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WORLDWIDE REGULATIONS AND LEGISLATION; THEIR EFFECTS ON PHARMACEUTICAL PRODUCT DEVELOPMENT

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ABSTRACT

The pharmaceutical industry has become one of the most legislated and regulated industries in the world. The worldwide regulations although differing in scope and intensity all target on the pharmaceutical development, testing and manufacture of drug products. The impact of the constantly changing worldwide legislation and regulations is a primary concern.

INTRODUCTION

There are presently more than 90 countries around-the-world that require some type of regulatory approval before new drug products can be marketed for use in humans. Pharmaceutical companies in order to remain viable must expeditiously plan and conduct their research and development activities to deal with the constantly changing regulatory situations.

ETHICAL DRUG PRODUCTS

The most costly expenditures of the pharmaceutical industry in terms of both time and money are those research and development efforts necessary to bring new therapeutic entities to the marketplace. The total worldwide R&D effort for the U.S.-based multinational company depends on both the United States and the international regulatory attitudes concerning the research and development of specific therapeutic agents. The location and degree of research and development efforts worldwide are changing ones, depending on the most advantageous conditions

at the time drug research and development programs are being implemented. It is logical that R&D programs will be reassigned overseas for those drugs which are difficult to investigate in the U.S. A majority of the drug entities synthesized in the U.S. find their way first into overseas medical practice. There are several reasons for this:

1. Overseas health schemes encourage the practice of medicine that includes a wide variety of drug products; some of questionable therapy;
2. The national health services are good customers for generalized medications;
3. Regulatory authorities overseas are years ahead of the United States in approving certain classes of drug medication.

The worldwide regulatory agencies are steadily controlling the destiny of drug products. The regulations in the U.S., for example, reflect political as well as scientific attitudes that have not been substantially supported by overseas regulatory agencies.

Until 1970, most of the first drug administrations in man were conducted in the U.S. The percentage of first in man administrations conducted overseas has risen sharply. The legislation and regulatory climate in the U.S. and overseas is certainly responsible for this shift. The result is that more and more pharmaceutical interest and effort are being concentrated overseas in the preclinical, clinical and pharmaceutical development areas. This effort is reflected in an overseas rate of growth and sales which exceed the domestic performance of many multinational companies.

The most efficient new drug research and development program complies with the complex regulations of the most demanding countries while including those special studies needed to satisfy the specific regulations of the remaining regulatory countries. This type of program often permits the introduction of new products in the marketplace overseas several years before these data are approved in the United States.

The world pharmaceutical markets ranked in order of drug sales are: first the United States, then Japan, followed by West Germany, France, Italy, Spain, Brazil, and the United Kingdom. The regulations in these particular countries are critical to the worldwide R&D effort since the overseas growth rate of prescription and veterinary pharmaceuticals is about 12 percent per year, or about twice that of the U.S. rate of growth. The First Table lists the major worldwide markets, first for Europe and then for the remainder of the world. The regulations concerning the acceptability of R&D data generated in countries other than that where the product is being registered are shown in this table. Acceptability of these "foreign data" are important to the location of the total R&D preclinical, clinical and technical program for pharmaceutical products intended for worldwide utility. France, Italy, and Japan are so restrictive in their internal regulatory requirements that most of the "foreign" R&D effort needs to be repeated

TABLE I

Foreign R&D Studies Accepted

COUNTRY	PRECLINICAL	CLINICAL	TECHNICAL
Belgium	Yes	Yes	Analytical data not accepted
Brazil	--	Acceptable if published	--
Canada	Yes	Yes Local trials usually required	Yes
W. Germany	Yes	Local trials may be required	Yes
France	Only experts approved by Minister of Public Health can conduct French trials.		
Italy	-- Yes/No	Published "foreign" data O.K. Local trials usually required	-- Yes/No
Japan	Yes/No	No	No
Mexico	--	Acceptable if published	Stability data not accepted
Spain	Yes	Local trials usually required	Yes
Sweden	Yes	Yes (Qualified)	Yes
United Kingdom	Yes	Yes Local trials usually required	Yes
U.S.A.	Yes/No	Local trials usually required	Yes

locally. The U.S., until recently, was in this same listing. The inclination of the U.S. Regulatory Authority to pronounce favorably on "foreign" preclinical and clinical data are still being evaluated. The Japanese Ministry of Health and Welfare (MHW) have recently considered regulations concerning the acceptability of foreign data in new product registration in Japan. There appears to be some agreement concerning the acceptance of "foreign" preclinical data but none in the clinical and technical areas at this time. At present, Sweden, The United Kingdom and Canada are able to utilize to the fullest extent R&D data developed elsewhere. Their own internal regulatory requirements must, however, be adequately programmed, researched, and documented into these "foreign" data before local regulatory approval is given.

International pharmaceutical regulations have been in existence for many years. Legislation to control physician and apothecary malpractice in Europe dates

back to medieval times. Concerning present day drug regulations, Table Two lists the year when the current regulatory legislation became effective in the major overseas markets. Several of these dates reflect major revisions in the existing regulations. The date when significant regulations are expected is also given. Several of the countries require a periodic reregistration of already approved drugs. This requires an updating of previously approved submissions with the latest preclinical and technical information as well as the latest clinical experiences found during the therapeutic use of the drug. The time, in months, required to register a new drug is shown. At present, between six months to three years time elapses between the official registration approval for the countries listed. Two reasons for this timing differential are: (1) The lag-time between lodging the application and the final consideration by the registering authority; (2) The necessity to repeat, locally, R&D studies that have already been completed elsewhere. The length of

TABLE II

STATUS - OVERSEAS REGULATORY LEGISLATION

Country	Current Laws Effective	New Laws Expected	Period (In Yrs.) Registration Granted	Time (In Mos.) To Register New Product
Belgium	1969	1977	5	6
Brazil	1954	--	Unlimited	6
Canada	1953	--	Unlimited	4-12
W. Germany	1961	1978	5	12-(36)?
France	1959	1976	5	6
Italy	1934	Continu-ously	Unlimited	24-36
Japan	1960	--	Unlimited	12-36
Mexico	1973	--	Unlimited	4
Nether-lands	1958	1977	Unlimited	6-12
Spain	1963	1975	3-5	12-24
Sweden	1964	--	Unlimited	24
United Kingdom	1968	1976	5	9

time for regulatory approval of a new drug application by comparison in the U.S. is now estimated at 23 months.

There are several extranational agencies that have now, or will have in the future, a significant role in the approval and regulation of drugs. The most important for the future in Europe is the European Economic Community (EEC). The EEC Council of Ministers has issued directives that include minimum regulatory acceptance standards for the nine members who comprise the European Economic Community. These nine members include: Belgium, Luxembourg, The Netherlands, Denmark, United Kingdom, Ireland, Italy, France and West Germany. Entrance of Greece into the EEC is under consideration. The pharmaceutical directives provide for the free movement of "branded" pharmaceutical products within the member countries of the EEC. This means that pharmaceutical products approved in any one of the EEC countries will be excluded from further regulatory examination for marketing in

the other eight countries. This is an idealistic situation at present. It is doubtful that the U.K., for example, would compromise its efficacy and safety requirements, or that Belgium would renounce its antibiotic overage regulations which are the most rigorous in the world. They would surely impose their own regulations on member country approved drugs that do not meet their rigid internal requirements. France has always required that French Visa or registration experts should conduct major preclinical, clinical, and technical trials within the country, even for products approved in other countries. A limited number of international research organizations, such as the Huntingdon Research Centre in England, are now producing acceptable data for France, since French approved experts are on the staff to certify the acceptability of the data for French Visa consideration.

It appears that these EEC Directives, which are being implemented in November 1976 will provide

the basic acceptance standards. The member countries will then include their own additional requirements for approval. The EEC regulatory impact on the pharmaceutical industry within Europe should become obvious in the near future. According to the EEC second Directive a drug product approved for marketing in a less demanding EEC country can now be submitted for marketing approval in five or more other member countries. Within a 120 day time limit the countries selected must indicate approval as is or disapproval with recommendations for further studies and/or data.

The European Free Trade Area (EFTA) Organization also has promulgated legislation concerning pharmaceutical products. EFTA is composed of: Austria, Finland, Iceland, Liechtenstein, Norway, Portugal, Sweden and Switzerland. Although Denmark and Britain have left EFTA for the EEC, they still are members of the EFTA Pharmaceutical Inspection Community. EFTA has recently agreed that regulatory data should be prepared according to a standard drug test certificate

to avoid time-consuming duplication of registration activity within the member countries.

The World Health Organization (WHO) has a widespread scope of regulatory activity. It exchanges knowledge and practical experience with the public health and medical professions of more than 140 countries. The WHO issues directives and guidelines covering a wide range of pharmaceutical and medical disciplines. The main objective is to develop norms and protocols leading toward unified systems that will ensure quality, safety and efficacy of drug substances. The WHO guidelines serve as a basis for many developing nations who cannot manage a complete drug approval system. Major countries, like Australia, Japan, Sweden, and West Germany, use the WHO Technical Reports as guidelines in drug evaluation. In order to assure drug quality in the "developing" countries, the WHO recently declared that drug exports should include a certificate showing that the drug is authorized for sale and the manufacturing plant has been inspected and approved

in the exporting country. The WHO is also active in monitoring and reporting adverse reactions. Through the World Health Organization, there are many countries now engaged in this reporting. Several countries, in turn, publish either quarterly or yearly lists of adverse drug reactons and among these are Sweden and the United Kingdom. The WHO are now active in assisting developing and third world countries in formulating and implementing national drug policies. This will enable the developing countries to have an effective regulatory control of drugs whether produced locally or imported.

Most major international markets, such as, Australia, France, Italy, Spain, Sweden and The United Kingdom, are controlled by National Health Insurance plans. The government is, therefore, the ultimate buyer of the new drug product. As the ultimate buyer, the government can impose formulation restrictions such as reimbursing only ready-made products since reconstituted products require an additional pharma-

cist compounding fee which the government often refuses to pay. There is, in addition to the variety of worldwide legislation and regulations, a broad time span for regulatory approval and reimbursement. This time span is an important consideration in product development since products are not marketed until government approval is given. The "me-too" type products often fail to receive government approval. Price negotiations are often a factor in gaining acceptance to the price-approved list of permitted drug products for compensation. Countries often use price negotiation as a method to minimize their "free medicines" lists.

The U.S. is still the world's largest free market for pharmaceuticals, followed in second place by Japan. Table Three lists the countries beginning with Japan in their decreasing rank of marketing importance. This listing has an important bearing on the development program for drugs intended for international markets. The first column indicates

TABLE III

SIGNIFICANT TECHNICAL REQUIREMENTS

Country	Approved Color List	Fixed Excess Limits	Impurities Declaration	"Foreign" Stability Data Accepted
Japan	Yes	Yes	Yes	No
W. Germany	No	No	Sometime	Yes
France	Yes	Yes	Yes	No
Italy	Yes	Yes	Yes	Sometime
Spain	Yes	Yes	Yes	Yes
Brazil	Yes	Yes	Yes	Sometime
United Kingdom	No	No	Yes	Yes
Mexico	No	Yes	No	Sometime
Argentina	Yes	Yes	Yes	Yes
Belgium	Yes	Yes	Yes	Sometime
Canada	No	Yes	Yes	Yes
India	Yes	Yes	Yes	No
Netherlands	Yes	Yes	No	Yes
Sweden	No	No	Yes	Yes
Australia	Yes	No	Yes	Yes

whether approved color lists have been issued in the indicated countries. The second column lists countries with regulations covering fixed overage limits for the active drug substance. Belgium has overage regulations

for antibiotics that limit the excess at the time of manufacture to not more than 115% of the labelled amount of the antibiotic substance and at not less than 100% of label at outdate. Very short outdatings for labile antibiotics are the result of this Belgian regulation. The next column illustrates countries where impurities must be declared. The U.K. authorities impurities requirement was responsible for the development of the sophisticated international analytical procedures during the early seventies. This methodology is now the standard around the world. The acceptance of "foreign" stability data is shown for 15 countries in the last column. Where "foreign" data are not accepted, local stability studies are required.

The last table is a composite list of the technical requirements for a worldwide pharmaceutical product. If these requirements are incorporated in the Chemical/Pharmaceutical/Analytical development programs and the results fall within the most rigid regulatory limits, the product from this standpoint

TABLE IV

COMPOSITE WORLDWIDE REGULATORY IND/NDA TYPE
CHEMICAL-PHARMACEUTICAL DATA REQUIREMENTS

Bulk Drug Substance
A. Synthesis* 1. Flow Diagram, Process Description, Stressing Purification & Crystallization 2. Proof of Structure-M.S., N.M.R., I.R. 3. Raw Materials and Specifications 4. Isomerism, Polymorphism, Hydrates 5. Particle Size 6. Bulk Specifications & Impurity Limits 7. Residual Solvents
B. Impurities 1. Possible Impurities & By-products 2. Methodology for Separation, Detection & Estimation 3. Identification & Limits in Finished Bulk
C. Batch Analysis Data 1. Batch Size & Date of Manufacture 2. Typical Batch Analysis 3. Batch Disposition (Toxicology, Stability, Clinical)
D. Stability Data 1. Storage at Three Temperature Stations 2. Three Lot Stability Program 3. Analytical Results 4. Degradation Observation

Formulated Drug Product

A. Formulation*

1. Complete Quantitative Formula
2. Overages or Excesses of Active Drug(s)
3. Method of Manufacture
4. Specifications for Excipient(s)
5. Specifications for Formulated Product
   a. Specific Identity Test Drug Substance(s)
   b. Specific Identity Test Excipient(s)

B. Stability Data

1. Storage at Three Temperature Stations
2. Three Lot Stability Program
3. Analytical Results
4. Degradation Observations

*Sterility Criteria Required Where Indicated

will be approved in the 90+ regulatory countries. Explicit documentation of the synthesis purification and crystallization steps are Commonwealth country requirements, along with a description of primary synthesis intermediates. Dissertations concerning potential isomerism, polymorphism and hydrate formations need to be included in the synthesis section. Impurity identification and limits in the bulk drug substance are a common requirement in countries with sophisticated regulations. Impurity levels greater than 2% often require toxicity profiles. Formulation aspects that must be considered include identity tests for excipient ingredients as well as the drug substance. Methods for detecting and quantitating degradation products during the products active shelf-life are becoming more prevalent.

There is increasing international regulatory concern about the microbiological purity (or contamination) of pharmaceutical preparations.

Sweden has been active in this area for some time. There are various degrees of microbiological purity considered for pharmaceutical products. These pharmaceutical products may be classified into four categories.

The first category is universal - injectable products which must be sterile. The second category includes ophthalmic products and topicals that are applied in areas normally free from organisms and those intended for use on burns and severe ulcerations. These products should be free from "revivable" organisms. The third group are the topical preparations applied to the skin or on lesions in the nose, throat, and ear. Here the limit level might be 100 revivable microorganisms per gram or milliliter with no enterobacteria, pseudomonas aeruginosa or staphylococcus aureau organisms present. The remaining category would include all remaining pharmaceuticals. This category would include all third category limit levels of revivable microorganisms and in addition have limits

on aerobic bacteria, yeasts and molds. In addition there should be no. E. Coli or salmonella organisms present. It is difficult to predict with certainty any regulatory decision concerning this controversial category.

Formulation ingredients should therefore be relatively free of microorganism contamination. Organism multiplication should be restricted during the shelf-life of all products. The selection of ingredients and preservatives that are acceptable within the increasing regulatory restrictions certainly presents pharmaceutical development with additional problems.

PROPRIETARY MEDICINAL PRODUCTS

Proprietary medicinal (O.T.C.) products are also under increasing regulatory review in various parts of the world. The Canadian Ministry of Health and Welare (M.H.W.) now requires that O.T.C. medications be registered with the Canadian Food and Drug

Directorate. Products containing laxatives, systemic bromides, antihistamines, analgesics and sympathomimetic amines are some of the initial products under review. The EEC Directives concerning proprietary medicinals adopted in 1975 will be implemented into law by 1977. These directives will assure that uniform analytical, pharmaco-toxicological and clinical testing are performed throughout the member states. Several countries including the U.K. and Japan have reevaluation and relicensing programs for the O.T.C. products.

COSMETIC PRODUCTS

There has been considerable regulatory activity in the area of cosmetic formulations. The Canadian Health Protection Branch (H.P.B.) has proposed extensive cosmetic regulations. The Canadian regulations prohibit the use of coal tar dyes in products applied near the eye. The H.P.B. has also restricted cosmetic products containing estrogenic substances to a prescription only basis.

The Council of European Community Cosmetic Directives first proposed in 1972 will be implemented into law in 1978. These EEC Cosmetic Directives are calculated to remove technical barriers to the exchange of cosmetic products within the member countries. Many of the currently used cosmetic formulation ingredients in these countries will be delisted when safety substantiation data are evaluated.

VETERINARY PRODUCTS

More than 80 of the 90 countries with ethical regulations also require regulatory approval fornew drug products intended for use in animals. The Netherlands and South Africa have proposed veterinary product regulations, the effective date of enactment is still to be announced. Virtually all of the registering countries require regulatory documentation of the formulated product. Extensive supporting documents,

e.g. Certificate of Free Sale, Price Certificates, Certificates of Analysis, and registration supplies are also requirements of the regulatory system. The quantity of R&D data required in an investigational new drug submission in an animal health product can be as extensive as that required for human products. In addition the veterinary products intended for meat producing animals requires documentation on tissue residues. Many countries including the EEC have also prepared directives or legislation concerning medicated feeds and growth promotion substances.

The regulatory climate for veterinary products is changing. There is a growing safety awareness of veterinary products. Since the target species can be observed for safety, more direct and meaningful evaluations can be made. The safety of the consumer of the animal product is measured against residues of the chemical substance remaining in edible animal tissue when consumed. The safety of the handlers at the factory where fabricated, at the food mill

where mixed and on the farm are added considerations. The ultimate effect of the environment must also be considered since pastureland may become contaminated with spilled feed stuff and fecal matter. The formulation of veterinary products is therefore further restricted by the active drug substance characteristics in both the formulation and the target animal species.

The time needed to produce adequate veterinary documentation data for regulatory approval has been increasing along with the escalating R&D costs. These costs are now averaging between 5-20 million dollars for the U.S. formulated R&D veterinary products. There is a growing concern that the research and paperwork required for veterinary regulatory approval will increase to the point where only the large multinational companies survive. Consequently, the numbers of new veterinary chemical entities reaching the market place have diminished. There were 40 new poultry products introduced in the U.S. in the

years 1950-1960. During the 1960-1970 period there were only 23 poultry products introduced. Since 1970, there has been only one new drug, a coccidiostat offered to the poultry trade.

CONCLUSIONS

It is evident from regulations and legislation in effect both now and anticipated in the future that the development of future pharmaceutical products will depend to a large extent on forces beyond the control of the pharmaceutical formulator. This is not to say that external regulation and legislation is all bad. The U.K. still serves as the example for rational scientific reasoning with respect to the approval of new drug products in all drug categories. The Medicines Act in the U.K. has established a scheme for new drug submissions that often serves as the world standard. The act itself, and the regulations established, permits more industry input. The result has been fewer volumes of more meaningful data needed for a more rapid registration approval. There is a reliance on education

rather than regulation to guide the proper utilization of the drug. The regulations also provide for an efficient post-marketing drug surveillance system. Under this system, during the years 1962-1972, four times the number of drugs in nine therapeutic categories were available in the U.K. when compared with the U.S. Britain gains from the less restrictive regulations leading the approval of drugs for marketing and the more positive programs of post-marketing surveillance.

What about the future concerning regulations and legislation that will affect the development of drugs for international markets? They will probably continue to be promulgated in three main categories:

1. Those dealing with the development of drugs, particularly their safety and efficacy;
2. Those dealing with the costs of drug products and their components and the prices established for the marketed product;

3. Those dealing with fiscal matters such as the registration procedure, taxes and customs duties.

We can expect the multinational pharmaceutical company research efforts will continue to spread throughout the world with the developing countries receiving the major thrust. There will be fewer but larger multinational companies operating under more unified worldwide regulations.

The future for growth in the pharmaceutical industry is therefore predicated upon two basic factors:

1. The productivity of research and development;
2. The ability to interact favorably with the regulatory authorities around-the-world since the pharmaceutical industry is one of the most legislated of all industries.

These two factors are closely related since the R&D effort is most productive in a compatible regulatory climate. The paramount objective of R&D will continue to be the development of useful, safe and efficacious

products for the health care of the world. Conflict develops when the regulatory climate becomes overly political and socioeconomic rather than scientific. The international regulatory climate still favors a strong R&D effort with no undue restrictions in evidence among the major overseas governments.