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Recent Regulation for Control of Marketing Authorization in Multisource pharmaceutical Products

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ABSTRACT

The primary purpose of the rules governing medicinal products is to safeguard public health. However, this objective must be achieved by means which do not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community. The Marketing Authorisation Holder (MAH) of a medicinal product is responsible for the quality, efficacy and safety of its products. The marketing authorization procedure includes an assessment of a dossier, in which the future marketing authorization holder (MAH) evidences the safety, efficacy, and quality of the product. Furthermore, the indications, contraindications, dosage of the product, general classification for supply, as well as the package leaflet for the patient and proposed texts on the labelling of the medicinal products are assessed. The Summary of Product Characteristics (SPC) forms part of the marketing Authorization. It serves as the key source of information about the medicinal product for doctors and healthcare professionals. Generic medicines are those where patent protection has expired, and which may be produced by manufacturers other than the innovator company. Use of generic medicines has been increasing in recent years, primarily as a cost saving measure in healthcare provision. Generic medicines are typically 20 to 90% cheaper than originator equivalents. As the Pharmaceutical industry is expanding by leaps and bound no single country is capable of manufacturing all the drugs in required quantities at competing prices. Hence the Marketing Authorizations has become an essential part of Global Healthcare. Till sometime back Marketing Authorization procedures were country specific. The present study describes a brief review of Marketing Authorizations in various countries and regions around the world (WHO)..

Keywords: Summary of Product Characteristics, Marketing Authorisation Holder, Safety, Efficacy.

INTRODUCTION

Introduction to regulatory affairs in pharmaceutical industry

Introduction to regulatory affairs

Regulatory Affairs(RA), also called Government Affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory Affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods). Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals. The success of regulatory strategy is less dependent on the regulations than on how they

are interpreted, applied, and communicated within companies and to outside constituents.

This department is responsible for knowing the regulatory requirements for getting new Products approved. They know what commitments the company has made to the regulatory agencies where the product has been approved. They also submit annual reports and supplements to the agencies. Regulatory Affairs typically communicates with one of the Centers (e.g., Center for Drug Evaluation and Research) at the FDA headquarters, rather than the FDA local district offices. Gimps do not directly apply to Regulatory Affairs; however, they must understand and evaluate changes to drug manufacturing and testing activities to determine if and when the FDA must be notified.

Importance of regulatory affairs

In today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence the company's success. The proper conduct of its Regulatory Affairs activities is therefore of considerable economic importance for the company.

Inadequate reporting of data may prevent a timely positive evaluation of marketing application. A new drug may have cost many millions of pounds, Euros or dollars to develop and even a three-month delay in bringing it to the market has considerable financial considerations. Even worse1 failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall. Either occurrence may lead to the loss of several millions of units of sales, not to mention the resulting reduction in confidence of the investors, health professionals and patients.

A good Regulatory Affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific endeavor with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources. The Regulatory Affairs department is very often the first point of contact between the government authorities and the company. The attitudes and actions of the Regulatory Affairs professionals will condition the perceptions of the government officials to the company for better, or worse Officials respond much better to a company whose representatives are scientifically accurate and knowledgeable than to one in which these qualities are absent.

The importance of the Regulatory Affairs function is such that senior Regulatory Affairs professionals are increasingly being appointed to boardroom positions, where they can advise upon and further influence the strategic decisions of their companies.

Responsibility of Regulatory Affairs Professional's

The Regulatory Affairs professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products. They also advise on the legal and scientific restraints and requirements, and collect, collate, and evaluate the scientific data that their research and development colleagues are generating. They are responsible for the presentation of registration documents to regulatory agencies, and carry out all the subsequent negotiations necessary to obtain and maintain marketing authorization for the products concerned. They give strategic and technical advice at the highest level in their companies, right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development program and the company as a whole.

It may take anything up to 15 years to develop and launch a new pharmaceutical product and problems may arise in the process of scientific development and because of a changing regulatory environment. Regulatory Affairs professionals help the company avoid problems caused by badly kept records, in appropriate scientific thinking or poor presentation of data. In most product areas where regulatory requirements are imposed, restrictions are also placed upon the claims which can be made for the product on labeling or in advertising.

PROVISIONS AND PREREQUISITES FOR REGULATORY CONTROL

Political will and commitment:

No DRA will be successful in implementing these guidelines if it does not have full and continuing government support, even when the government changes.

The government must provide:

1. Clear, firm, and equitable legislation that addresses all the relevant issues and carries appropriate sanctions for violations (see Annex 1);
2. Support in the form of financial and other resources that are commensurate with the designated functions, particularly in relation to staffing and the resource needs for the

GMP inspectorate and quality control laboratories;

3. Advocacy in the political arena, and particularly a willingness to defend decisions and policies which may be unpopular with vested interests but which are to the benefit of public health;
4. Support when legislated sanctions are imposed for violations of legislation.

- The relevant political authority is usually the Minister for Health but may be a person or persons under a different title, depending on the country's legislative system.
- The appropriate level of financial support depends on what functions the government intends the DRA to undertake. If an authority is expected to review only *well-established drug products,* not products containing new chemical or biological APIs, and to rely mainly on decisions made by DRAs in other countries, it would be reasonable for financing to be sufficient for only these functions, with further allowance for the evaluation of interchangeability and of locally developed and manufactured products. More extensive responsibilities would require additional resources. A system of fees for evaluation of applications and subsequent *retention fees* to maintain the marketing authorization is one means of recovering costs and is further discussed below.

The budget should be subject to adjustments according to the resources required for the DRA's functions as they evolve.

A number of decisions of principle must be made by government at a very early stage (see particularly Part II "Rational selection of drug products", and Part IV "Initial decisions on options for premarket evaluation").These decisions should be issued in writing, and should not be changed so often that a coherent and consistent approach becomes impossible.

Legislation

The minimum provisions required for national drug regulatory legislation are set out in the guiding principles reproduced as Annex 1.

Accountability

Accountability means being required to account for one's conduct and actions, usually to an individual or group but ultimately to the public. Both individuals and organizations may be accountable. There is some overlap between accountability and *transparency.*

Because the field of medicines is highly commercialized, it is characterized by extreme pressures on the DRA and by intensive lobbying from stakeholders at many levels. A system of accountability is essential in managing these tensions. A DRA is usually accountable to an individual official, such as the Minister for Health, or to a body, such as the parliament.

Mechanisms for ensuring accountability include:

- A requirement to provide public reports on a periodic (e.g. annual) basis;
- Publication of decisions, processes and policies;
- A mechanism for appeals against DRA decisions;
- A procedure for complaints about the actions of the DRA and the conduct of individual staff;
- A code of conduct describing the behave our expected of DRA staff;
- Regular presentations at government hearings;
- Formalized mechanisms for consulting independent experts;
- Public hearings on new policies, or on applications to register new pharmaceutical products or products containing new APIs. It should be borne in mind that public hearings can be expensive and time-consuming;
- Electronic publication of information about the DRA;

It is not necessary to implement all the mechanisms. The appropriate mechanism(s) will depend on the local context, but should be defined and recognized by the government and the DRA in published documentation.

Resources for the marketing authorization function

Definition of responsibilities

As noted above, ultimate responsibility for the marketing authorization function lies with the country's government.

The minimum necessary activities are as follows:

- Establishing and maintaining an inventory of the products available on the local market;
- Premarket evaluation of new products:
- Ensuring that a complete data-set on quality is available;
- Evaluating, as appropriate, either data on quality or relying on a WHO-type certificate (see glossary and Annex 2);
- Ensuring that newly authorized products

containing well established drugs are interchangeable (as defined in Annex 3) with locally marketed products, and that the approved product information is accurate and locally useful;
- Issuing a written marketing authorization (or rejection) on completion of the assessment process.
- Evaluating applications to make changes to product information and to pharmaceutical aspects of existing marketing authorizations;
- Noting possible breaches of legislation and referring them to the investigatory arm of the DRA.

In addition to marketing authorization activities, DRA staff may be given responsibilities such as promotion of rational drug use, provision of drug information, control of company promotion, monitoring of adverse drug reactions, publication of information on pharmaceuticals (e.g. a newsletter), and studies of drug utilization to enhance rational drug use and assess the impact of regulatory decisions. In some countries, the cost of a product may be a consideration in reaching a decision on marketing authorization. As already indicated, resources provided to the DRA for performing marketing authorization activities should be consistent with the defined responsibilities.

OPERATING ACTIVITIES

Transparency

Transparency means (1) defining policies and procedures in print and publishing the printed documentation, and (2) giving reasons for decisions to the party concerned. DRAs should adopt a policy of transparency because it is the simplest and most efficient way of conducting business. While the circulation of some documentation may need to be restricted, for example during policy development, the majority of finalized written documents (and particularly those concerning policy and administration) should be made available to DRA staff, the pharmaceutical industry, the parliament and the general public. DRAs with limited resources may achieve cost savings by posting their guidelines on the Internet.

Transparency has these advantages:
- Applicants and the DRA do not spend time trying to clarify each other's policies and attitudes.
- Staff within the DRA do not spend time determining what their own agency's policies are ("reinventing the wheel").
- Communication at all levels is facilitated if each party understands the other's starting point for discussions.
- Terminology is defined in policy documents so that the parties use the same terms to mean the same thing.

Transparency also means giving reasons for decisions. For example, letters rejecting applications should include reasons for the decision.

Policies

General policy should be documented and published. Policy documentation may specify, for example:

- Situations in which data on bioequivalence are required;
- Whether and under what circumstances evaluation reports prepared by another DRA will be accepted;
- Which fixed-dose combinations are considered rational, safe and effective.

The advantage of such "in principle" policies is that decisions on individual applications become easier and less time-consuming.

Administrative procedures

Administrative procedures should be documented and published. Correspondence and data are far less likely to go astray when clear procedures are in place. It is particularly important that all DRA staff have copies of administrative documentation and understand their own role in the procedures.

If pharmaceutical companies have access to the written administrative procedures, they will better understand how to submit applications, whom to contact when they have questions, and how to respond on receipt of correspondence. When they have an inquiry, they can ask more precise and sensible questions. The industry and DRA staff should be informed of the appropriate lines of communication.

Guidelines for applicants

In keeping with a policy of transparency, the DRA should publish guidelines on the data to be provided with the different types of applications. It is not necessary to write a completely new guideline

when several such documents exist worldwide. The simplest approach is to adopt the content and format of an already existing guideline, such as that of Canada, the European Union (EU), Japan, South Africa, the United States Food and Drug Administration (FDA) or the International Conference on Harmonisation (ICH) with, if necessary, modifications to accommodate the local situation. More than one guideline can be adopted, in which case applications may follow either guideline. It will often be appropriate to add technical requirements appropriate to local circumstances, such as requirements for higher temperature and/or humidity data to reflect the climate, or for interchangeability.

VARIATIONS

After a product has been authorized for marketing, the manufacturer will often wish to make changes (variations) for a number of reasons. The two common areas for change are pharmaceutical aspects of the product (quality control, manufacturing, shelf-life, etc.) and product information.

Changes should not be discouraged on principle, because they are often intended to improve quality (e.g. stability, batch-to-batch consistency, analytical methodology) or product information (e.g. updates to information on adverse reactions). In an application to vary, the company advises the DRA of an intended change and submits appropriate validation data. To encourage companies to give prior advice of such changes, variations should be processed as quickly as possible. If feasible, the DRA should have a separate unit for processing changes. A balance must be maintained between not placing the company at a disadvantage because it has made the application and yet ensuring that the change has been adequately validated.

Even well-resourced agencies find it impossible to evaluate all pharmaceutical changes made to all products. It is necessary, therefore, to define those changes that can be made without the DRA's involvement and those that require prior approval. Some authorities establish an intermediate category of changes which do not require prior approval but which must be notified ("notifiable" changes).

Some DRAs find difficulty in getting the industry to comply with the requirement to apply *inadvance* to make pharmaceutical changes. Better compliance can be achieved by thesemeans:

- Definition of minor changes which do not require prior approval or are notifiable;
- A policy that a complete evaluation of the product will *not* be routinely triggered whenever a company applies to make a change (though if an application discloses a major defect, the DRA must take action);
- Where prior approval is required, definition of data requirements in published guidelines so that companies can plan ahead;
- Rapid turn-round of evaluations of applications to make changes;
- Random review, during GMP inspections, of company documentation for consistency with information submitted for marketing authorization purposes;
- A strong and effective system of enforcement of legislation when unauthorized changes are detected.

A model list of variations (changes) that do not need prior approval appears in Annex 10. Some changes are so major that they constitute a new pharmaceutical product. These should be considered to be an application for a new product and should not be accepted as a variation. Such changes include:

- A change of the API to a different API;
- Inclusion of an additional API, or removal of one API from a multi-component product;
- A change in the dose of one or more of the APIs;
- A change in dosage form, including:
- Change from an immediate-release product to a slow- or delayed-release dosage form, or vice versa;
- Change from a liquid to a powder for reconstitution, or vice versa;
- Change in the route of administration.

It should be noted that a change in the recommendations for use (e.g. indications or patient population) would make the product *not* interchangeable with other brands and hence would not be acceptable unless the product information of all other brands were changed in the same way. However, as mentioned previously, differences in product information may have to be tolerated where local legislation allows new uses to be patented (e.g. new indications in the case of pharmaceuticals) or where market exclusivity arrangements apply.

CONCLUSION

ASEAN is a model of a regional integration initiative undergoing dynamic development and changes. It has become one of the most successful regional groupings of developing nations, to promote cooperation, and trade in the face of wider

international competition and economic upheavals. Since its inception four decades ago, ASEAN is now at a crucial stage in transforming itself from a regional Association into a dynamic, integrated economic Community. ASEAN's drug regulatory authorities and industry have worked very close regionally but also increasingly with global organizations to develop a number of harmonized documents. These are the common submission dossier known as the ASEAN Common Technical Dossier and the ASEAN Common Technical Requirements, which are steadily evolving. Largely they have been realized already, the next step will be to focus on mutual recognition of pharmaceutical registrations and implementing a harmonized placement system. There is still much work to be carried out in the implementation. The future will show if this can be achieved by the versioned end goal of economic community in 2015. Already now ASEAN can be regarded as an example of having developed a successful pharmaceutical harmonization scheme. ASEAN is increasingly playing a major role in pharmaceutical industry

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