

PN-ACE-091

WHO/DMP/RGS/98.2
Original English
Distribution Limited

How to Implement Computer-Assisted Drug Registration

A Practical Guide for Drug Regulatory Authorities



Regulatory Support Series, No 2



World Health Organization
Geneva
1998

©World Health Organization (1998)

This document is not a formal publication of the World Health Organization (WHO). All rights are reserved by WHO. This document may not be reviewed, abstracted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or any means - electronic, mechanical or other - without the prior permission of WHO. The views expressed in this document by named authors are solely the responsibility of those authors.

This publication was made possible through support provided by the United States Agency for International Development under the terms of cooperative agreement HRN-A-00-92-00059-13. The opinions expressed herein are those of the author(s) and do not necessarily reflect the views of the United States Agency for International Development.

Other titles in the Regulatory Support Series are in preparation

1 - Report of a Training Workshop for Drug Regulatory Officials on the Assessment of Applications for Marketing Authorizations - Nicosia, 14-18 December 1997 (WHO/DMP/RGS/98 1)

3 - SIAMED Model System for Computer-assisted Drug Registration User manual (WHO/DMP/RGS/98 3)

4 - QCL Model System for Handling Sample Information in a Quality Control Laboratory User manual (WHO/DMP/RGS/98 4)

5 - Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products A Manual for a Drug Regulatory Authority (WHO/DMP/RGS/98 5)

6 - Practical Guide to the Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in the International Commerce (WHO/DMP/RGS/98 6)

7 - SIAMED Model System for Computer-assisted Drug Registration Introduction and Brief Description of Functions and Facilities (WHO/DMP/RGS/98 7)

Acknowledgements

Technical and financial support for the development of this guide have been received from

- Direzione Generale per la Cooperazione allo Sviluppo (DGCS), Ministry of Foreign Affairs, Rome, Italy
- Gesellschaft für Technische Zusammenarbeit (GTZ), Eschborn, Germany
- United States Agency for International Development (USAID), Washington, DC, USA, through the Rational Pharmaceutical Management Project of Management Sciences for Health (MSH)

This guide would have not been possible without the technical inputs provided by the MSH Drug Management Program, and selected officials of national regulatory authorities where early work has been done to develop, field test, and/or implement the WHO Model System for Computer-Assisted Drug Registration. In particular, the World Health Organization (WHO) extends thanks to regulatory officials of Brazil, Cuba, Czech Republic, Guatemala, Mexico, Morocco, Mozambique, Nepal, Poland, South Africa, Syria, Tunisia, Venezuela, and Zimbabwe, from whom a great deal has been learned and findings incorporated into the model system and this guide.

The text presented here has been written by Valerio Reggi, WHO, Geneva, and Julie McFadyen, MSH, Arlington.

Suggestions, comments, and technical inputs have been provided by

Raffaella Balocco, WHO, Geneva

Elvira Beracochea, MSH, Arlington

Guillermo Bierzwinski, Direccion General de Control de Insumos para la Salud, Mexico

Kari Bremer, WHO, Geneva

Esperanza Briceño, Instituto Nacional de Higiene, Caracas

Peggy Casanova, WHO/PAHO, Washington

Enrique Fefer, WHO/PAHO, Washington

Daphne Fresle, WHO, Geneva

Rafael Garcia, Direccion General de Control de Insumos para la Salud, Mexico

Sônia Gil Costa, Centro de Vigilância Sanitária, São Paulo

Juhana Idanpaan-Heikkilä, WHO, Geneva

Pamela Jude, WHO, Geneva

Douglas Keene, MSH, Arlington

Youssef Khaddar, Direction de la Pharmacie et du Medicament, Tunis

Bal Krishna Khakurel, Department of Drug Administration, Kathmandu

Esther Kriel, Directorate of Medicines Administration, Pretoria

Imed Lassoued, Direction de la Pharmacie et du Medicament, Tunis

David Lee, MSH, Arlington

Marisa Lima Carvalho, Centro de Vigilância Sanitária, São Paulo

Miguel Angel Lopez, WHO/PAHO, Caracas

Gugu Mahlangu, Medicines Control Authority, Harare

Abir Makarem, WHO, Beirut

Aleksander Mazurek, Drug Institute, Warsaw

Tom Moore, MSH, Arlington

Fadwa Murad, Ministry of Health, Damascus
Ana Padilla, WHO, Geneva
Mirtes Peinado, Centro de Vigilância Sanitária, São Paulo
Veronica Pinell, MSH, Arlington
Jim Rankin, MSH, Arlington
Eduardo Saman, Universidad Central de Venezuela, Caracas
Celeste Sanchez, Centro Estatal para el Control de Medicamentos, Havana
Tadeusz Sawicki, Drug Institute, Warsaw
Theophile Sdogandji, WHO, Geneva
Amor Toumi, Direction de la Pharmacie et du Medicament, Tunis
Maria J Valdez, Direccion General de Control de Insumos para la Salud, Mexico
Eshetu Wondemagegnehu, WHO, Geneva

The views and comments provided by the persons listed here above are not necessarily reflected in the document. Some of the comments were in fact so conflicting that accommodating them all would have been impossible. We believe that two issues should be mentioned here:

- Some commentators thought that the document should have been more narrowly focussed on “computerization” with simple bibliographic reference to other documents for the discussion of broader issues related to legislation and the drug registration process. Others proposed that the “computerization” issue should be presented in “a context,” and therefore the general issues of drug legislation and the registration process should be discussed. We have leaned toward the second view.
- Some commentators felt that the document is unsuitable for those who are not already familiar with the drug registration issues. Others felt that some parts of the document were excessively simple or detailed. We have tried to focus on writing for those who have already been exposed to the concepts of drug registration. At the same time, we tried to produce something that could be used as a reference tool by those regulatory officials who are trying to generate the necessary political will in support of effective drug regulation in their national contexts.

Table of Contents

| | | |
|-----|--|----|
| I | INTRODUCTION | 1 |
| A | Background | 1 |
| B | Purpose of Guide | 1 |
| C | Benefits of Computer-Assisted Drug Registration | 2 |
| D | Key Concepts | 3 |
| E | Summary of Implementation Process Steps | 5 |
| II | PRE-REQUISITES FOR COMPUTER-ASSISTED DRUG REGISTRATION | 7 |
| A | Legislation and Regulations | 7 |
| B | Human Resources | 8 |
| C | Adequate Financing Mechanisms | 9 |
| D | Hardware and Software | 12 |
| III | PREPARING FOR COMPUTER-ASSISTED DRUG REGISTRATION | 15 |
| A | Planning the Process | 15 |
| B | Review and Update Procedures | 20 |
| C | Review and Update Forms and Certificates | 22 |
| IV | COMPUTERIZING DRUG REGISTRATION | 25 |
| A | Data to Be Computerized | 25 |
| B | Preparing Data | 26 |
| C | Options for Entering Data into the System | 29 |
| D | Using the Computer in the Drug Registration Process | 33 |
| E | Train Staff | 35 |
| F | Ensure Computer System Support | 36 |
| V | MAINTAINING A COMPUTER-ASSISTED DRUG REGISTRATION SYSTEM | 39 |
| A | Written Procedures | 39 |
| B | Checking Quality of Data | 41 |
| C | Retaining Staff | 42 |
| D | Political Support | 42 |
| E | Maximize Existing Resources | 42 |
| | Annex 1 List of Acronyms | 47 |
| | Annex 2 The Drug Registration Process | 49 |
| | Annex 3 Specific Aspects of Drug Registration Legislation | 53 |
| | Annex 4 Minimum Requirements for a Drug Regulatory Authority | 57 |
| | Annex 5 Glossary | 61 |
| | Annex 6 Sample Data Entry Form | 63 |
| | Annex 7 Further Reading | 65 |

I INTRODUCTION

A Background

On the basis of the World Health Assembly's recommendations, the World Health Organization (WHO) has prepared guidelines for a simple drug regulatory authority, and is supporting governments in setting up or strengthening drug regulatory authorities. To assist in this, WHO has developed a number of technical guidelines (see Annex 7) and updated the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

To complement these technical and administrative instruments, WHO has developed a Model System for Computer-Assisted Drug Registration (SIAMED), which is now available after consultation and field testing in several countries. This software programme was designed with the requirements described in this guide in mind.

The main objective of the model system is to improve the efficiency of drug regulatory authorities, enabling them to ensure that marketing authorizations are consistent with their national drug regulatory laws and regulations. This objective is to be achieved through the provision of technical advice, a cheap, specifically designed, locally adaptable computer system, and assistance to make effective use of it.

The development of the WHO model system has been undertaken with the realization that computerization alone is unable to replace proper regulations, qualified staff, and efficient work procedures and conditions. The provision of the software package and the present guide is therefore intended as a component of a broader national programme aimed at efficient drug regulation and registration, and encompassing legislation, regulations, human resources, and appropriate facilities.

Thus, the implementation of computer-assisted drug registration requires a feasibility study to define local specifications, the establishment of an appropriate organizational structure and reliable working procedures, the appointment of competent staff, allocation of resources, the adaptation of the software to meet local needs, and data entry and validation. Support, if required, can be provided by WHO for these activities.

This manual is based on experience gained from the implementation of the WHO Model System for Computer-Assisted Drug Registration software. Although this guide applies to any effort to computerize a drug registration system, when the text refers to "the system" or "this system" it is referring to the WHO software.

B Purpose of Guide

The purpose of this guide is to provide advice on introducing any computer-assisted drug registration system. This entails undertaking preparatory work to meet prerequisites, organizing working procedures, establishing information formats, securing resources, and training staff on the new system. This is not a guide on drug registration and contains only minimum guidance on that process in order to provide an appropriate context for the discussion. A brief description of the drug registration process can be found in Annex 2.

The target audience of this manual is officials of national drug regulatory authorities at the decision making and operational levels. Decision makers need to understand the implications of introducing a new system, in terms of organization of work, distribution of tasks, and automation of certain correspondence and certification procedures. Operational staff need to understand how their work may be changed by the new system. In particular, it will require a more systematic approach to handling information, but in return the system will provide a greater degree of freedom of access to information and reduction of repetitive tasks.

C Benefits of Computer-Assisted Drug Registration

Computers have changed the ways in which people work in virtually every sector of industry and services. It is important to understand that the computer is a tool to assist in nearly every stage of the drug registration process. Properly used, it is not simply for recording information and decisions at the end of the process. Some benefits of computerizing that regulatory authorities will realize are detailed below.

More time for professional work

Initially, the introduction of computer-assisted drug registration will put an additional burden on staff, especially when existing information needs to be examined and organized. However, once the system is operational, staff will face less routine and clerical work, and will have more time available for technical and professional work because many frequent tasks, such as searching for information on similar items and producing certificates, will be simplified or automated.

After adopting SIAMED, staff in an African country had time to read technical literature to update their professional knowledge. This was made possible by being able to use the system to ascertain in a few seconds, for example, whether marketing authorizations had been given before for a given active substance or excipient. They could also easily see what decisions had been taken before on similar drugs. Most importantly, correspondence and certificates are generated automatically by the system, so staff did not need spend time correcting typing mistakes.

Fewer imprecisions, oversights, and mistakes

In a manual system it is very common that substance names or quantities are stated incorrectly, or in a different way in different documents related to the same drug item. This causes confusion and gives the impression that regulatory work is done unprofessionally. A computerized system will greatly reduce these types of errors, because it is designed to help ensure consistency in data entry.

Improved communication within the regulatory authority

Operational links between drug registration, quality control (QC) laboratory, and drug inspectorate officials need to be effective and timely. In a manual system, when information needs to be exchanged, officials may contact each other on the phone or by visiting the appropriate office. This may require several days when officials are out on field visits or work on different shifts. A computerized system permits recording information on inspection results and ensures its linkage to drug registration data, and the computer data is easily accessible at any time to users with the appropriate level of access.

Increased efficiency

Most correspondence and certificates issued by regulatory authorities can easily be standardized. The adoption of a computerized system allows the authority to issue such documentation almost automatically.

in a predefined format. In addition, computerization greatly facilitates preparation of reports.

Improved quality of work

In a manual system, data recorded to identify a drug product and its status are generally stored in the application file itself and only selected data are transferred to a manual card system to permit retrieval. This, in the best situation, may include marketing authorization number, company name, drug item name, and name of “main” active ingredient. Usually, no other criteria can be used to retrieve information. In this situation, the preparation of reports is a time-consuming exercise that requires intensive editing to overcome inevitable copying and typing mistakes.

In a computerized system it is very easy to retrieve and review decisions previously made on a similar drug item. This ensures that technical decisions are made with a proper degree of consistency and transparency. The ease of retrieval and access to a great variety of up-to-date reports reduces the likelihood of inappropriate duplications, and permits a global view of the drugs already authorized. A computerized system can also track any application process, allowing the regulatory authority to determine the status of an application at any given time, and raise alarms when the process is delayed beyond user-defined limits.

D Key Concepts

In the design of computer applications a number of assumptions and choices need to be made with regard to terminology and format of information. The following definitions are those that have been used in the design and development of the WHO model system. Although they are derived from work with national authorities, the choice of terms is to a large extent arbitrary, and this list should not be seen as a recommendation to adopt them. These concepts are presented only for sake of clarity and with the understanding that terms routinely used by national regulatory authorities have considerably different meanings in different parts of the world. Please see the glossary in Annex 5 for additional terms.

In this manual, the issuance or denial of a marketing authorization is the result of the drug registration or licensing process.

Application for marketing authorization An application generally consists of a number of documents regarding quality, efficacy, and safety of the product gathered in a file, often called an application dossier. Dossiers have different contents depending on national requirements, the nature of the drug for which a marketing authorization is sought, and the capability of the applicant to assemble a complete set of information. Each application for marketing authorization is given a number, by the regulatory authority, called the application number.

The elements that make an application unique in a software system are

- A company responsible before the national authorities for all the implications that can arise from product marketing (this company is called marketing authorization holder, or licence holder, it is not necessarily the manufacturer)
- A product name (either a generic name or a trademark)
- A dosage form
- One or more active ingredients and their quantities

- A primary container
- A manufacturer (this is the manufacturer of the finished product responsible for releasing it for distribution)

A change in any of these elements should require a different application number. In a computerized system the application number can be automatically generated by the computer or can be entered by a user who has the appropriate rights.

Application for variation to marketing authorization An application for changing selected information related to an existing, valid marketing authorization (MA). Depending on established regulations, the type and extent of variations permitted vary from country to country, variations admitted in some countries entail, elsewhere, issuance of a new marketing authorization and cancellation of the previous one. To accommodate such a variety of requirements, the registration software should permit recording variation of all marketing authorization data except the number and validity date. In all cases the history of variations must be recorded.

Application for marketing authorization renewal An application for extending the validity of an existing marketing authorization that has been issued for a given time period.

Application processing steps A processing step is any event in the processing of an application characterized by a date on which the event starts or is expected to start, a technical or operational decision, a date on which such decision is made, and an assessment report. The WHO software system is designed to permit users to define as many different steps and sub-steps as required.

By making proper use of this feature, users will be able to trace applications and know their status at any time during processing. They will also be able to produce statistics on the duration of assessment as a whole or by step. However, the use of this feature is not obligatory. Regulatory authorities with very limited staff do not usually have difficulty in tracing pending applications. They can ignore this feature of the software system.

Generic Name generic names are also called common names for pharmaceutical substances or, when available, *INNs* or *modified INNs*. In a computerized system, information on substance names can be entered in two separate database fields:

- 1) fields describing the composition, called "ingredient name fields". In these fields, substance names are entered specifying the exact form, e.g., chloroquine phosphate.
- 2) a field indicating only the active part of the molecule used to prepare the dosage form, e.g., chloroquine. This field will contain chloroquine for all products containing any salt of chloroquine, regardless of dosage form or strength. This field is called the "generic name field," referring to the active component. Two drug products may have the same generic name but have different ingredient names, dosage forms, and strengths.

To use this concept of generic name in the context of computer-assisted drug registration, the following principles apply:

Drug products with only one active ingredient

The generic name is the name of the base that constitutes the active ingredient, regardless of the form used in the formulation, unless a specific salt has unique therapeutic uses unrelated to those of the base. For example, the generic name ampicillin applies to all drugs containing either ampicillin trihydrate, ampicillin sodium, ampicillin hydrochloride, etc. This simplification applies only to the generic name field of an application. It does not limit the possibility for users to record the full name and quantity of the active substance(s) in the ingredient fields. Thus, searches can be based on either the generic name or the individual full substance names of the ingredients.

Drug products with two active ingredients

The generic name reflects the names of the base that constitutes the two active ingredients regardless of the form used in the formulation, unless a specific salt has unique therapeutic uses unrelated to those of the base. These two names need to be entered in the same field. It is therefore recommended that, to avoid repetitions, a fixed format is used to enter them. For example, one could use a plus sign to separate the two names and enter them always in alphabetical order: e.g. amoxicillin+clavulanic acid instead of clavulanic acid+amoxicillin.

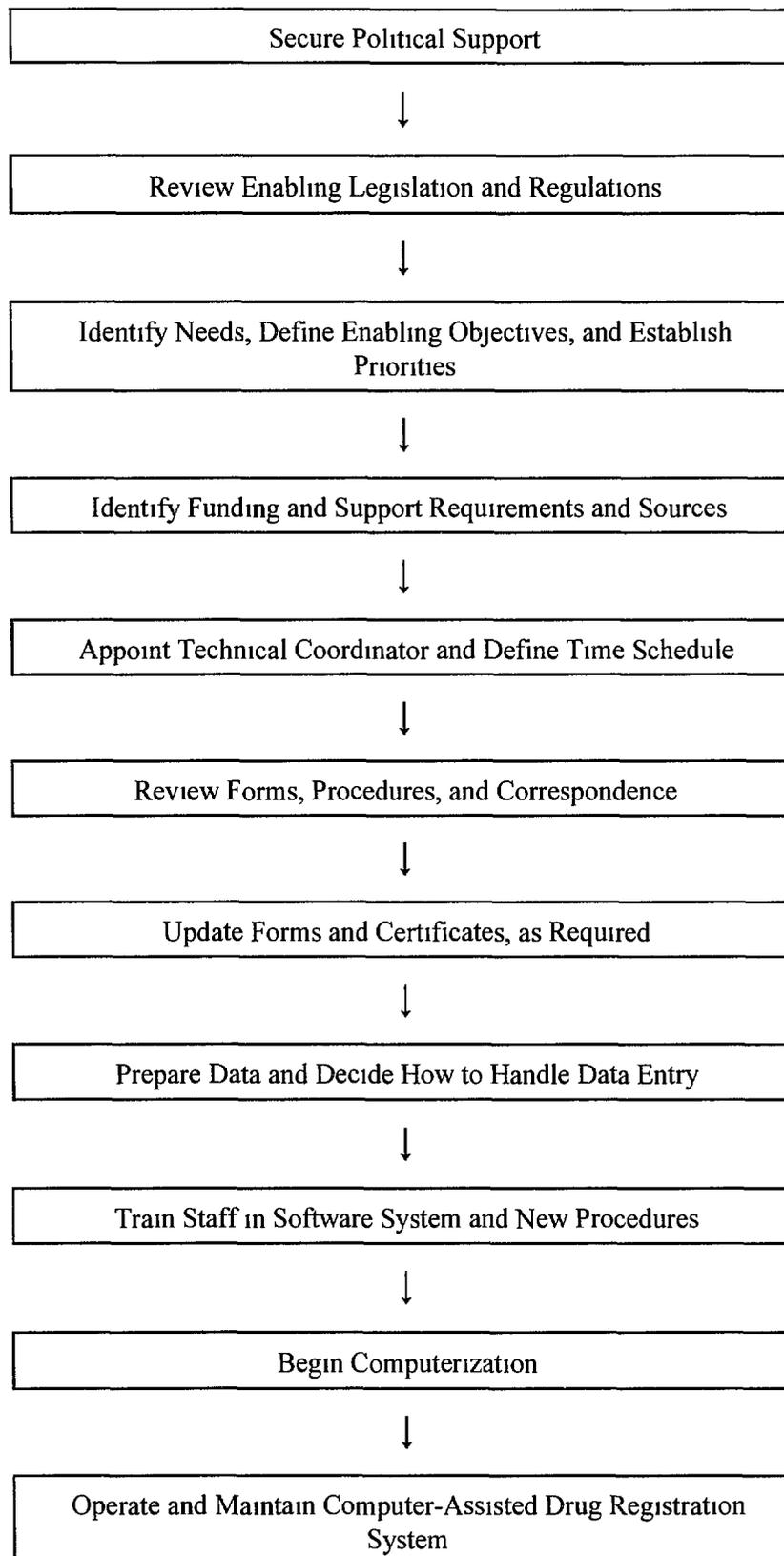
Drug products with more than two active ingredients

Building a generic name by adding those of several individual components is not practical. In addition, a rational drug rarely has three or more active ingredients. The proposed approaches are these: 1) enter, in the generic name field, the same predefined term for all drugs, e.g., combination, see composition, or 2) enter an arbitrary term to indicate a loosely homogeneous group, and use a predefined term for those drugs for which a homogeneous group is not easily identified, e.g., multivitamin, minerals, minerals+multivitamin, electrolytes, electrolytes+glucose, cold preparation, combination, see composition.

Marketing authorization An authorization by a competent drug regulatory authority for a product to be placed on the market for sale or to be made available to the general public free of charge. In some countries it is called product licence, or simply, licence. Each marketing authorization has a number called the marketing authorization, registration, or license number. The marketing authorization is made unique by all of the elements described in its application.

E Summary of Implementation Process Steps

The table shown below illustrates the successive steps that need to be followed in order to move smoothly from a manual drug registration system to a computer-assisted system. The points outlined here will be discussed individually later in this guide.

Moving from a Manual to Computer-Assisted Drug Registration**The Implementation Process**

7.

II PRE-REQUISITES FOR COMPUTER-ASSISTED DRUG REGISTRATION

KEY POINTS OF THIS CHAPTER

- ☞ Legislation and regulations must support the work of the regulatory authority, rather than hindering it, either directly or indirectly
- ☞ The DRA's scientific experts should be complemented by a suitable number of administrative staff, computer specialists, and legal experts
- ☞ The cost of computerization is marginal when compared to what governments are actually spending in the area of regulation and control
- ☞ Registration fees applied in most developing countries are too low to support the work of their regulatory authority, and sometimes too low for what the countries' markets could bear without having an adverse effect on access to pharmaceutical products
- ☞ At a minimum, there should be at least one computer dedicated exclusively to the core database of company and drug product information
- ☞ To the authors' knowledge, the only programmes available on the market specifically for drug regulatory work are the WHO system, and Regulator produced by PharmaSoft in Uppsala, Sweden

Certain aspects of a drug regulatory authority and related functions must be in place for successful computerization. Consideration should be given to legislation and regulations, human resources, and financing, in addition to computer hardware and software. If a drug regulatory authority was not functioning well before computerization, this alone will not solve all of the problems. For countries that do not have a functioning drug regulatory authority (DRA) in place, minimum requirements for particulars such as reference books, and administrative tools and procedures are listed in Annex 4.

It is possible that external support may be a pre-requisite for implementing computer-assisted drug registration, including for maintenance of the system. If this is the case, arrangements should be made to secure support early in the computerization process. Support in the form of technical or financial assistance could be useful, for example, for

- Review of legislation and regulation
- Specific technical issues related to assessment of applications and review of product information
- Improving communication and information interchange with other regulatory structures such as QC lab and inspectorate
- Engage in drug safety monitoring and pharmacoepidemiological studies
- Maintaining the computer system

A Legislation and Regulations

There is little doubt that pharmaceuticals need to be regulated, primarily because consumers are not able to assess the efficacy, safety, and quality of pharmaceuticals before buying them. Therefore, the government needs to establish an appropriate body to perform the assessment that consumers cannot conduct. To achieve this, it must pass legislation and regulations to govern and enforce the efficacy, safety, and quality of pharmaceuticals.

What is the difference between legislation and regulations? Legislation is passed by the legislative body of a country, and establishes the general framework of principles within which the government is expected to act and within which regulations are issued. Regulations are issued by the government, by an individual minister, or by a designated authority within, or under the supervision of, a ministry. While the process of preparing or reviewing legislation is usually long and complex, the preparation and updating of regulations is a more dynamic process.

Therefore, legislation does not need --and in fact should not-- include detailed indications and prescriptions, but should only state general principles that do not require regular updating. Details of application of such general principles are included in regulations. For example, legislation can establish the requirement for registration fees and indicate which operational body, e.g., the minister of health, should determine the amount and extent of the fees. Then, regulations issued by, in this example, the minister of health, will indicate and keep up to date the fee system.

The introduction of computer-assisted drug registration is a major undertaking. Therefore, before embarking in such an enterprise, it is necessary to carry out a critical review of existing legislation and regulations in order to ensure their efficiency and the adequate empowerment of a regulatory authority. The review should identify weaknesses in the laws and, if necessary, make proposals for changes. It should also clarify the framework, in terms of scope of activities and enforcement powers, in which the regulatory authority will operate. In addition, the legal review should check that the regulations ensure the best possible outcome of the legislation. A published review also helps to ensure transparency of regulatory decisions, and helps to make decision makers aware of the legal scope and limitations of regulatory work.

WHO has created model legislation for drug regulation that can be used for drafting or updating legislation (see Annex 7). In reviewing legislation for the drug registration procedure, there are some specific points that should be considered, and these are listed in Annex 3. It is very important to ensure that the legislation and regulations support the work of the regulatory authority, rather than hindering it, either directly or indirectly.

B Human Resources

In principle, staff requirements should be defined on the basis of the functions to be performed. In practice, in many countries drug regulatory authorities are assigned staff on the basis of the resources available, not on the basis of their responsibilities. It therefore becomes necessary for DRAs in this latter situation to decide what can be done with the available staff. This fact, and the varying sizes of DRAs in different countries, makes it impractical to discuss how many pharmacists, chemists, physicians, etc., should be staffing a DRA, and in what roles. Minimum staff requirements are listed in Annex 4.

Obviously, decisions concerning quality, therapeutic equivalence and product information/labelling must be made by persons with suitable knowledge of the subject and practical experience. The quality control of drug products requires a knowledge of pharmacy and chemistry. Evaluation of therapeutic equivalence and product information (PI)/labelling requires a knowledge of the actions, uses, quality, and safety of medicinal products. At a minimum, the team of evaluators of therapeutic equivalence and PI/labelling should be qualified in pharmacy, clinical pharmacology, and medicine, and have practical experience in these fields. While external expertise should also be available, the authority's own staff must be capable of understanding and implementing any advisory body's recommendations, acting on information (e.g., on safety or quality) made available by WHO or other DRAs, and taking action on their own initiative in critical situations.

Scientific and medical skills must be continuously updated to keep pace with new developments, including new means of formulating, controlling and using well-established drugs. It is therefore essential that suitable training be offered to staff on a regular basis.

Some part of the DRA needs the capacity, including staffing, to investigate possible breaches of the law and, if necessary, to initiate legal action in cooperation with legal officers. A knowledge of the local laws and legal procedures is essential. The DRA must have access to reliable legal advice.

Any organization needs the skills of competent administrators. The scientific experts should be complemented by a suitable number of administrative staff, including computer specialists, or access to them. A DRA has a particular need for persons experienced in handling large quantities of documents and daily correspondence, which may need to be retrieved at short notice.

The number of staff to be employed in registration activities should be determined by the responsibilities to be undertaken. The major determinants of staff numbers are

- The degree to which the authority is prepared to rely on decisions made and assessment reports prepared by other national DRAs
- Whether there is a local pharmaceutical industry in the country, and hence whether there are local applications for which a foreign evaluation may not be available
- The number of applications to be processed annually
- The inclusion of “qualifying” elements of the regulatory work, such as publishing decisions, conducting post marketing studies, etc

A final point is worth mentioning. Some technical professionals seem to think that using a computer challenges their status. It is important that they understand that this is not correct, and that most of the information that needs to be stored in a computerized drug registration system is of a technical nature and its handling requires technical judgement. Applications are not always professionally prepared and often contain inaccuracies. Retyping these same mistakes into the DRA system is not the right way to achieve effective drug registration, so it is necessary for a technical professional to enter the correct data into the computer.

C Adequate Financing Mechanisms

1 Costs of regulatory work

Key functions of a national regulatory authority are illustrated below. This diagram is presented only for the purposes of this manual and should not be seen as a indication on how to organize the work of a DRA. For example, the handling of variations and renewals are indicated as part of “Drug Registration,” while they are conceptually also part of “Post-Marketing Activities.” This diagram is meant to illustrate priorities for developing DRAs. It also suggests that DRAs may have difficulty engaging in the activities listed under “Post-Marketing Activities” if they have not consolidated those under “Drug Registration.”

| Drug Registration | Quality Control Laboratory | Inspectorate | Post-Marketing Activities | Regulation of Pharmacy Profession |
|---|--|---|--------------------------------------|--|
| Marketing authorizations for new products | Pre-registration/first marketed batches testing | GMP inspections | Control of drug promotion | Licensing and monitoring of pharmacists and pharmacies |
| Renewals | Routine controls | Inspections of distribution channels | Promotion of rational drug use | |
| Variations | Forensic testing | Control of importations | Monitoring of adverse drug reactions | |
| Clinical trials | Training and validation of peripheral laboratories | Training of peripheral inspectors | Pharmacoepidemiological studies | |
| Special drug importations | | Licensing Manufacturers and Wholesalers | | |
| Providing input on pricing issues | | Clinical Trials (GCP Inspections) | | |

Most countries are carrying out some or all of the above functions, although this may take place through different organizational setups. In all cases, the cost of these operations is high. In most developing countries where bodies have been established to perform regulatory functions, the number of staff involved ranges from 50 to 300. This means that salaries and minimum running costs (e.g., office space and equipment, electricity) alone add up to a considerable amount. Given this fact, it is crucial that available resources are used in the most effective way. Computerizing drug registration is a critical element that can contribute dramatically to improving the efficiency and effectiveness of regulatory work. Certainly, the cost of computerization is marginal when compared to what governments are actually spending in the area of regulation and control, regardless of the visibility and effectiveness of such activities.

The following table provides information on the costs specific to computerization

| Item | Cost and Information |
|-------------------------|---|
| Stand-Alone Computer | Costs vary from country to country. However, at the time of writing this text, a stand-alone computer of the appropriate configuration to run the WHO system, and including a modem, was available for approximately US\$2 000 or less in most countries. |
| Network | When contemplating the installation of a network, it is important to consider what other software applications are going to be used along with drug registration software, how many users are going to be linked, and what kind of permanent support is available. The presence of all these variables makes it impossible to outline an ideal configuration and hence average cost. The biggest components of the cost are a server (central) computer, the hubs and wires to link the computers together, the network operating system software, and the labour to install, administer, and maintain the network. |
| Printer | Again, costs vary from country to country. However, at the time of writing this text, a laser printer was available for approximately US\$1 000 or less in most countries. |
| UPS | An uninterruptible power supply (UPS) is essential to protect the server and/or data against unexpected power outages or surges. Costs vary, but at the time of writing this text a UPS was available for approximately US\$400 or less in most countries. |
| E-mail/Internet Service | A budget of about US\$500 , per year, would allow the DRA to take advantage of such services and buy a new, basic, modem every three or four years. |
| Fax Machine | Again, costs vary from country to country. However, at the time of writing this text a fax machine was available for approximately US\$500 or less in most countries. |
| Software | The WHO system is provided free of charge and of copyright to interested national regulatory authorities. The only other commercially available software known to the writers is Regulator, produced by PharmaSoft in Uppsala, Sweden. It is a copyright-protected product, and in May 1998 a single-user license cost US\$12 000 and a two-user license cost US\$22 000 . |
| Technical Assistance | Because very few authorities can introduce computer-assisted drug registration just on the basis of installation diskettes and a few written instructions, there may be costs involved in the provision of training, advice, and technical assistance. These, depending on specific local needs, may range from US\$10 000 to US\$40 000 over a two-year time period for the WHO system. |

Unfortunately, in many countries the DRA's budget, although sizeable, can cover little more than salaries and minimum running costs. It is frustrating for officials of a DRA to have no funds available when resources are needed to, for example, carry out an inspection, update the available technical literature, or buy new office equipment. Governments may be unable to provide more resources for effective regulatory work. One possible solution to this problem is for the DRA to recover costs through fees for the services it provides.

2 Registration fees

In a number of countries, the imposition of application and licence fees provides a practical way to help meet the running costs of the drug regulatory authority, of inspections and other regulation enforcement activities, and to filter out superfluous and irrelevant applications. If a decision is made to establish fees, the following points should be considered

- In line with the market size, fees should be high enough to permit, or at least to contribute significantly to, the efficient and effective functioning of the national drug regulatory authority, including registration, inspectorate and quality control. Therefore, appropriate mechanisms must exist within the government administration to ensure that funds collected as fees are made available to the drug regulatory authority to ensure that pharmaceuticals on the market are acceptable in terms of quality, safety, and efficacy, and that they are rationally used.
- Provisions should be made for variation of fees. Fee reduction or exemption should be made in order to ensure that vital drugs with a limited market are reliably available. Such provisions may also be needed for other purposes (e.g., to encourage nationally manufactured drugs). Fees may be higher for widely used drugs with a sizeable market, if these can be identified.
- The risk that the collection of fees may induce approval of a greater number of applications should be taken into account. This can be contained by appropriate mechanisms such as transparency of the evaluation process, setting no relation between fees and assessment results, and involvement of institutions external to the drug regulatory authority in decision making.

Worldwide, the drug regulatory fees for registering a new product on the market range from US\$1 50 to over US\$300 000. The average fee for industrialized countries is more than US\$10 000. Registration fees applied in most developing countries are too low to support the work of their regulatory authority, and sometimes too low for what the countries' markets could bear without having an adverse effect on access to pharmaceutical products. In most developing countries, fees can and should be raised, in line with the three considerations discussed in this section.

D Hardware and Software

1 Hardware

Three major factors determine whether a stand-alone computer or a network is necessary to carry out the work in any given authority. These are: 1) the number of applications that need to be processed, 2) the amount of information that authorities wish to record for each application, and 3) the number of staff available.

At a minimum, there should be at least one computer dedicated exclusively to the core database of company and drug product information. This computer should be used to issue standardized correspondence and certificates. Other correspondence (i.e., other than that generated by the computerized drug registration system) and administrative work should be done on another computer.

When necessary and feasible, two or more computers can be linked to create a local area network. In this case, data entry or access can be carried out simultaneously from the two, or more, machines. Data entry or retrieval should never be done on separate stand-alone machines. Doing this will not facilitate entering the backlog data faster, on the contrary, it will be a waste of time since merging the separate databases will not be possible. See additional considerations on necessary technical support for computer networks in chapter IV.

At least one reliable printer should be configured for use with the drug registration database. The specifications of this printer should match the number of copies expected to be printed in a given period of time, the type and format of paper to be used, and the available resources. Dot matrix printers are no longer cheaper than other types, and their use should probably be reserved for those who need to print on special papers (e.g., continuous forms or multiple layers), or those who have no access to other printers. Laser printers are probably the best option. Maintenance and a regular supply of toner cartridges must be available.

One or more telephone lines should be available to ensure communication with applicants, external institutions, and other DRAs. A separate external line dedicated to a fax machine and/or e-mail access is also quite helpful. Providers of electronic mail and Internet access services are now available virtually in every country, and an account with them to provide e-mail and Internet access would be very useful for a DRA. As more and more commercial information exchange moves to the Internet, access for the DRA will become essential.

2 Software

The WHO has developed a Model System for Computer-Assisted Drug Registration software programme (SIAMED), which is now available after consultation and field testing in several countries. The programme is designed to meet the requirements described in this and other WHO manuals for comprehensive drug registration systems. The minimum hardware requirements to run the WHO system are a 486 personal computer with at least 4 MB of RAM and 100 MB of free space on a hard disk. Eight MB of RAM are required if changes to the source code are to be made. A colour monitor and a mouse are recommended. This software package is ready to be run on a network. The programme has been used with the following network operating systems: LANtastic 6.0, Novell DOS, Windows NT (which of course entails much higher RAM requirements than those mentioned above), and Novell 3.11. Specific instructions and assistance should always be requested from WHO for proper network installation.

It is necessary to use a software programme specifically designed for use by drug regulatory authorities. To the authors' knowledge, the only programmes available on the market specifically for this work are the WHO system, and Regulator produced by PharmaSoft in Uppsala, Sweden. It should be noted that the purchase of the PharmaSoft product does not allow for local adaptation and does not include licensing rights. While it is possible for a country to develop its own system, it is strongly recommended that available tested and reliable programmes be considered first. Designing and developing a software programme almost always takes much more time and money than originally budgeted, and should be considered only if existing programmes are deemed unsuitable after careful review.

More information on the WHO system can be obtained from

Division of Drug Management and Policies
Regulatory Support Unit
World Health Organization
Avenue Appia, 20
1211 Geneva
Switzerland
Telex 415416
Fax +41 22 791 47 30
E-mail reggiv@who.ch

More information on Regulator can be obtained from

PharmaSoft AB
P O Box 1237
S-751 42 Uppsala
Sweden
Phone +46 18 185400
Fax +46 18 109200
E-mail marketing_eu@pharmasoft.com

III PREPARING FOR COMPUTER-ASSISTED DRUG REGISTRATION

KEY POINTS OF THIS CHAPTER

- ☞ The planning process should begin with an assessment and overview of the current drug regulatory situation in the country, and an inventory of the market
- ☞ A DRA has usable data if its files physically contain all the pieces of information that are required to enter into the new system, and these data are accurate and reflect the current situation of the marketed drugs
- ☞ The time required to enter existing information into the system will depend on whether the current system is manual or computerized, and whether the existing data is usable or not
- ☞ In preparation for computerizing the drug registration system, it is essential to review and update the regulatory authority's procedures
- ☞ It is very useful to review the forms and certificates used by the DRA, and update them as needed

After the pre-requisites have been addressed with the involvement of other agencies and offices, preparation for computer-assisted drug registration enters a phase that is assumed to be fully under the drug regulatory authority's control, and will primarily be its responsibility. A technical coordinator should be appointed, and will be responsible for overseeing the implementation process of computer-assisted drug registration. This person should ensure that progress proceeds according to plan.

A Planning the Process

1 Assess current situation

The planning process should begin with an assessment and overview of the current drug regulatory situation in the country, and an inventory of the market (see IV C 2, page 32). Knowing whether the present system is manual or computerized and whether its data is reliable and usable is crucial to determining how to proceed with computerization. Through document review and a series of structured interviews with drug regulatory and MOH officials, obtain the following information:

| Assessment Element | Relevance and Remarks |
|---|--|
| Presence of requirements to submit applications for New MAs, Renewal of existing MAs Variation of existing MA Issuance of certificates Other | If requirements are not in place or are notoriously not complied with, it is necessary to delay the implementation of computer-assisted drug registration until requirements are effectively and reliably implemented. |

| Assessment Element | Relevance and Remarks |
|--|---|
| <p>How many applications are received/expected every year for New MAs, Renewal of existing MAs Variation of existing MA Issuance of certificates Other</p> | <p>If this information is not readily available or cannot be reliably obtained from existing files, there can be doubts about the reliability of the drug registration system in place. This does not imply that computerizing is not feasible, but it makes it difficult to estimate the amount of time required to reach routine functioning of the new system. The number of products to enter into the computerized system is obviously a major variable in determining length of time for entering backlog data.</p> |
| <p>Presence of a validity term limit for MAs and length of validity</p> | <p>If MAs are valid indefinitely, their number could be very high (in some developing countries it is above 30 000). In these cases, entry of backlog information from a manual system may entail an enormous amount of work. Although entering the backlog may be a legal requirement, the amount of work it would require cannot always be justified on public health grounds. It is necessary to identify mechanisms to minimize the DRA's efforts to manage backlogs.</p> |
| <p>How many pieces of information on each drug item are recorded in the current system, and how many are expected to be recorded into the new computer system</p> | <p>Computer systems can accommodate and permit retrieval of much more information than most developing countries' DRAs may need or want to use. Deciding the extent of information to be recorded in a computer system is a crucial decision that will influence the pace at which a new database can be reliably built.</p> |
| <p>Presence of an efficient inspection system covering manufacturing and distribution channels</p> | <p>The absence of regular inspections of the distribution channels poses a serious challenge to the credibility of the information on marketed drugs available at the DRA.</p> |
| <p>Presence of written procedures and compliance with them</p> | <p>This element is important when assessing the possibility of using existing information in order to computerize. If there is no assurance that standard procedures (especially regarding completeness of information) have been followed in the past, it is very likely that the existing information is incomplete or inconsistent and, therefore, unsuitable for direct transfer into the new computerized system.</p> |

2 Estimate time required to enter existing information into the new computerized system

The amount of time required to enter data will vary from country to country, depending on a wide variety of factors. The assessment described above should enable the user to determine which of the following situations is most like his or her own. For the purpose of this guide, "usable data" means MA data that reflect the reality of the drug items actually being marketed, and that have sufficient consistency and completeness to permit their use to build the new computerized system. Therefore, a DRA has usable data if its files physically contain all the pieces of information that are required for entry into the new system,

and these data are accurate and reflect the current situation of the marketed drugs

Nothing in Place

This is the situation where no regulatory authority is in place. The market is usually regulated simply by means of import permits and sometimes positive and/or negative lists broadly indicating which drugs can be imported. There is either no assessment of technical documentation, or it is limited to ensuring that imported drugs are related to a WHO-type product certificate, or to other informal types of certificates called "free-sale certificates." In these situations there is no way to know what is actually being marketed at the present time.

The obvious starting point in a situation like this is to seek political commitment to approving or reviewing, and/or enforcing proper drug legislation and regulations, thus establishing a drug regulatory authority capable of ensuring that the principles of the national drug policy are respected.

The second step is to identify and license all persons and premises that are involved with pharmaceuticals. Such licensing should cover pharmacists, manufacturers, importers, wholesalers, and distributors. The third step necessary for any further operations is an inventory of the market situation, as described in the "Inventory of Market Situation" section in Chapter IV. During the time that is required to carry out the inventory of the market situation, a DRA can continue to receive applications for new marketing authorizations but should establish priority criteria to deal with them. These criteria should be published to ensure transparency and avoid conflict with applicants. In establishing such priority criteria, a balance needs to be struck between the need to review data on drugs marketed prior to the creation of the new regulations and the need to ensure that vital new drugs are made available.

Manual System with No Usable Information

This is probably the most common situation. A manual system has been in place for some time but information on the pharmaceutical products authorized for marketing is not properly organized, not consistent, and/or not current. After having ensured that proper legislation and regulations are in place and that the regulatory authority can reliably function, the only viable approach is to ask all concerned persons to resubmit applications to be licensed as companies/individuals. Then an inventory of the market must be carried out as described in Chapter IV.

Computerized System with No Usable Information

This situation is essentially the same as a manual system with no usable information, and the same strategy indicated above should be followed.

Manual System with Usable Information

If the existing manual system has been kept up to date and the information is reliably retrievable, computerization of information can start directly from the existing files by typing the information from the manual records into the computer software.

Computerized System with Usable Information

If the existing system has been kept up to date and the information is reliably retrievable, changing easily to the new system depends on whether data can be converted from the existing system to the new one. It is also necessary to determine whether additional information must be input into the new computer system, beyond the data contained in the old one. If the format of the existing data is not compatible with the new system, then the existing information must be re-entered into the new software.

The status of existing information systems will be the primary determinant of the time required to enter backlog data and achieve routine functioning of the new computerized system. Additional issues that need to be taken into account when estimating time requirements are

- Entry of backlog information does not entail assessment of applications, but simply entering what is available or has been collected with future assessments in mind. Thus, when estimating time requirements, this is referred to as simple data entry. When all the necessary information is obtained and has been transferred to a data entry form (see section IV B), its entry into the computer system can be estimated at an average of 10 minutes per drug item if there is no need to re-type the full text of the product information sheet. This, in fact, can be avoided when using the WHO system because it has a feature to import this sheet from a diskette, leaving only the editing work to be done.
- The WHO system has a function to copy an application or MA already entered, and to edit it. This is particularly useful when entering several different strengths or dosage forms of the same product, or different brands of pharmaceutical equivalents. In these cases, data entry is limited to editing the few fields that require different information, and can be estimated to take up to four minutes per drug item.

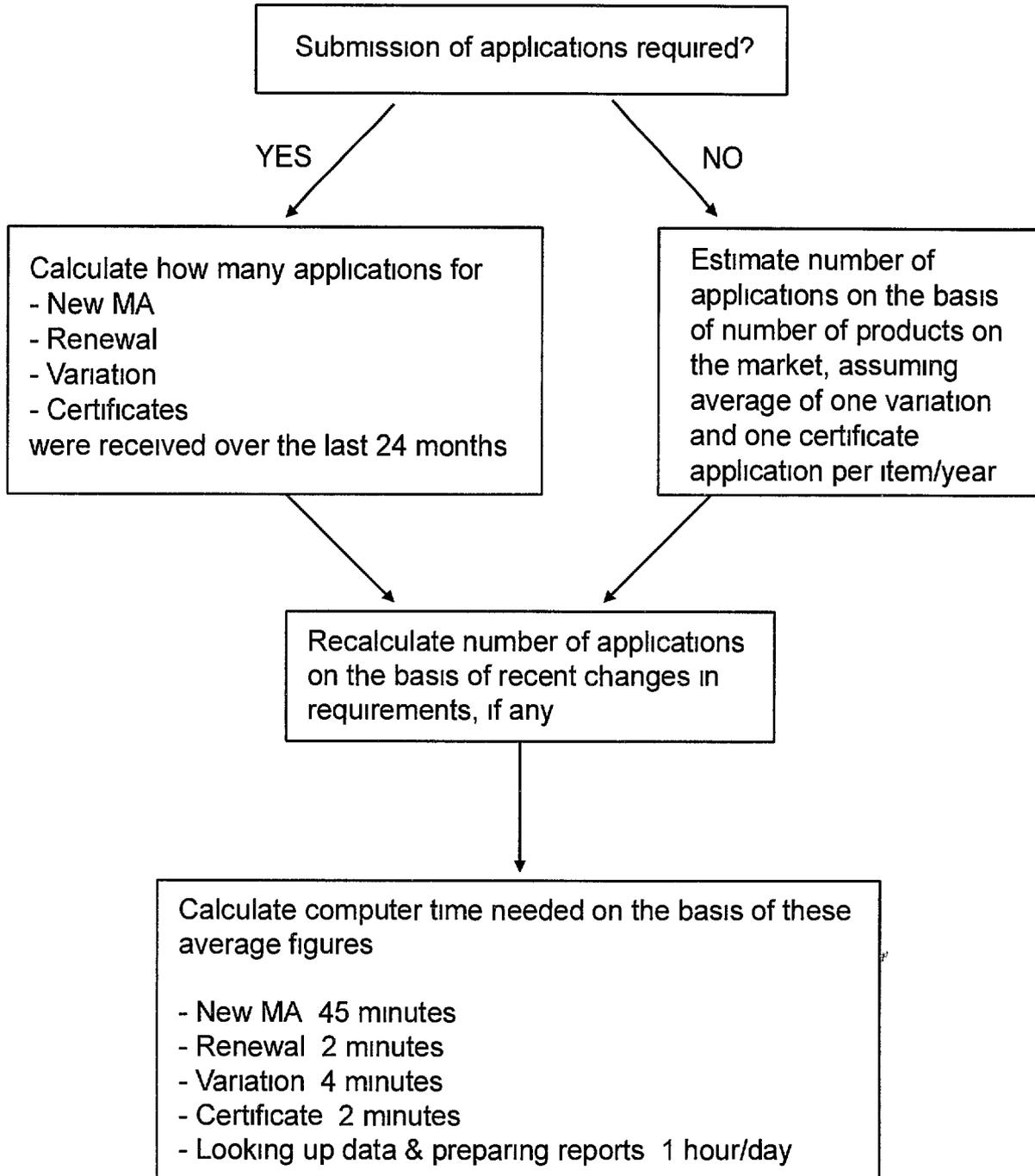
3 Estimate computer use for routine operation

The chart shown on the next page provides a schematic description of a possible way to assess how much computer time will be necessary when the system has reached the phase of routine use. The first thing to look at is whether there has been --and for how long-- a requirement for applications to be submitted. If requirements were in place and were complied with, DRAs should be able to calculate how many applications have been received in the last 24 months. Otherwise an estimate of the possible flow of applications can be made on the basis of the number of drug items that are currently on the market. If the latter figure is unknown and it is not possible to make a reliable guess, it is necessary to carry out an inventory of the market situation (see Chapter IV) to assess how much computer time will be needed.

When calculating the number of applications, specific figures for four different types of applications need to be obtained: applications for new MAs, applications for renewal of existing MAs, applications for variations to existing MAs, and applications for certificates. The number of renewal applications can be estimated on the basis of the length of validity of MAs established in law or regulations. After the number of applications has been calculated or estimated, this should be adjusted if any changes in requirements have been made that may have an impact on that number.

ASSESSING HOW MUCH COMPUTER TIME IS NEEDED

This refers to routine operation, i.e., after backlog data have been entered



The chart shows average time estimates that can be used to calculate the total time of computer use. It should be noted that these time estimates are only for actual time spent using the computer, they do not include time for technical assessment, testing, etc. The box below presents an example of the reasoning behind those estimates.

Experienced users need **3 minutes** when applications are received to record the application number and date, applicant, drug name, strength, dosage form, and primary container. In addition to this, for each application, **2 minutes** are required to record when and to which assessment step(s) the application is assigned. Then, each assessor will require up to **15 minutes** to complete drug item data (e.g., active substances, excipients, therapeutic classification, etc.) and record his or her report. Finally, another **10 minutes** will be required to record the final decision and issue standard correspondence or certificates. In all, for an application with no more than two assessment reports and three printouts (i.e., letter confirming reception, letter informing of final decision, and MA certificate) the computer use will be about **45 minutes** distributed over a period of several days or weeks. If the assessment faces problems that entail extensive correspondence with the applicant, computer use may reach **60 minutes** or more.

4 Estimate staff needed

It is impossible to estimate here how many staff will be needed for the computerization process, and for running the computer-assisted drug registration system. The amount of work, skills of staff, workload distribution, and other variables will be very different from case to case. Therefore this estimation is a matter of local judgement. It is mentioned here because it is a necessary part of the planning process.

A tip for finding staff to accomplish the work, that a number of countries has found successful, is to recruit pharmacy students on a temporary basis to carry out the bulk of the backlog data entry job. This has usually been a cheap and substantially positive experience.

B Review and Update Procedures

In preparation for computerizing the drug registration system, it is essential to review and update the regulatory authority's procedures. A list of written procedures that a DRA should have can be found in Chapter V.

Define processing steps to assess new drug product containing new chemical entities (NCE), new drug product (generic), renewal of MA, variation to MA, etc.

This is a crucial decision for most regulatory authorities. The use of a computerized system allows the authority to keep track of all applications, identify those that have been awaiting assessment decisions for a long time, and describe their status at any given time. Obviously, to achieve this users must enter the necessary information into the computer system. Since different types of applications require different types of assessment, it is necessary to carry out some preliminary work so that the types of assessment procedures and the steps each entails can be entered in the setup of the computer system.

Decide how applications are received, distributed for assessment, assessed, and how/when/by whom each action is entered into the computer (specifying what needs to be done by a technical professional)

The use of a computer system demands a systematic approach to organizing workloads and workflow. An example is described in the table below. Correspondence or certificates may be generated at any step.

| Step | Who Performs | Data Entered in the Computer |
|---|---|--|
| 1 Receipt of applications | This activity requires no technical judgement. Therefore data entry is not necessarily done by a technical professional. | A new entry is created in the computer system. In the case of applications for new MAs, the new entry entails application number, applicant name, drug name, dosage form, and primary container. In the case of renewal or variation applications, the new entry entails application number and linkage to the existing MA data. |
| 2 Admission of applications to the assessment process | A technical professional carries out a preliminary review of the application to identify possible flaws that would not justify its admission to the assessment process. | The decision not to admit the application entails issuing a letter to the applicant indicating the reasons for such decision. |
| 3 Assignment of assessment procedures | When applications are admitted, a technical professional assigns them to an assessment procedure according to the nature of the application. | Data entry entails selecting the appropriate procedure and indicating the date on which documentation is sent to each assessment step. To ensure proper follow up, the same coordinating person/unit assigns applications for assessment and receives assessment reports. The coordinating person/unit may decide not to complete the assessment procedure if the results of any assessment step recommend rejection of the application. |
| 4 Assessment and preparation of assessment reports | Technical professionals assess the applications. | Technical elements describing the drug item under assessment (e.g., substance names, roles of manufacturers, etc.) and assessment reports are entered into the computer system. Assessors inform the coordination person/unit of the completion of their work with a summary conclusion and the date on which this was reached. |

| Step | Who Performs | Data Entered in the Computer |
|------------|--|---|
| 5 Decision | The coordinating person/unit submits a proposed decision to the decision-making body | The coordinator records the decision into the computer system. Data entry entails indicating the decision and its dates of submission and decision. In the case of new MAs it entails numbering the new MA and indicating validity dates. In the case of renewal of MA it entails entering a new expiry date. |

Procedures must also be defined for archiving and access to hard copies of submitted documentation after the assessment has been completed. Legislation may dictate how long the documentation must be kept, or establish how and when it can be destroyed. In general, it is only necessary to have access to the last five years' records for routine reference.

C Review and Update Forms and Certificates

In addition to updating procedures, it is also very useful to review the forms and certificates used by the DRA, and update them as needed. The first step is to define the types of forms required, based on the country's legislation and regulations.

- Application for licensing of manufacturing premises, wholesaler, importer, retail outlet, etc
- Application for MA of new medicinal product, renewal of MA, minor or major variation to MA, etc
- Application for the issuance of certificates
- Application for withdrawal of application or cancellation of MA
- Certificates
- Standard letter to applicants
- Instructions to applicants

Application files

Distinguish between pieces of information that should be entered in a form and those that should be attached to a form, declare a rationale/purpose for each piece of information, establish presentation standards for critical pieces of information (e.g., sources of substance names, drug classification, dispensing categories, limitations of distribution, storage conditions, etc.), and establish numbering rules and validity criteria.

Detailed discussion of application documents and an example of an application form go beyond the scope of this document. See *Marketing Authorization of Multisource (Generic) Pharmaceutical Products: A Manual for a Drug Regulatory Authority* for more details. Additional considerations on the preparation of data entry forms are found in section IV B of this guide, and a sample form found in Annex 6.

Standard correspondence and certificates templates

Develop standard letters to acknowledge receipt of application, request additional information, and inform applicant of decision made. Develop standard certificates such as the WHO-type product certificate, or other certificates.

Instructions for applicants

Provide guidance on how/when/by whom applications are to be submitted. Critical issues are

- Applications by mail cannot be accepted unless provisions are made to ensure that an application is considered received and valid only if, and from, the date on which receipt is acknowledged by the regulatory authority
- If the DRA has published criteria to standardize information (e.g., names of substances, therapeutic classification, etc.), provisions should be made to prevent the burden of converting information found on non-compliant applications from falling on the DRA
- Smaller regulatory authorities may decide that applications are received only on selected days or hours to ensure both that staff can review formal completeness of applications before accepting them, and so that the staff has time to concentrate on other tasks when offices are closed to applicants
- Applicants must be identifiable with a local company, which shall be liable for any administrative or penal consequence of marketing inappropriate drug items

Substance names very often cause data inconsistency in computerized systems. Applicants should receive precise instructions on how to submit substance names. An example follows

→ Always use the INN when it exists, or state that it does not exist. If it does not exist, state the source of the substance name submitted, any known synonyms, and add photocopies of the relevant technical documentation, as well as proof that the submitted name has been accepted by other regulatory authorities

→ Salts can be indicated as modified INNs (INNS), i.e. INN+name of salt

→ Always add the CAS Registry number, or state that this does not exist

→ For excipients mentioned by their proprietary name, add photocopies of the relevant documentation where the exact composition(s) is described. The DRA can develop a nationally-accepted non-proprietary name for these substances

→ Non-compliance or inaccuracy in the implementation of the above principles results in the rejection of the application

IV COMPUTERIZING DRUG REGISTRATION

KEY POINTS OF THIS CHAPTER

- ☞ Preparing data for computerization includes completing a data entry form, deciding on a drug classification system, and preparing codes and catalogues for standardized data entry
- ☞ If data are usable, they can be entered in the system by converting old data, stopping new applications and entering the backlog, or entering the backlog gradually while accepting new applications
- ☞ If data are unusable, an inventory of the market situation must be made, requiring that companies with products on the market that wish to keep marketing them make this known in writing to the DRA. The other option is that companies submit a full application for marketing authorization based on published documentation and standards
- ☞ When computerizing, automation of drug registration work takes place at various steps
- ☞ Whatever software system is selected for use at a DRA, staff will need to be trained in how to operate it
- ☞ For a computer-assisted drug registration system to function effectively, adequate computer support and maintenance must be available, and the type of support needed differs for a network versus a stand-alone system
- ☞ The DRA budget should contain adequate funds for computer system supplies, upgrades, and maintenance

Once the preliminary activities described above have been completed, the focus shifts to computer-related work. The first issues to be addressed are identifying and preparing data.

A Data to Be Computerized

Data to be recorded may include any or all of the following elements, some of these data are applicable only to domestic companies.

Data Describing Companies and Institutions

| | | |
|--|---|---|
| Code | Activity (e.g., manufacturer, importer, retail pharmacy, QC laboratory, etc.) | Authorization to handle psychotropic and narcotic drugs |
| Full name (e.g., Pharmachem Laboratories of Karibland, Ltd.) | Status (e.g., currently active, cancelled, operational licence expired, etc.) | Reports of previous inspections |
| Short name (e.g., Pharmachem) | Date of validity of status | Planned inspections |
| Mailing address | Responsible pharmacist | Various types of authorization numbers |
| Plant address | Property/functional relations with other companies | |
| Phone and fax | | |
| E-mail | | |
| Contact person | | |

Data Describing the Item for which the Application Is Submitted

| | | |
|---|--|---|
| Application number | Limitations of distribution/use | Official product information sheet (indications, contraindications, etc) |
| Date of reception | Origin | |
| Applicant name | Human/veterinary | |
| Representative of the applicant (or other company related in some way to the application) | Linkage code with social security or other system | Internal evaluation sheet (information not to be published, assessment reports) |
| Drug product name/trademark | Physical location of the application files | Prices |
| Type of product (brand/generic) | Shelf life and storage conditions | Distributors/importers |
| Product generic name | Manufacturers involved in the different phases of production and their roles and responsible persons | Veterinary information |
| Dosage strength | | General description of the appearance of the drug item |
| Dosage form | Active and inactive ingredients and their quantities and functions, using INNs when available | Analytical information |
| Primary container and its specifications | | Regulatory status in other countries |
| Presentation(s) | | |
| Type of MA requested/issued | | |
| Dispensing category | | |
| Narcotic/psychotropic | Therapeutic classification | |
| Routes of administration | | |

Data Describing Status

- Decisions made at the different steps of the assessment process, indicating dates at which each step starts/ends, and responsible person
- Date and type of final decision
- Date and cause of rejection of applications or cancellation of marketing authorization
- Date of issuance of marketing authorization and renewal of marketing authorization
- Date on which marketing started, was suspended, was resumed
- Post-marketing information on adverse drug reactions (ADR), stability, other, and date on which each of these was valid

Data Describing Variations

- Data before and after variation, date of variation, person who authorized the variation

B Preparing Data**Organizing information for data entry**

Application forms and documentation submitted by applicants are seldom suitable for direct data entry. Usually information is scattered throughout several pages and may require review/adaptation before it is used for data entry. It is usually most convenient to develop a data entry form, particularly when information is prepared for entry of backlog data. Obviously, the type and format of a data entry form depends both on the amount of information that needs to be recorded in the computer and on the data entry strategy that is being adopted, e.g., how much information is going to be entered by professional staff and how much by support staff.

In addition, to ensure consistency of data, it is necessary to develop separate data entry forms for information on companies, for abbreviations (see section on codes later in this chapter), and for other types of applications such as renewals, variations, cancellations/withdrawals. Data entry forms should always be prepared by professionals. They are also responsible for checking the accuracy of entered information. Ensuring accuracy of information is a task that cannot be delegated to support staff.

An example of a data entry form for applications for new marketing authorizations is provided in Annex 6. In this example, there is no need to enter detailed information on companies because this is done through a separate procedure. The company code or unique name is entered on the form, and this is linked to the company information entered separately in the computer, so there is no need to enter company contact information twice.

Decide on drug classification

There is no classification system that is suitable for all purposes. DRAs need to ask themselves what use they wish to make of a drug classification system in order to choose or build one. Most DRAs do not have the means to do more than their minimum institutional tasks. If the DRA is not planning to embark on regular drug utilization studies, or does not need a linkage to a social security system, then it is likely that the classification system will be used only in periodic reports to state how many drugs of each group have been registered during the previous year. In this case, it is advisable to build the simplest classification that is meaningful to the specific situation and matches the outline of the reports expected to be required. Most regulatory authorities use the classification system only for administrative and reporting reasons, but a classification system can also be useful in routine work for identifying products with the same or similar active substances already registered.

The regulatory authorities that are involved in drug utilization studies may be interested in using a classification system suitable for this. The Anatomical Therapeutic Chemical (ATC) classification system is a very powerful tool that can be used to carry out drug utilization studies. If the Defined Daily Dose (DDD) methodology is used in conjunction with the ATC classification, comparative analysis of quantities of drugs consumed as well as comparative analysis of costs of drugs consumed in different geographical areas and/or within a given therapeutic group (see *Guidelines for ATC Classification*) can be made. The drawbacks of this attractive picture are that

After trying several approaches to ensure consistency and accuracy of information, the regulatory authority of a North African country has developed a two-tier system

→ Applicants attach data entry forms to their applications. When these are received, support staff enter data from these forms.

→ For new marketing authorizations, applicants have the option to submit the data entry form information on diskettes provided by the regulatory authority. When these are received, support staff check diskettes for viruses and import data into the system through a software feature that filters out incompatible data.

When professionals are assigned an application for assessment, they find the basic information already in the system and need only to review its accuracy, complete parts that require their technical judgement, and type in their assessment reports.

In an African country, the first three levels of the ATC classification were used as a basis to develop a national classification. This is used during assessment of new applications to check what other drugs of the same therapeutic group have already been authorized. The classification is also used to prepare annual reports on the work done.

- The ATC classification is a five-level system that must be studied in order to ensure proper application. Therefore, DRAs need to be sure that staff clearly understand the ATC system and are ready to review applications in order to apply the system correctly. In addition, regular staff meetings need to be held to discuss how to classify new drug items that have never been classified before, or to review previous decisions that in practice did not meet expectations. In addition, for the system to work, appropriate mechanisms should exist for collection of consumption data. In fact, it is a very demanding task and only a few, advanced DRAs are involved in this.
- The ATC system is updated every year by the technical group responsible for maintaining it. Updates include new drugs that have never been classified before, as well as changes in the classification system (new groups, drugs moved from one group to another, etc.). This has obvious implications for those using the system on a routine basis, because existing data need to be reviewed to accommodate changes. Alternatively, users of the ATC system who are not able to ensure updating of all their data may simply keep the version of the classification with which they started and state, when presenting data/reports, that this is based on version 199X of the ATC system.

Other DRAs use a classification system to link information to that of social security reimbursement schemes, reimbursement level is related to classification in specific therapeutic groups. There is no point for this type of users to adopt another classification system, unless they have strong motivation to do so.

Most countries use an existing national classification system. For those that don't have a system, or wish to change their system, it is wise to study existing classification schemes, and adopt or adapt one of these, rather than building a new one. In addition to the ATC classification, other examples of existing systems are the WHO *Model List of Essential Drugs*, the American Hospital

Formulary Service (AHFS) Pharmacological and Therapeutic Classification System, and the Veterans Administration (VA) Medication Classification, which is listed in the annual USP-DI.

In an African country, public sector drugs are classified in a national list and assigned specific codes based on their main therapeutic utilization. At the time of drug registration, officials of the drug regulatory authority consult the procurement list to see whether a drug that has the same composition strength and dosage form of the product for which they are issuing a marketing authorization is there. If it is there, they enter into the drug registration system the code of the drug in the procurement list. This code establishes a linkage between the procurement and registration systems. When necessary, the drug regulatory authority provides the procurement agency with a printout sorted on the procurement code where all drugs that have a marketing authorization and belong to the procurement list are listed in the appropriate order.

Prepare codes and catalogues

Computer systems require that information is entered systematically to ensure that it is accurate and retrievable. In the WHO system, any file containing an abbreviation (or code) and its description is called a catalogue. Thus, there is a catalogue of countries where all country codes and their descriptions are stored (for example, AFG is the code for Afghanistan and ZIM is the code for Zimbabwe), a catalogue of dosage forms (e.g., GRAN for granules), etc. These abbreviations are used to store standard information in files and to reduce data entry work to a minimum. In fact, when entering information on applications, none of the items included in catalogues will need to be retyped, it will be simply selected from a list.

The standardization of abbreviations is crucial to avoid situations where the same country has three or more different names, e.g., Tanzania or United Republic of Tanzania or Tanzania, United Republic. For a computer, these three names are not the same. Thus, retrieving companies that are from Tanzania would not include the companies in which the country name has been spelled differently, including when it has been mistyped.

The same type of problem is applicable to many other pieces of information: dosage forms, primary containers, dispensing categories, types of authorization, company names, currency names, company activities, limitations of distribution, types of price, etc.

In the WHO system, many catalogue files have already been filled with examples to make familiarization with the system easier. Codes such as "TABS" rather than "0234" for "tablets," and "BAYUK" for "Bayer UK," etc. have been chosen. This is because this type of code is more informative in those printouts and screens where only the code can fit. However, this type of coding system is not required; users may employ whatever system is convenient and relevant for them, as long as it is logically consistent and is used methodically.

To ensure consistency of information, only a few users should be permitted to enter data into the catalogues. All other users who identify the need for adding a new entry (e.g., a new dosage form, a new company, etc.) must tell the appropriate staff in order to have the update made. For this reason, it is useful to define codes for use when the code is "not applicable," "pending," or "not known." These will be used as appropriate during entry of applications, rather than leaving the field empty when information is not available. It is important that codes be defined as completely as possible prior to engaging in routine data entry.

C Options for Entering Data into the System

As discussed in chapter III, different situations may require different approaches. These are discussed below.

1 Data Usable for Building the New Computerized System

For the purpose of this guide, usable data means MA data that reflects the reality of the drug items actually being marketed, and that have the sufficient consistency and completeness to permit their use as the basis on which the new computerized system is built. Therefore, a DRA has usable data if its files physically contain all the pieces of information that are required for entering into the new system, and if these pieces of information actually reflect the situation of the marketed drugs.

Convert old data

If the DRA is changing from a previous computer system to a new one and the data in the existing one are usable, it may be possible to convert that data for use in the new system, without having to re-enter all of the information. This conversion is best done in close consultation with a technical advisor on the new software programme, who will be able to assist in determining if the data can be converted, and how. Manipulating data for direct entry into a programme's databases, rather than entering it through the programme's data entry screens, should only be done by those very skilled in both database management and the new software programme's structure.

A Latin American country was unable to maintain and adapt its existing system to permit tracking of applications, but the system was working and had up to date information. When SIAMED the WHO software - was adopted, a programme was written to transfer data from the existing system to SIAMED, and no data were lost. However, the new system could not be used immediately because some information in the old one was incomplete or inconsistent. This was due to the fact that the two systems were designed in different ways: the old system did not check for synonyms of substance names, had no standardization of a number of abbreviations, and permitted any user to enter new company and substance names. The data "cleaning" process took about one year for the approximately 3,000 items that the old system contained.

In most cases, partial conversion of existing computerized data is possible. Examples of scenarios with data that may be difficult to convert are

- If the previous system did not have a facility to check consistency of substance names and track synonyms, direct conversion of data would not solve the problem of inconsistency of substance names. Therefore a specific activity should be started to progressively "clean" the existing database.
- If the previous system did not store substance names as database fields, but as text fields, it will be difficult to import the data into database fields.

Data Conversion Steps

| Step Number | Action |
|-------------|--|
| One | Compare the database structures of the two programmes, looking for similarities and differences. If the differences are too great, it may not be possible to convert the old data. |
| Two | If there are enough similarities between the two database systems, decide which data will be converted, and how. |
| Three | Import the data into the new programme, testing for data integrity and compatibility. |
| Four | Determine what data still need to be entered in the new programme. |
| Five | Complete databases of new programme by entering remaining data manually. |
| Six | Test and check new programme to ensure that all necessary data is there and complete. |

Stop new applications, enter backlog, reopen

This approach requires notifying applicants that no new applications for MAs or variations will be accepted between certain dates, i.e., the “ban period.” During the period when no applications are coming in, DRA staff --with additional temporary staff if possible-- can concentrate on entering all backlog information. When this is completed and data quality has been reviewed, applications will be accepted again and entered in the system as they are received.

The ban period must be as short as possible. In addition, criteria should be set to allow applications for vital drugs with no available alternative to be received and processed even during the ban period. The main advantage of a ban period is that staff can concentrate on preparing a clean database before new information is accepted. The main risks are that a) it may be “politically” difficult to stop receiving applications and b) existing information on file may be incomplete and the expected clean database may not be achieved in the time frame anticipated.

In a Latin American country, the regulatory authority decided to establish a computerized database of the existing marketing information. In order to ensure that staff concentrated on this, the DRA agreed with the applicants that they were going to be “closed” to the public for three months. During this time, in which no new applications nor applicants’ inquiries were accepted, the staff, helped by ten pharmacy students, organized and entered information into the system. Unfortunately, at the end of the established period, not even half of the work had been completed. It was impossible to extend the “closure” of the regulatory authority. Therefore, the DRA had to continue entering the backlog information while accepting new applications.

Enter backlog gradually while accepting new applications

If it is not possible to stop receiving applications as outlined above, the only other choice is to enter the backlog gradually while new applications are being received. In countries where the validity of marketing authorizations is fixed by law or regulations to a given number of years, the simplest approach is

- 1 Start to enter information with the most recently approved drugs and proceed backwards. In this way, older authorizations for which no renewal is sought will expire before they are entered into the computer system and will never be recorded.
- 2 Marketing authorizations regarding registered products for which applications are received while entering the back log are recorded when a decision is made, regardless of their validity date. In this way, the computer system will issue the relevant certificate (renewal or variation). In fact, in these cases one assumes that the fact that an application is submitted implies that the drug is actually being marketed and that the MA holder is interested in keeping it on the market.
- 3 Applications for new marketing authorizations are entered as they arrive.

If sufficient staff are available, separate staff and/or separate working hours, could be dedicated to entering the backlog information according to the “reverse order” method and to the authorizations triggered by incoming applications.

Countries where marketing authorizations are valid indefinitely, and that cannot change this regulation while reviewing legislation and regulations, need to decide whether they must enter information on all MAs or only on those of products actually marketed. Possible approaches are shown below.

- *Enter same data on all MAs* Choose any work programme and start data entry.

- *Enter data only on MAs of products actually marketed* If no reliable system to identify products actually marketed is available, start entering data only for applications for new MAs and MAs for which certificate, renewal or variation applications are received
- *Enter full data only on MAs of products actually marketed and minimum data on MAs of products not actually marketed* Give priority to entering data only for applications for new MAs and MAs for which certificate, renewal or variation applications are received Whenever time permits, carry out data entry of basic information starting from MAs that were issued over 10 years ago and go backwards from then

2 Unusable data

Unusable data are those that are so incomplete, outdated, inaccurate, or unreliable that they cannot safely be used in the new computer system There is no specific method to identify whether data in a DRA is unusable DRA staff should know whether data on MAs accurately reflect the drug items actually being marketed, and whether those data are sufficiently consistent and complete to permit their use as the basis on which the new computerized system is built If DRA staff are unable to determine this, then data is not usable If existing data cannot be used, there are two options, described below, for creating a database for a computer-assisted system

Inventory market situation

An inventory of the market situation is necessary in all cases where no reliable or up to date information is available about all medicinal products actually being marketed Such an inventory requires that companies with products on the market who are willing to continue marketing them make this known in writing to the regulatory authority This notification will entitle companies to a temporary marketing authorization Products for which no notification has been given by a certain date will no longer be allowed on the market, and companies responsible for their importation or sale will be penalized (e.g., seizure, plus cost of destroying them, plus fine)

The DRA's request for notification on existing products may be simple, i.e., require only minimum information to be provided, if it is reasonably certain that a formal assessment for registration (see below) will eventually be conducted The minimum data to be collected in a notification are

- Name of the medicinal product (either generic or brand name)
- Name of active ingredient(s) using the INN (International Nonproprietary Name), if available
- Dosage form, strength and route of administration
- Purpose of use (although this may not always be an approved indication)
- Manufacturer, name and full address
- Manufacturing country
- Package sizes and prices

If a formal assessment is not going to be made, it may be appropriate to introduce additional elements in the notification request, requiring that other documents are submitted with the notification in order to make it valid In addition to the minimum data listed above, the notification form should include at least the following details

- Main therapeutic group
- Importing agent, name and full address (if applicable)
- Complete composition with active and inactive ingredient(s) and their quantities
- Therapeutic indications

- Copy of all labelling, including any package insert
- WHO-type product certificate from the country of origin

If the manufacturer or importer (distributor) does not provide the required information, the sale of the product after a fixed date may be forbidden

Before, or immediately after, the end date for companies to submit a notification, the regulatory authority should publish criteria for issuing regular marketing authorizations and plan, on the basis of the estimated workload entailed, a more formal assessment of the drug items that have been given temporary marketing authorization. At least three different approaches are possible

- Start, without defining a precise schedule, asking companies (all together, in alphabetical order, or otherwise) to submit the required documentation as when applying for an MA for the first time. This approach does not allow the DRA to determine how long it will take to assess all drugs with temporary MAs, and will require extending their temporary validity indefinitely. This is the approach taken by most industrialized countries
- Establish a predefined schedule for assessment of temporary MAs and endeavour to meet deadlines
- Establish priorities according to any preferred criteria (e.g., fixed-dose combination drugs, imported drugs, therapeutic classes, etc.) and start requesting submission of documentation on the basis of these

Resubmit all applications, build database gradually

This approach is similar to that of carrying out an inventory of the market situation, but with a major difference. Companies are not asked simply to notify and submit minimum information on the products they are already marketing and wish to continue marketing, they are asked to submit a full application for marketing authorization based on published requirements and standards. This means that the DRA should be prepared to receive and process large amounts of documentation

Compared to the notification approach, this has the advantage of establishing a baseline documentation against which all future routine controls and applications for variations and renewals can be checked. The disadvantage is that the DRA may be so overwhelmed by large amounts of documentation that it cannot even classify it properly, or verify whether it is accurate and complete. As in the case of the market inventory, products for which documentation is received are granted a provisional marketing authorization, which will be valid until technical assessment of the submitted documentation is done

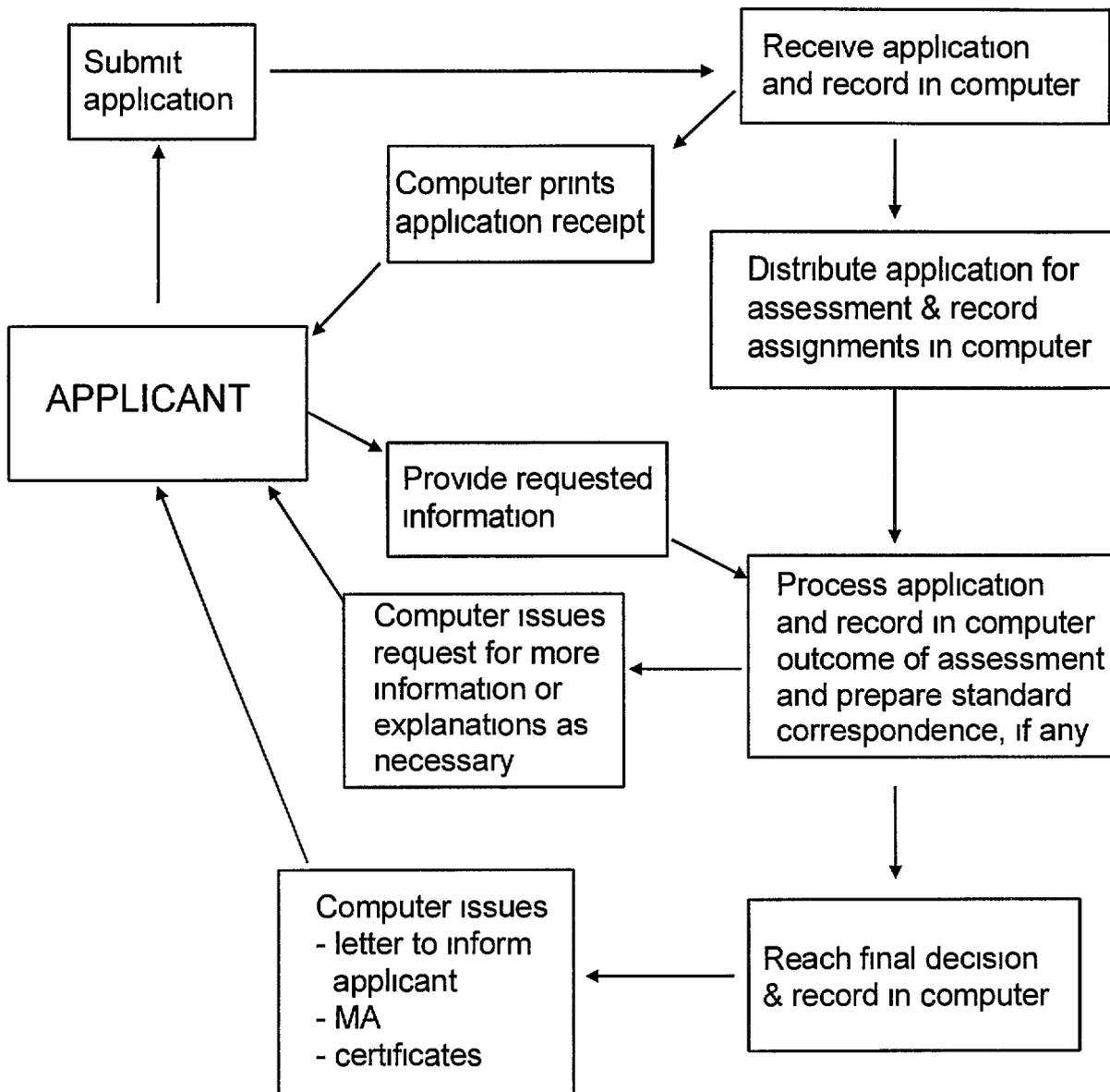
D Using the Computer in the Drug Registration Process

When computerizing, automation of drug registration work takes place at various steps, as summarized in the table below

| Step | Action in the Software | Explanation |
|---|---|--|
| Receipt of applications | Enter application number, date, applicant, drug name, strength and dosage form, and print receipt of application | This creates a new entry to which all system users will be able to refer. It allows the authority to start monitoring steps of assessment process and calculate step-by-step and overall duration of assessment. |
| During assessment | Retrieve selected information on previous decisions, similar drug items, product information sheets Enter decisions made at each individual step, and print letter requesting additional information if required | Individual assessors enter information related to their specific area, retrieve information on, and check status of similar products. They also record (summary) assessment reports and decision proposals. |
| The final decision | Retrieve selected information on previous decisions, similar drug items, product information sheets Enter final decision | Users with appropriate password rights can take a global view of assessment reports and proposed decisions, can retrieve information on and check status of similar products, and issue new marketing authorizations, renewals, or variations as appropriate. |
| Notify applicant and issue MA | Print standard notification of decision on application and send to applicant Print standard marketing authorization and deliver to applicant | When a decision is reached, the software can be used to generate pre-defined correspondence, marketing authorizations, and certificates for the applicants, greatly reducing the time needed to produce such documentation. |
| Report preparation | Retrieve necessary information, using predefined report formats, or custom selection criteria | Preparing complex reports is extremely easy. Reports can be prepared based on any combination of searching criteria. In addition to printing, the report output can be sent to a file in order to change its format or to e-mail it. |
| Issuing other correspondence and certificates | Retrieve items on which correspondence and certificates are to be issued and print correspondence and certificates based on standard predefined formats | The advantages of automation of issuance of correspondence and certificates are immense, especially when staff or facilities are reduced. It saves time and tedious work, and reduces the number of mistakes. In addition, the promptness and reliability of the response improves the image of the authority. |

The chart below illustrates the process in which drug registration data are entered into the software, from the time an application is received, through all of its processing steps.

USING THE COMPUTER IN THE DRUG REGISTRATION PROCESS



E Train Staff

Whatever software system is selected for use at a DRA, staff will need to be trained in how to operate it. In addition, if a network is newly installed, all staff will also need to be trained in how to use it effectively. Provisions must be made for adequate training of all necessary staff members when the new software is installed, and for training any staff member hired after the initial training. It would be best for this training to be done professionally by the technical support team of the software programme, and geared toward making two or more DRA staff members internal experts on the programme. At least one week should be dedicated to training and practice with the new system, preferably without any outside distraction or interruption. All staff members who will be using the computer system should be required to attend training on the software, done either by the external trainers, or by the internal experts.

The training objectives are

- Ensuring that everyone is aware of the reasons for introducing or changing the computer system and knows what is expected from the new situation
- Ensuring that staff attitudes toward the use of computers are appropriate in view of the new environment
- Creating or improving skills to match the new tasks or the new ways in which usual tasks will be carried out
- Learning how to operate the software system

Assuming that decision makers within the DRA have made the decision to computerize and are therefore already motivated, the first focus of training will be on key staff members whose support is critical in order to motivate the others

Unless needs are identified for training in specific new procedures that are being introduced concomitantly with computerization, training should be of the hands-on type, using real data and in the usual working environment

F Ensure Computer System Support

For a computer-assisted drug registration system to function effectively, adequate computer support and maintenance must be available. The type of support needed differs for a network versus a stand-alone system. Consistent support, regular maintenance, and periodic upgrades necessarily require money, although, as explained above, the expenses are low when compared to the cost of the entire regulatory structure. The budget for the DRA should include funds annually for this type of operation. Important points to consider in computer support are summarized below

Stand-Alone Computer

There is no need for permanent, full-time computer experts to support stand-alone computers at the DRA. Users need to understand the importance of making regular backups (see below) of existing data, learn how to do that, and learn how to reactivate the system after a breakdown. Experts will be needed for training, but if users can learn these things, they can manage on their own. Hardware maintenance will be necessary when there are hardware problems with the computer, so arrangements must be made for prompt, reliable service and repair, even if the computer is still under warranty.

Network

Depending on the type and size of the network in place and the variety of applications that are expected to be running on it, the DRA will need specialized personnel, dedicated full-time or immediately available on call, for maintenance, administration, or repair. The availability of such personnel does not replace the need for regular backups of existing data. Nor does it replace the need for written procedures for users to follow when using the different facilities available from the network. The same hardware maintenance needs described in the section above apply, and are even more crucial for the server computer in the system. If the server is not functioning, the entire network is either handicapped or unusable, depending on the network design and configuration.

Backup

Copies of existing information made on diskettes or on separate hard disks are called backups. Users need to understand that computer systems may fail for different reasons. In some cases, data cannot be recovered and damaged data need to be replaced from backup copies that are made on a regular basis. If backups are done daily, the maximum amount of information lost is one day of work. If they are done weekly, it can be a week! It is crucial to perform backups regularly and comprehensively, and to verify that the backup is functioning correctly. Check the diskette, hard drive, or tape to verify that the correct data was recorded during the backup, so that its absence is not discovered when it is urgently needed.

Supplies and Upgrades

The DRA budget should contain adequate funds for computer system supplies such as toner cartridges and paper for the printer. Money should also be budgeted for regular hardware upgrades, such as more memory, faster processors, larger hard drives, or new or additional computers, as needed, but at least every three years. Finally, funds must be allocated for maintenance contracts for servicing the printers and computers. Approximately US\$750 should be budgeted annually for each computer, and US\$400 for each printer, although these figures can vary greatly in different parts of the world. These figures should be adequate for both maintenance and upgrades.

V MAINTAINING A COMPUTER-ASSISTED DRUG REGISTRATION SYSTEM

KEY POINTS OF THIS CHAPTER

- ☞ Written procedures are necessary to ensure consistency of data, proper use of the system, access to the available features, and to help prevent system breakdowns
- ☞ No matter which implementation approach has been selected, it is necessary to review the quality of the information entered for internal consistency
- ☞ DRAs should try to ensure that critical staff are not lost to the private sector or other agencies
- ☞ No DRA will be successful in the performance of its duties if it does not have full and ongoing government support, particularly during changes of government
- ☞ DRAs should establish mechanisms to regularly receive technical support from other institutions and individuals
- ☞ DRAs should establish effective and meaningful communications with other regulatory authorities

A Written Procedures

Beyond instructions for applicants and guidelines for staff to assess applications, written procedures are necessary to ensure consistency of data, proper use of the system, access to the available features, and to help prevent system breakdowns. The table below outlines the issues for which written procedures, aimed at ensuring proper use of a computerized system, need to be prepared.

| For Completeness of Information | |
|---|--|
| Amount of information that needs to be recorded | DRAs need to decide on the minimum amount of information entered for each application/MA and assign responsibilities to ensure that this is done. Experience has shown that it is necessary to establish and implement the minimum amount of information for data entry at the very beginning of computerization. Any plan to enter only part of the data on each application in each phase (e.g., enter the minimum information now, and more comprehensive data in a future phase) should be avoided because it is virtually impossible to manage. |
| Assessment reports | The decision whether to record the full text of assessment reports or simply the final recommendation (i.e., accept, don't accept, pending) in the computer system is a matter of local judgement. A suitable compromise would be to record full reports only for decisions that have required detailed, lengthy technical work and search. This would allow easy access to the information in the event of a similar situation. |

| | |
|------------------------------------|---|
| Communication s with applicants | Most --if not all-- types of communications with applicants can be anticipated and a standardized format can be developed for each of them DRA staff should be encouraged to make use of computer-generated correspondence This is not only to ensure consistency of interchange with applicants, but also to ensure that the computer system has a copy of the correspondence sent out and that this copy is internally linked to the application or MA to which it refers This allows all issued correspondence to be readily accessible when viewing application/MA data |
| Decision | It is very important that the outcome of the assessment and decision making process on an application be issued as a document generated by the computer system The system needs to be a vital part of the registration process and should not be seen as an addition to it, required only for the purpose of preparing reports In addition, issuing MAs from the computer helps to ensure that all the necessary information is there |

For Consistency of Information

| | |
|---|--|
| How to establish classifications and categories | <p>To ensure consistency of information and to avoid dispersing data in too many categories, it is important that access to entry of abbreviations, classifications, substance names and other categories, be restricted to one or two users Therefore, procedures need to be established so users understand how the existing abbreviations and categories have been developed and how they can propose new entries Decisions of this type need to be made for most or all the elements that may be used as searching criteria for data retrieval and for presentation criteria for reports It is prudent to make this type of decision prior to engaging in routine data entry and avoid changing it after information has been entered according to one criterion Lists of categories and entries can be posted in the office for easy data entry reference</p> <p>Example When establishing a list of possible dosage forms, users may decide to have an open-ended number of oral solid forms or may decide to limit it to a number of basic ones (e g , capsule, tablet, modified-release capsule, and modified-release tablet), assuming that all the other modifications of these four would fall into one of them</p> |
|---|--|

| | |
|--------------------|--|
| Substance names | Several substances used in pharmaceutical preparations have been assigned different names in different parts of the world The number of synonyms that exist, therefore, mean that there is a risk of using different synonyms for the same substance even within the same DRA Unfortunately, computer systems work in such a way that two different names, even if they refer to the same substance, are considered two different items When computerizing, it is crucial that DRAs establish rules for both applicants and staff on criteria for using substance names Users need to follow appropriate procedures when adding new substance names to the system to ensure data consistency |
|--------------------|--|

For Computer Operation

| | |
|---|---|
| How to switch the computers on every morning | Local area networks have requirements that must be met to ensure their proper functioning Depending on the setup of the system, users may need to make sure that a given sequence is followed for switching on and off the computers each day |
|---|---|

| | |
|--|--|
| Troubleshooting | Users need to know how to recognize when something is not working properly, how to rectify the situation, alone or with assistance from other staff, and how to prevent the situation becoming worse when problems have occurred. They must also know to call for support when needed. |
| How to perform each administrative procedure | Users need to refer to written procedures indicating, for each administrative procedure, which computer system options are available and what are the procedures and for selecting and using the proper option. |

B Checking Quality of Data

In earlier sections, the importance of having data entry done by professionals and establishing procedures to ensure consistency of data has been discussed. It may be advisable to spot-check the quality of data entered against the hard copies. A few months after computerization has started, no matter which implementation approach has been selected, it is also necessary to review the quality of the information entered for internal consistency. This review should focus on

- Incomplete entries (e.g., MAs for which some pieces of information have never been recorded)
- Duplication of codes/abbreviations (e.g., entries for both "Slow release tablet" and "Tablet, slow release")
- Duplication of substance names (i.e., synonyms not linked to each other)
- Inconsistent information in applications and MAs (e.g., a dosage form of "tablet," with route of administration of "intravenous")

Although a computerized system usually has features that permit users to check data, a thorough analysis of the data usually requires assistance from technical computer professionals who have been involved in the development of the software. There are two reasons for this

- In many cases, the biggest problem is not to identify incomplete entries or duplications, but rather to find ways to provide immediate solutions to inadequate or incorrect data, and to avoid repeating the same mistakes in the future
- Experience has shown that the most common causes of poor quality of data are a) letting too many staff have access to establishing codes and substance names, and b) insufficient training of users

Ensuring quality of information is a crucial part of maintaining a computerized system. If the review of data is not undertaken seriously and regularly, the risk is that the inconsistent information may grow to such a level that the reports and statistics prepared by the computer are not reliable. This seriously affects the credibility and value of the DRA.

C Retaining Staff

The introduction of computer-assisted drug registration is a major undertaking and investment. The investment also involves training of staff. If staff leave the DRA, most of the effort put into their training is lost. Therefore, DRAs should try to ensure that critical staff are not lost to the private sector or other agencies. Some ways to retain staff may include opportunities for training, fair salaries, and establishing an appropriate level of status for the positions.

Several countries in Africa and Latin America have been successful in retaining qualified staff by providing incentives, such as training opportunities, and by ensuring that salaries are maintained at a level competitive with the private sector. This has been made possible by creating a regulatory authority that has a separate administrative set up, while remaining under the control of the Ministry of Health.

D Political Support

No DRA will be successful in the performance of its duties if it does not have full and ongoing government support, particularly during changes of government. The support required is

- Clear and firm legislation that addresses all of the relevant issues and carries appropriate sanctions for violations (see sections on legislation)
- Financial and other resources, consistent with the designated functions, particularly in relation to staffing, office facilities, communications, inspection activities, and a quality control laboratory
- Willingness to defend decisions and policies that benefit public health, but that may be unpopular with those that have vested interests
- Support in the implementation of sanctions

Certainly a DRA cannot control political will. However, DRAs may be able to undertake initiatives to advocate their case with national politicians and consumers. For example, arguments that could be used to improve the image and visibility of a DRA are

- Consumers, especially when they are sick, are unable to assess quality, safety and efficacy of pharmaceuticals, and this assessment cannot be left to pharmaceutical companies alone to conduct
- Regulatory activities can be almost entirely self supported through an appropriate fee collection mechanism
- A strong registration process, along with a qualified team of GMP inspectors, can improve the quality and reliability of domestic manufacturing and, hence, increase the likelihood of exportations

E Maximize Existing Resources

Because resources are usually limited, it is important to take steps that will make the most of them. Several options are listed below, and a regulatory authority could benefit from some or all of these suggestions.

Establish mechanisms to regularly receive technical support from other institutions and individuals

In several countries, one or more technical advisory groups or committees are established to provide technical advice to the DRA. Such advisory groups may consist of national experts in clinical pharmacology, pharmacology, pharmaceutical sciences, clinical medicine, and other areas. The group or theme-specific subgroups could meet once or twice a month to provide advice on specific issues. The group could also define a list of basic criteria, e.g., which fixed-dose combinations are acceptable, a common basic data sheet for drugs of the same profile (as in the WHO Model Prescribing Information, the *British National Formulary*, the *Guide National de Prescription*, the American Medical Association's Drug Evaluations, and other publications), labeling criteria, a "positive" list of active principles (e.g., all accepted benzodiazepines, systemic corticosteroids, etc.), or acceptable excipients. On the basis of these documents the regulatory authority will be able to process registration applications for widely used drugs more expeditiously.

Establish effective and meaningful communications with other regulatory authorities

Regulatory authorities with limited resources (both human and material) may wish to proceed cautiously in licensing drugs containing active ingredients that have not been widely used. When facilities or resources do not allow for analysing a large amount of technical documentation or for conducting appropriate studies (e.g., sufficiently large clinical trials, laboratory analysis, and post-marketing surveillance), ad hoc connections with more advanced regulatory authorities in other countries could be established. This would allow the DRAs to learn from each other's experience and to have a reasonably solid basis for a decision about licensing active ingredients.

A simplified approach that regulatory authorities with limited resources may adopt is the establishment of continuous working relations with two or three highly evolved drug regulatory authorities of countries with a sizeable pharmaceutical market. The DRA could then exclude from registration all active ingredients not registered in at least one of the reference countries, unless exceptional circumstances demonstrated a local need.

In addition, the evaluation, for registration purposes, of manufacturers based abroad is not an easy task for many regulatory authorities. Foreign manufacturers' premises can be visited only sporadically (if at all), and such visits may not be sufficient to allow sound judgements to be made, or have any legal impact. The most practical approach seems to be to establish connections with the regulatory authorities of the countries where manufacturers are based. This would ascertain whether there is a regulatory authority, what task it performs, and on the basis of which criteria it grants manufacturing licences and monitors production meant for national use and for export.

The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce is an administrative tool for the exchange of information among regulatory authorities. Its regular and proper utilization may contribute to a significant reduction in the risk of being confronted with substandard or spurious drugs. However, the value of certifications issued pursuant to the Scheme is determined by the credibility of the issuing DRA.

Create simplified and meaningful procedures and documentation analysis

This may significantly contribute to the efficiency and the reliability of the evaluation of applications. In all cases where the safety and efficacy profile of the product for which registration is sought is well established, and the licensing authority is satisfied with the available information showing that this item meets recognized therapeutic needs, quality becomes the most important concern in evaluating an application. If regulatory authorities with limited human and material resources limit most of their licensing activities to well-established drugs, they will be better able to evaluate the manufacturing process and its controls, the specifications of the medicinal product and its regulatory status in other countries, and the GMP profile of the manufacturer.

Example Assessing marketing applications in a very small, yet computerized, regulatory authority

In this example, a “very small” regulatory authority is one that does not have enough staff to carry out its own assessment for all applications for marketing authorizations that it may receive. Apart from situations of war or long-lasting civil unrest, there are two situations where “very small” regulatory authorities can be found:

- Countries where the market size is sufficiently large and the political situation is sufficiently stable to motivate domestic and foreign companies to engage in drug manufacturing and trade. In this situation, the DRA should try to build the necessary political support to establish a full fledged regulatory body. However, until this is achieved, the approach described here may be considered.
- Small countries with a very small market, often with communication or transportation difficulties. In these situations, the market size for many drugs is so small that the number of potential suppliers is also small. Virtually no manufacturer submits applications for marketing authorizations, and only a few importers ensure regular supply and, if required, submit applications for import permits.

Very small DRAs need to establish priorities to ensure that the best outcome is achieved. In most cases, local production is very small, therefore the priority of regulatory work is to ensure reliable quality and a regular flow of imported supplies. To achieve this, collaboration with importers in both the public and private sectors is crucial. Such collaboration should aim at identifying the most favourable balance among these options:

- Too many regulatory/administrative requirements may overburden small companies, causing a negative impact on drug prices, and reducing the number of companies willing to do business in or with the country.
- Too little regulatory control would put consumers in the hands of importers --who are not necessarily properly qualified-- without sufficient protection from the state.
- Limiting the sourcing of pharmaceuticals to a predefined number of countries with effective regulatory capacity, and making regular use of the WHO-type product certificate may significantly reduce the risk of being confronted with substandard or spurious drugs, but may yield satisfactory results for a limited list of drugs in terms of price and accessibility.

With limited staff and resources, computerization of information can be helpful. However, with limited resources it may be impossible to include every piece of data about an application or MA. An example of the minimum information that a very small regulatory authority may consider is

- application number and date
- applicant
- drug name
- strength
- dosage form
- primary container
- active ingredients & their amounts by dosage unit
- indications for use
- manufacturer responsible for releasing final dosage form for marketing
- dispensing category
- therapeutic classification
- origin

Access to this basic information on authorized products and efficient handling of import permits are crucial elements that permit sound management of the regulatory aspects of drug supply and guarantee credibility for the DRA, even when the institution is very small

In an African country with three manufacturing units producing only oral solid and liquid forms, two pharmacists and a secretary have been assigned to drug registration activities, and one chemist and three laboratory technicians for the QC laboratory. No GMP inspectors are available.

In this situation, it has been decided that

→ Since no thorough assessment of applications for marketing authorization can be carried out, authorizations will be given only to products accompanied by a reliable WHO-type product certificate

→ A list of reference countries whose certificates are accepted is established and kept up to date

→ Drugs that are not included in the national drug formulary are registered only under exceptional circumstances of documented high public interest and after the decision of a specialized committee

→ QC lab activities should focus on domestic products, and on imported products that are manufactured in reference countries, have acceptable certification, but are not identical to those marketed in the exporting country

→ Resources will be made available to permit the two pharmacists engaged in drug registration to visit other regulatory authorities and receive ad hoc training in order to improve their skills and knowledge

Annex 1 List of Acronyms

| | |
|--------|--|
| ADR | Adverse Drug Reaction |
| AHFS | American Hospital Formulary Service |
| ATC | Anatomic Therapeutic Chemical (classification scheme) |
| CADR | Computer-Assisted Drug Registration |
| CAS | Chemical Abstract Service |
| DDD | Defined Daily Dose |
| DGCS | Direzione Generale per la Cooperazione allo Sviluppo |
| DOS | Disk Operating System |
| DRA | Drug Regulatory Authority |
| GCP | Good Clinical Trial Practices |
| GMP | Good Manufacturing Practices |
| GTZ | Gesellschaft für Technische Zusammenarbeit |
| INN | International Nonproprietary Name |
| INN.M | International Nonproprietary Name, Modified |
| MA | Marketing Authorization |
| MB | Megabyte |
| MOH | Ministry of Health |
| NCE | New Chemical Entity |
| OTC | Over the Counter |
| PI | Product Information |
| QC | Quality Control |
| RAM | Random Access Memory |
| USAID | United States Agency for International Development |
| USP-DI | United States Pharmacopoeial Convention - Drug Information |
| VA | Veterans Administration |
| WHO | World Health Organization |

Annex 2 The Drug Registration Process

Drug registration is a system that subjects all pharmaceutical products to pre-marketing evaluation, marketing authorization, and post-marketing review to ensure that they conform to required standards of quality, safety, and efficacy established by national authorities. The outcome of the drug registration process is the issuance or the denial of a pharmaceutical product marketing authorization or licence.

The registration process entails the steps described in the following diagrams. The first, "Assessment of Applications for New Marketing Authorizations," provides a global description of the registration process. Not all the areas of assessment (i.e., those indicated in boxes in the chart) are relevant for all drug products. For example, safety and efficacy assessment is required for new chemical entities (NCE) only, interchangeability applies only for generic products, and not all countries include price as part of the assessment of an application for MA. The second chart describes assessment of imported well established products.

Decisions on applications are made on the basis of assessment reports prepared by qualified staff. To carry out drug registration a DRA may

- Prepare its own reports,
- Rely on reports prepared by other national authorities,
- Rely on decisions made by other national authorities, or
- Apply a combination of the above options, which is the most frequent case.

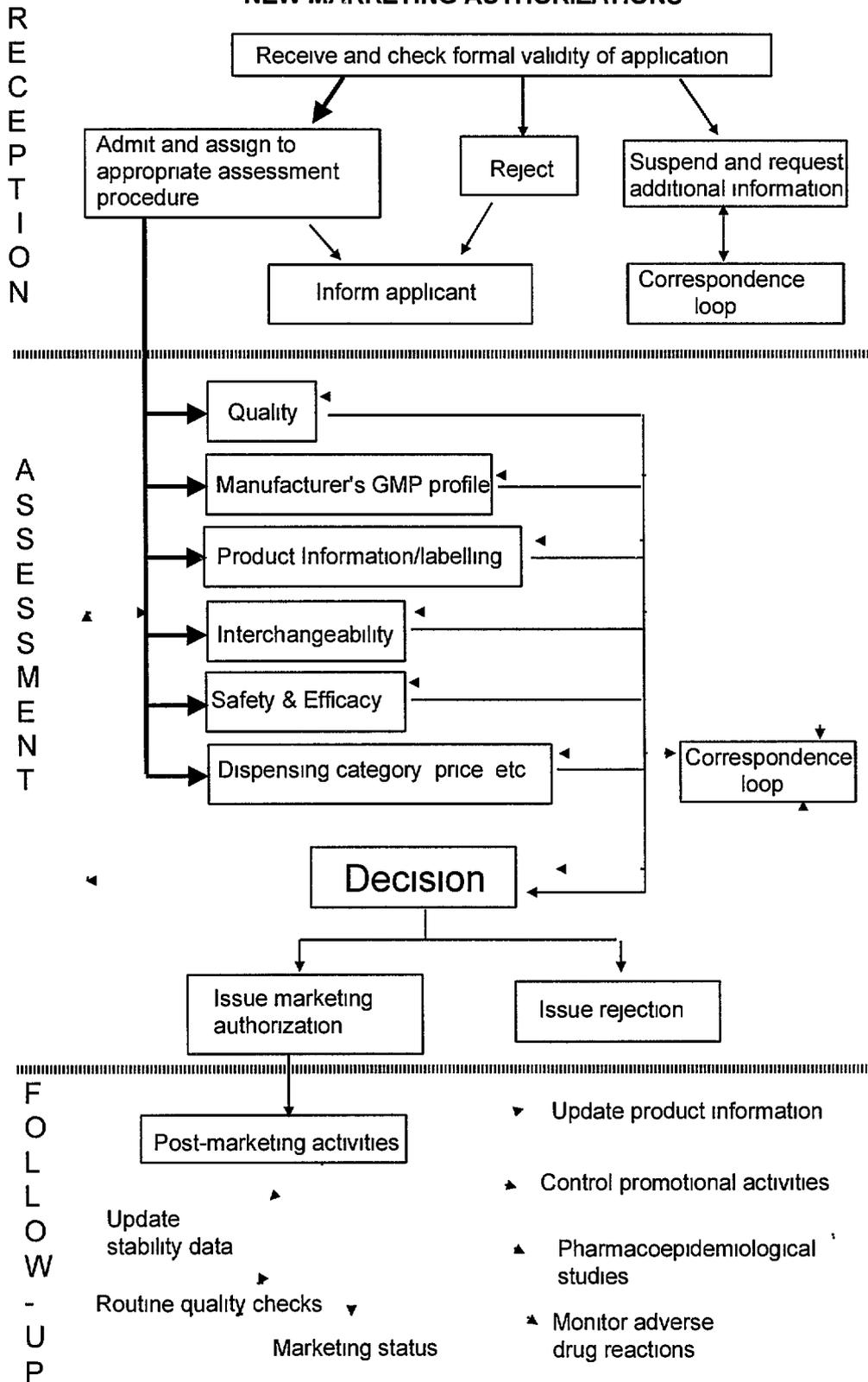
An assessment report may include

- A brief outline of the information provided in the application
- The reasons for any disagreement with the applicant's proposals
- A summary and evaluation of information on interchangeability (when applicable), with recommendations and reasons
- A proposal of final decision

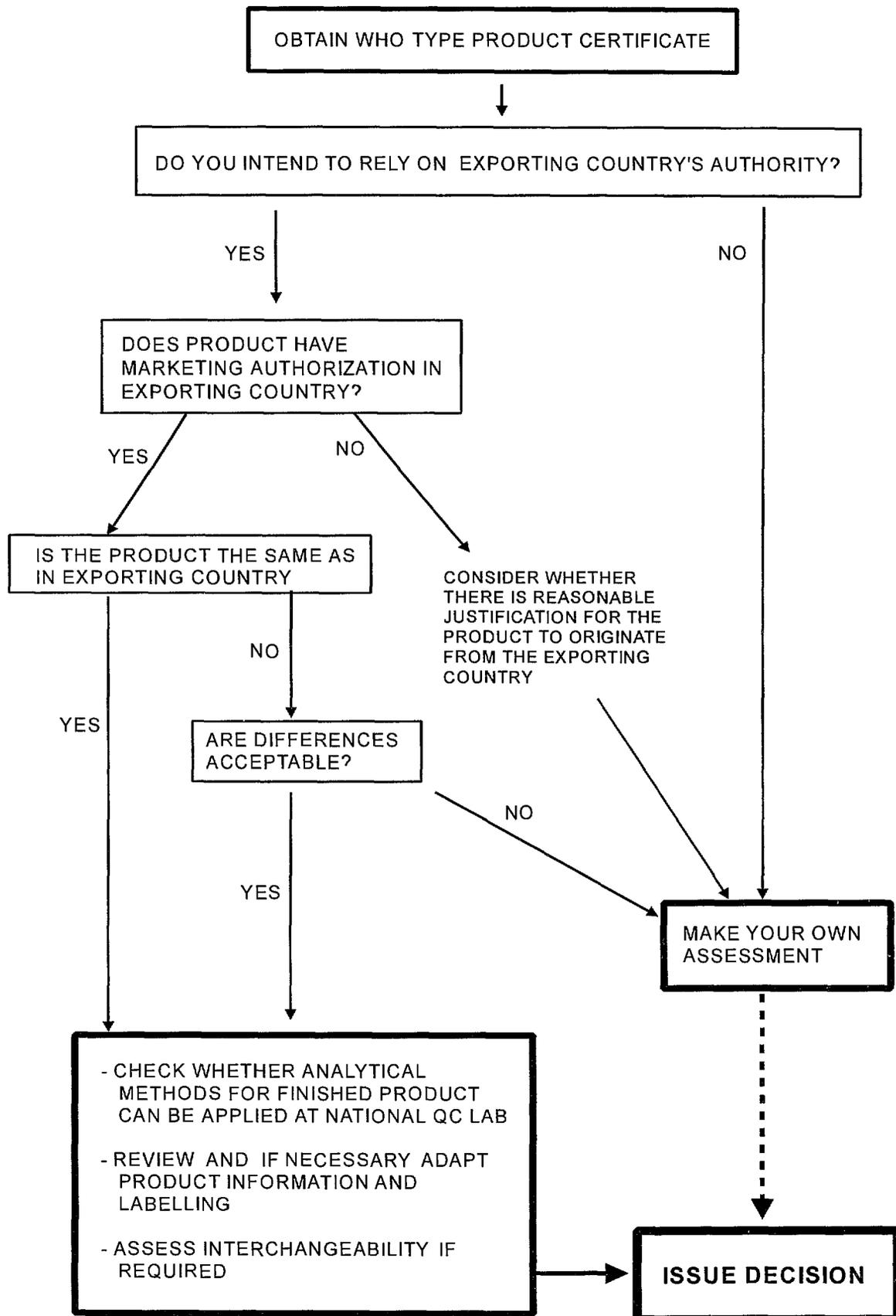
If the DRA finds that the information submitted is incomplete or does not agree with statements, conclusions, or proposals made by the applicant, an appropriate letter is usually sent to the applicant. In general, such letters are requests for additional information or explanation on specific issues. They are referred to as the "correspondence loop" in the first chart. Relying on a scientific report prepared by another national authority may entail starting a correspondence loop, if the data set submitted is not the same as the one submitted to the other regulatory authority.

When assessing imported products, it is recommended that a WHO-type certificate with approved product information be obtained in all cases, together with assurance by the applicant that the product to be supplied is identical in all aspects of manufacturing and quality to that approved in the exporting country. As presented in the second chart, it will also be necessary to consider whether the proposed product information is appropriate in the importing country.

ASSESSMENT OF APPLICATIONS FOR NEW MARKETING AUTHORIZATIONS



DECISION CHART FOR MARKETING AUTHORIZATIONS USING WHO-TYPE PRODUCT CERTIFICATE



Annex 3 Specific Aspects of Drug Registration Legislation

When reviewing pharmaceutical legislation and regulations, there are certain provisions and definitions that should be considered. Below is a list of legislative features and functions that should be carefully reviewed to ensure that the drug regulatory authority has the appropriate rights and responsibilities to function effectively.

- 1 **Definition of Terms** If definitions of any terms are ambiguous, vague, and/or leave room for too many exemptions, then all of the rules and regulations that follow from them may become invalidated or ineffective.
- 2 **Range of Objects to Be Regulated** The scope of the items under the control of the DRA should be clearly stated. The inclusion of items such as veterinary drugs, products of natural origin, or herbal remedies, may be controversial. In principle, the criterion that should be applied is that regulation must encompass all items, of whatever origin, that are sold, intended or used for therapeutic or diagnostic purposes, anaesthesia, or contraception. In addition, consideration of the potential indirect intake of substances from food-producing animals explains why, in some countries, the same DRA assessing human drugs also regulates pharmaceuticals for veterinary use.
- 3 **Obligatory Procedure** Provisions should exist that prohibit and inconvenience importation, sale, and distribution of pharmaceuticals before an application has been submitted and a marketing authorization has been issued by the appropriate authority.
- 4 **Right and Purpose of Inspection** A provision that allows the DRA
 - to dispatch inspector(s) to manufacturing sites to ensure compliance with necessary regulations and standards, such as GMP, that cannot be assessed from submitted documents alone, and that need verification, and
 - to suspend or withdraw manufacturing or marketing licences whenever the necessary conditions for their validity are no longer in place.
- 5 **Restriction of Availability/Distribution** A provision that allows the DRA to limit the availability of selected pharmaceuticals to hospitals, designated centres, and/or specialist's prescription.
- 6 **Exceptional Import** A provision that allows the DRA to grant exemptions for importation of unlicensed pharmaceuticals, based upon the completion of an established procedure, when special reasons arise (e.g., clinical trials, specific patient requirements, emergency situations, etc.).
- 7 **Need Clause** A provision that permits rejection of applications or cancellation of marketing authorizations for medicinal products on the basis of considerations of their capability to meet a recognized therapeutic or commercial need. Examples of such considerations are
 - cost of treatment course is equal to or higher than that of products already marketed for the same indications, which have comparable therapeutic efficacy and adverse reaction profile, and are marketed in sufficient number to permit competition and regular availability, and
 - it is irrational to maintain the validity of the marketing authorization of a drug that, although effective when compared to placebo, is inferior to a new therapeutic strategy in terms of efficacy, safety, and/or cost profile.
- 8 **Non-Reimbursability of Application Fee** A provision that establishes that the payment of

application fees is final. No reimbursement of fees should be permitted, including in the case of rejection or in the case of withdrawal of the application by the applicant.

- 9 **Request for Supplementary Information** A provision that allows the DRA to request information or documentation supplementary to that required in application forms, in order to better establish safety, efficacy, quality and need of the pharmaceuticals under assessment for registration as well as pharmaceuticals already authorized.
- 10 **Consultation with External Experts** A provision that allows the DRA to summon external specialists to act in an advisory capacity whenever deemed necessary.
- 11 **Cancellation, Suspension, or Withdrawal of Marketing Authorization or Product Recall/Withdrawal** A provision that allows cancellation or suspension of marketing authorization, and/or recall or withdrawal of product batches already available at distribution outlets, when any of the following happens
 - manufacturer does not meet the required conditions,
 - the marketing authorization is found to have been obtained with fraudulent or inaccurate information,
 - safety concerns due to new serious adverse reactions,
 - necessary circumstances under which the marketing authorization was granted cease to exist,
 - no export authorization of the exporting country is available for certain imported drugs classified as controlled drugs,
 - unethical promotion, or
 - it is considered in the public interest to do so.
- 12 **Good Manufacturing Practices** A set of principles, technical indications and provisions that guides the work of pharmaceutical manufacturers and inspectors. These can be fully developed at the national level or adopted/adapted from existing documents such as the WHO Guidelines for Good Manufacturing Practices (GMP).
- 13 **Empowerment for the Establishment and Regular Update of Regulatory Categories and Classifications** Provisions that empower the DRA to establish and keep up to date dispensing categories (e.g., prescription, OTC, etc.), therapeutic classifications to be used for marketing authorization purposes, other definitions of product categories (e.g., generic drugs, reference products, etc.).
- 14 **Empowerment to Perform Specific Regulatory Functions** Provisions that empower the DRA to establish and keep up to date regulations on advertisement, promotion, distribution of free samples, clinical trials, etc.
- 15 **Empowerment to Establish Sanctions** Provisions that empower the DRA to establish and impose realistic and proportionate sanctions when regulations are infringed.
- 16 **Prohibition of Offer of Inducement** A provision that prohibits distributors, and manufacturers when acting as distributors, to offer cash, equipment, merchandise or any gift to prescribers and/or purchasers as an inducement to purchase their products.
- 17 **Post-Marketing Surveillance** Provisions to establish obligation, exemption, ways, responsibilities, and use of information obtained concerning post-marketing surveillance.

18 **Obligations of the Drug Regulatory Authority** To ensure transparency of decisions and credibility, the DRA should have certain obligations. These should include at least the following:

- to regularly (e.g., quarterly) publish information on approved pharmaceuticals: name, dosage form and strength, final manufacturer, authorization number and validity, approved indications, contraindications and limitations of use, dispensing category, storage conditions, and, if applicable, price and social security reimbursement status,
- to promptly convey information about cancellations or restrictions of validity of marketing authorizations, as well as all other important announcements of their major variations,
- a confidentiality agreement that binds staff and consultants of the DRA regarding all information obtained in the performance of their duty (inspection of premises, assessment of applications, or administrative work) unless otherwise required by law or criminal investigation,
- an obligation for all staff and consultants of the DRA to have no financial interest in the pharmaceutical industry,
- separation of drug regulatory functions from manufacturing or procurement functions

Annex 4 Minimum Requirements for a Drug Regulatory Authority

A Office Space and Equipment

- **Computer room** The room should be at least 12 square metres with tables and shelves to store reference books and files under consideration. It should be a climate-controlled, secure room that is not susceptible to leaks or flooding. This room should be used for the server computer in a networked office, or the primary computers in a non-networked office.
- **Room where applications are received** This room should be at least 12 square metres with a desk to receive people submitting applications and to provide information, forms, and materials. It should also have tables and shelves to store reference materials and files before distribution for assessment, and shelves or cupboards to temporarily store samples and packaging.
- **Waiting room** The room should be at least 12 square metres with a sitting area and, on the walls, instructions for applicants (e.g., a list of documents to submit for each type of application).
- **File room** This room should be at least 50 square metres with a desk and shelves to store files after assessment is completed and decision published. Files are stored by an established criterion, e.g., registration number, product name, or MA holder name in alphabetical order.
- **Staff offices** If there are separate offices, they should have desks with a computer terminal.
- **Computers/Printers** At least two computers, one dedicated to the drug registration software system, and one for correspondence and other purposes, should be available. The minimum recommended specifications for these computers are 486 processor, 4 MB of RAM, and 100 MB of free hard drive space. At least one printer should also be available for use with the drug registration software system.

B Staff

An experienced pharmacist or medical doctor with special training and experience in assessing MA applications should be appointed as team leader/chief/director. At least two additional technical professionals should be assigned to assess applications, prepare reports, and propose final decisions. An appropriate number of support staff should also be assigned to the DRA.

C Legislation, Regulations, Guidelines, Instructions

Several updated copies of all relevant legislation, regulations, and other written materials should be reliably available (at least one per technical professional staff, plus spare copies to permit on-site public consultation).

D Reference Books and Manuals

The following materials should be available, in numbers proportionate to the size of the staff:

- **Software package user manuals**

- **Lists and criteria** for definitions, abbreviations, and codes used in the recording of information and decisions made during assessment of applications
- **Reference books** At least the following should be reliably available
 - ▶ INN Cumulative List, Color Index, Merck Index, and Martindale to help identify active and inactive substance names These do not waive applicant's obligation to submit source of substance names used in applications
 - ▶ Books and/or compact disks publishing approved product information in reference countries, e g , USP-Dispensing Information, British National Formulary, Vidal, to help assess product information (indications, contraindications, adverse effects, etc) These do not waive applicant's obligation to submit, in the case of imported products, or products also marketed in other countries, an up to date certificate providing the same information as in the WHO Certification Scheme

E Administrative Tools

- **Registers**
 - ▶ new drug applications log
 - ▶ renewal applications log
 - ▶ variation applications log
 - ▶ MAs log
 - ▶ national essential drugs list
 - ▶ hospital use only drug list
 - ▶ other special lists as appropriate
- **Model certificates and correspondence**
 - ▶ MA
 - ▶ revised MA
 - ▶ letter informing of rejection of application
 - ▶ letter informing of cancellation of/variation to MA
 - ▶ letter requesting additional information/documentation to support application
 - ▶ application follow-up form
 - ▶ WHO-type product certificate
 - ▶ other forms/letters as applicable
- **MAs and revised MAs should include at least**
 - ▶ product name
 - ▶ dosage form
 - ▶ dosage strength
 - ▶ presentation
 - ▶ primary container
 - ▶ MA holder name and address
 - ▶ name and address of final manufacturer
 - ▶ approved names and quantities of active ingredients
 - ▶ approved names and quantities of inactive ingredients that may be of concern for a number of potential consumers (e g , tartrazine, ethanol, saccharose)
 - ▶ approved product information (ie, indications, mode of administration, contraindications, adverse reactions, precautions, use in children/elderly/pregnancy/other special situations (if any), food and drug interactions)
 - ▶ shelf life and storage conditions
 - ▶ registration number

- **Application folder** An application folder should be used to keep
 - ▶ application
 - ▶ copy of MA in other countries, WHO-type certificate, any other required certificate
 - ▶ proposed price and proof of price in other countries
 - ▶ receipt of payment of application fee
 - ▶ technical documentation supporting application
 - ▶ reports prepared by regulatory staff or external experts during assessment
 - ▶ report of national quality control laboratory, where applicable
 - ▶ any other documentation concerning the application and its assessment

F Written Working Procedures

There should be written working procedures available at least for the following items

- Reception, classification, and numbering of applications
- Preparation of application folder
- Recording of application data into computer system
- Distribution of application, or parts of it, to those in charge of its assessment
- Assessment criteria, guidelines, and procedures
- Preparation of assessment reports
- Preparation of decision proposal
- Decision
- Communications with applicants

Annex 5 Glossary

Applicant/licence holder This is the company submitting the application. Usually it is the owner of the trademark, where applicable. If the application results in a marketing authorization, this company becomes the holder of such authorization. Licence holder and marketing authorization holder are synonyms. For each product only one company can be the applicant/licence holder.

Application for certificate An application submitted by the MA holder to obtain a certificate describing the regulatory status of a given product or the GMP status of manufacturing premises. Product certificates are usually requested in order to export products. When product certificates are issued, it is important that no less than the minimum information required should be released. For a pharmaceutical product, the minimum information required is what established in the WHO Certification Scheme.

- Presence of an MA in the exporting country
- Reasons for not having an MA, if applicable
- Conditions under which MA has been issued (i.e., validity of MA, full product information, and dispensing category)
- GMP profile of manufacturer
- Statement on regularity of inspection to manufacturing of the dosage form object of the certificate

The elements contained in a certificate of this type complement each other. Certificates including less than this information may lend themselves to misinterpretation.

Distributor In some countries, regulations establish that importation or wholesale of a given drug product can be done only by selected companies. A drug registration system should accept several different distributors. Up to fifty different distributors can be related to each individual drug product in the WHO system.

Generic product See multi-source product.

Innovator product Generally, the innovator pharmaceutical product is that which was first authorized for marketing, usually as a patented drug, on the basis of documentation of efficacy, safety, and quality (according to contemporary requirements and criteria). In the case of drugs that have been available for many years, it may not be possible to identify an innovator pharmaceutical product.

Manufacturer This is any company that in some way participates in the manufacturing of a drug product. A drug registration system should accept several different manufacturers for the same drug product (the WHO system can accommodate up to 50), permitting specification of the role for each of them, e.g., source of starting materials, preparation of semifinished product, formulation, labelling, repackaging, etc. The fact that the software permits several manufacturers to be listed should not mislead users from the widely accepted and recommended understanding that the manufacturer who last manipulated the drug product, albeit only for repackaging, and releases it for marketing bears the entire responsibility for the quality of the product and for ensuring that any starting material, intermediate, or finished dosage form meet the required standards.

Multi-source product A multi-source pharmaceutical product, also called a generic product, is a product pharmaceutically equivalent to an innovator product (see definition above). It is usually intended to be interchangeable with the innovator product. It is usually manufactured without a licence from the innovator company and marketed after expiry of patent or other exclusivity rights. A multi-source product can be sold under a brand name (sometimes called a branded generic) or under its generic name (usually the INN of its active ingredient).

Operating licence

- **Company operating authorization** This refers to an authorization given to company to perform a given activity falling under the control of the drug regulatory authority. It is also called an operating licence or permit. If a company carries out more than one activity, it may have separate operating licences for each individual activity.
- **Other types of company-related authorization** In some countries, the regulatory authority needs to record information linking companies with other institutions, e.g., Ministry of Industry, Ministry of Finance, or Customs. These pieces of information are called various things, e.g., Ministry of Industry Number, Customs Number, etc.

PI See Product Information

Product Information A complete document giving indications, contraindications, mode of administration, adverse reactions, precautions, use in selected population groups (newborns, infants, children, pregnant/breast feeding women, elderly, other as appropriate), and any other information that should be considered in connection with the clinical use of the product. The PI is the reference document on the basis of which prescribing information, patient information, and promotion materials must be prepared.

Summary of Product Characteristics See Product Information

Variation Any change made to selected information related to an existing, valid marketing authorization. Depending on established regulations, the type and extent of variations permitted vary from country to country. Variations admitted in some countries entail, elsewhere, issuance of a new marketing authorization and cancellation of the previous one. To accommodate such a variety of requirements, the registration software should permit recording variation of all marketing authorization data except the number and validity. In all cases the history of variations must be recorded and be available for future reference.

Annex 6 Sample Data Entry Form

Below is an example of a data entry form for an application for a new marketing authorization
Depending on type of data, entry can be a code or the full description or name

| | |
|---|--|
| Application number | |
| Date of receipt | |
| Applicant name | |
| Representative name | |
| Medicinal product name | |
| Strength | |
| Dosage form | |
| Route(s) of administration | |
| Presentation(s) | |
| Generic name | |
| Primary container | |
| Specifications of primary container | |
| Circle appropriate entry Domestic/Imported Generic/Branded Human/Veterinary | |
| Therapeutic classification | |
| Dispensing category | |
| Restrictions on availability | |
| Shelf life | |
| Storage conditions | |
| Fees and date of payment | |
| Manufacturer responsible for lot release Name Responsible person | |

65.

Annex 7 Further Reading

Ethical Criteria for Medicinal Drug Promotion Geneva, World Health Organization, 1988

Good Manufacturing Practices for Pharmaceutical Products, in *WHO Expert Committee on Specifications for Pharmaceutical Preparations Thirty-second report* Geneva, World Health Organization, 1992 14-79 (WHO Technical Report Series, 823)

Guidelines for ATC Classification and DDD Assignment Oslo, Norway, WHO Collaborating Centre for Drug Statistics Methodology, 1996

Guidelines for Implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, in *WHO Expert Committee on Specifications for Pharmaceutical Preparations Thirty-fourth report* Geneva, World Health Organization, 1996

Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances Geneva, World Health Organization, 1997 (WHO/PHARMS/NOM 1570)

Guiding Principles for Small National Drug Regulatory Authorities in *WHO Expert Committee on Specifications for Pharmaceutical Preparations Thirty-first report* Geneva, World Health Organization, 1990 64-79 (WHO Technical Report Series, 790)

Marketing Authorization of Multisource (Generic) Pharmaceutical Products A Manual for A Drug Regulatory Authority Geneva, World Health Organization, 1998 (In print)

National Drug Legislation Guiding Principles for Small Drug Regulatory Authorities, in *WHO Expert Committee on Specifications for Pharmaceutical Preparations Thirty-fifth report* Geneva, World Health Organization, 1998 (In print)

“Pharmaceutical Legislation and Regulation,” chapter 7, in *Managing Drug Supply*, second edition Management Sciences for Health/World Health Organization West Hartford, CT Kumarian Press, 1997

The Use of Essential Drugs Seventh Report of the WHO Expert Committee on the Use of Essential Drugs Geneva, World Health Organization, 1997, WHO Technical Report Series, 867,

User Manual for SIAMED, the WHO Model System for Computer-Assisted Drug Registration Geneva, World Health Organization, 1998

WHO Model System for Computer-Assisted Drug Registration A Brief Description Geneva, World Health Organization, 1996