality of Dose Form

III Analytical Expert's Dossier
A Critical Report Concerning all Items of the Technical Dossier, and Stability Studies.

Regarding the third item, the Analytical Expert Dossier, the use of experts or consultants by European regulatory bodies is widespread, but France and Germany have included an expert's opinion as part of the drug application. France, more than any other country, has institutionalized the expert. Not only is a seperate section of the French application devoted to the expert's opinion, but the French government lists recognized and approved experts. The applicant in France must choose from the list experts in chemistry/pharmacy, toxicology/pharmacology and clinical medicine to complete their respective sections

of the health registration application. The expert, a recognized authority in his field, is intended to serve the regulatory agency as an objective third party in the registration process although he is retained by the applicant. Many experts have academic affiliations, and in the case of the analytical expert they are expected to have access to independent laboratories to conduct testing on the product which is the subject of the application. The analytical expert comments critically on quality control and certain manufacturing aspects of the application. Emphasis is given to the appropriateness of the finished product specifications and test methods, the specifications for raw materials and the stability studies. The expert's job is expected to be more than a paperwork exercise. He has the option of either visiting the applicant's facilities to participate in q.c. testing and observe the manufacturing operations, or conducting testing on his own. Typically, the expert will perform all the q.c. release testing for the products and may select certain testing of raw materials. It is not uncommon for the expert to conduct limited stability work. Because of this mandated close working relationship between the applicant and expert, it is very difficult to imagine a French application for a new drug without local manufacture and development work, such as a local stability program.

The selection of an expert is an important part of the registration process. The reputation and prestige of the expert can make the difference between a blanket endorsement of his review by the regulatory agency or a critical review of the the applicant's dossier. This is particularly true in Germany where expert reports are required, but the government does not list approved

experts. Obviously, an opinion submitted by the applicant's q.c. director, who may act as the expert in

> composition including polymerizing residues, stabilizers, plasticizers and coloring agents shall be reported.

As an indication of this trend, Austria has a four page form requiring a detailed disclosure.

Among the information required by Austria is tradename, chemical name and percent composition for the following:

	Tradename	Chemical Name	%
A) Monomers			
B) Catalysts			
C) Emulsifiers			
D) Stabilizers			
E) Lubricants			
F) Fillers			
G) Plasticizers			
H) Others			

Providing this type of information is an increasingly difficult problem for exporters of pharmaceutical who often do not find plastic manufacturers willing to disclose this proprietary information to anyone, even foreign regulatory agencies.

Last in the review of guidelines is Germany. As stated earlier, Germany has not yet issued the equivalent of MAL-2 from the UK or the Nordic Guidelines. The German BGA has issued forms that

Germany, would certainly be viewed differently than a recognized independent authority such as a professor of pharmaceutical sciences from a university.

In Sweden, guidelines have been available since 1974 as the Registration of Pharmaceutical Specialities - Instructions for Submission of Applications, popularly known as the Blue Book. The Blue Book had a total of five pages dedicated to chemistry and pharmacy requirements, under headings similar to those found in the UK. The Blue Book was superceeded in 1983 by Nordic Guidelines, which was a cooperative effort by the regulatory agencies of Sweden, Denmark, Finland, Norway and Iceland. The Nordic Guidelines have expanded chemistry/pharmacy requirements to eight pages. A point of interest, which is a trend in recent years, in Europe, is detailed disclosure on plastics coming into contact with the product. Here are the requirements from the Nordic guidelines.

Nordic Guidelines 1983

C.3 Packaging Material

> Detailed information shall be given about the compositions and physical properties of plastics coming into contact with the product. The name of the material, name of manufacturer, chemical structure, physico-chemical properties shall be presented. Complete

organize the submission and itemizes topics to be covered, the substance of which does not differ from topics covered in the French and British applications.

There is one notable exception that is included in the Germany Drug Law. The new drug law requires that pharmaceutical excipients, in so far as they exhibit an activity of their own or the influence the activity of active constituents, must appear on all labeling. Thus the German application requires distinction between excipients used in the dose form according to inactive excipients and active excipients. Active excipients are classified as Active Pharmaceutical Aids, Pharmaceutical aids that are potentially hazardous for a high risk group and excipients that affect pharmacological activity.

Examples have evolved from the regulatory dialogue between the BGA and industry in each of these categories. For active pharmaceutical aids examples are anesthetics, all preservatives, any substance that alters the pH of gastric fluid or intestinal fluid, antioxidants, stabilizers, and chelating agents. High risk excipients are tartrazine, parabens, benzyl alcohol, sucrose (diabetics) and fructose (fructose intolerance). Examples of excipients considered to modify pharmacologic activity are substances used to retard the release of a drug and barriers for entirc coated tablets.

The Human Element

This review has covered the importance of planning, the legislative basis of regulation, guidelines, and items of general interest in the four European countries. It is important not to overlook what is certainly a very significant aspect and often the pivotal factor for success of health registrations in Europe, or for that matter, anywhere in the world. The

person managing the registration in each country, whether its a person dedicated to regulatory affairs, or part-time responsibility for someone such as the quality control manager or the medical director, is a crucial link in the development chain for new pharmaceutical products. The relationship of this individual with the local authorities, his ability to negotiate and advocate the company's position on controversial issues are essential elements for success in health registration. His role is that of both communicator and advocate. The registration manager who lives in the halls of the regulators inevitably has far greater success than the manager who conducts his business from the security of his office by correspondence. The former measures registration time in months; the latter in years.

CONCLUSIONS AND SUMMARY

Health registration is a goal that must be achieved as part of the successful development and introduction of pharmaceutial products. Careful planning is essential to efficiently and successfully achieve this goal. To be efficient means the pharmaceutical development program is performed once to meet basic scientific and regulatory concerns. To be successful, the product must not only be registered, but the registration must take place in a timely fashion. The basis of planning for health registration knowledge of regulatory requirement in the proposed markets. This knowledge is based on two elements. First published regulations and guidelines, available in varying degrees of detail, and second, customary requirements. Finally, an essential element in the successful development and introduction of new products is the local health registration manager who sets the pace for registration.