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Current Trends in Follow up Procedures with MOH for the Registration of the Pharmaceutical Products

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Abstract: Regulatory Authorities in both developed and developing countries share the responsibility of ensuring the access to safe and effective medicines to patients. For better treatment safety and efficacy of the drugs must be justified and rationalize for public security. The quality, safety, efficacy data has its own importance in the registration dossier. The International Conference on Harmonization (ICH) Common Technical Document (CTD) can serve as a resource for most local Marketing Authorization (MA) applications. Additionally, a significant amount of mandatory and highly country specific documentation require strategic planning and allocation for successful and timely local approvals. Regulatory involvement in the drug approval process which directly/indirectly accelerated the launching of the drug into the market. The regulatory documents whether in-house of documents to be submitted to regulatory authorities should be carefully reviewed by the skilled person to minimize raised by the regulatory agencies and speed up the approval process.

Keywords: Regulatory Authorities, International Conference on Harmonization (ICH), Common Technical Document (CTD), Marketing Authorization (MA)

INTRODUCTION

Introduction to Regulatory Affairs

Regulatory Affairs (RA) is also called as government affairs, are a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory affairs also have a very specific meaning within the healthcare industries. Regulatory affairs is a comparatively new profession which developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.**[1]**

History of Drug Regulation

The history of drug regulation in India dates back to British rule when the majority of drugs were imported. The Indian Council of Medical Research (ICMR) was created in 1949 to guide and manage medical research. The first Drugs and Cosmetics Act came into effect in 1940 and was later amended as the Drugs and Cosmetics Rules of 1945. The 1945 amendment established the CDSCO and the DCGI. The document is in constant evolution and has included multiple amendments covering new developments. The most recent additions are likely to take effect this year. A specific sub-Drugs and Cosmetics Act was developed, called Schedule Y, to regulate clinical research conduct. The Department of Biotechnology was created in 1986 to facilitate various aspects of biotechnology. ICMR issued the Ethical Guidelines for Biomedical Research on Human Subjects in 2000, and the CDSCO released the Indian Good Clinical Practice Guidelines in 2001. Together, these agencies assist the licensing authority in issuing final marketing approvals for the product.**[3]** In India, drugs are regulated both at central and state level. At the central level, CDSCO (Central Drugs Standard Control Organization) under the Ministry of Health and Family Welfare is responsible for approving new drugs, clinical trials and licensing of drugs. At the state level state drug regulatory authorities issues licenses to manufacture approved drugs to monitor the quality of the drugs along with CDSCO.**[2]**

OBJECTIVE

The primary objective of this guidance documents is to provide transparent and clear guidelines and procedures for the registration of pharmaceutical products manufactured, imported, exported, distributed products conform to acceptable standards of quality, safety, and efficacy.

DISCUSSION

Global market is divided into

1. **Regulated market: The** US, EU (UK, Germany, France, Ireland and Sweden etc.), Japan, Australia, New Zealand, Canada, and South Africa.
2. **Semi Regulated Market (ROW countries):**
   - **A. Asia:** (Srilanka, India, Bangladesh, ASEAN 10 Counties group- Philippines, Vietnam, Singapore, Malaysia, Thailand, Indonesia, Laos, Cambodia, Brunei, Darussalam, Myanmar)
   - **B. African countries:** (Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe etc.)
   - **C. Middle East countries:** (Gulf cooperation council countries i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE)
   - **D. Latin America**: (Mexico, Brazil, Peru, Colombia, Chile, Argentina, Venezuela, Cuba, Panama)
   - **E. CIS (Commonwealth of independent states):** Russia, Ukraine, OFSUs (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirgizstan, Moldova, Tajikistan, Turkmenistan, Uzbekistan etc.)**[3]**

I. INDIA

Approval of New Drug in India

When a company in India wants to manufacture/import a new drug it has to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population, it has to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in the specified format.

But a provision is there in Rule - 122A of Drugs and Cosmetics Act 1940 and Rules 1945 that the licensing authority may waive certain trails if he considers that in the interest of public health he may grant permission for import of new drugs basing on the data of the trials done in other countries. Similarly, there is another provision in Rule - 122A which says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries.

Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required.

Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed with Phase III clinical trials.

Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that the licensing authority may require pharmacokinetic studies (Bioequivalence studies) first to show that the data generated in Indian population is equal to data generated abroad and then require him to proceed with Phase III trials.

In summary, the exact requirements of Clinical trials may change from case to case and depend on the extent to which licensing authority is satisfied with its safety and efficacy. The process of approval of the new drug in India is a very complicated process, which should meet necessary requirements along with NDA to FDA. The need of the present work is to study and document the requirements for the process of approval of the new drug in India with emphasis on clinical trials as per Drugs Control Department, Government of India.**[4]**

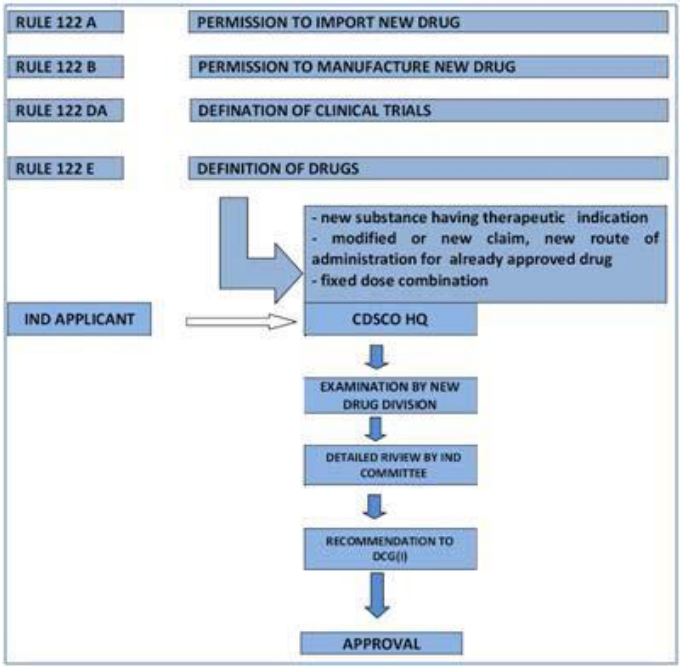

Figure 3: Pictorial representation drug approval process in India [5]

Stages of approval

1. Submission of Clinical Trial Application for evaluating safety and efficacy.
2. Requirements for permission of new drugs approved.
3. Post approval changes in biological products: quality, safety and efficacy documents.
4. Preparation of the quality information for drug submission for new drug approval.**[6]**

1. Submission of Clinical Trial Application for Evaluating Safety and Efficacy

All the data listed below have to be produced.

(a) **Phase-I & Phase- II clinical trial:**

- General information
- Introduction about company: Brief description about company
- Administrative headquarters: Provide address of company headquarters
- Manufacturing Facilities: Provide address of company headquarters
- Regulatory and intellectual property status in other countries.
- Patent information status in India & other countries
- Chemistry manufacturing control
- Product Description: A brief description of the drug and the therapeutic class to which it belongs.
- Product Development
- Strain details
- Information on drug substance
- Information on Drug Product
- Non-clinical data: References: schedule – Y, amendment version 2005, Drugs and Cosmetics Rules, 1945
- Proposed phase-I / II studies: protocol for phase-I /II studies

(b) **Phase-III clinical trial:**

All the information is as same as phase-I & Phase- II clinical trial

- General information
- Chemistry manufacturing control
- Non-clinical data
- Proposed phase-III studies

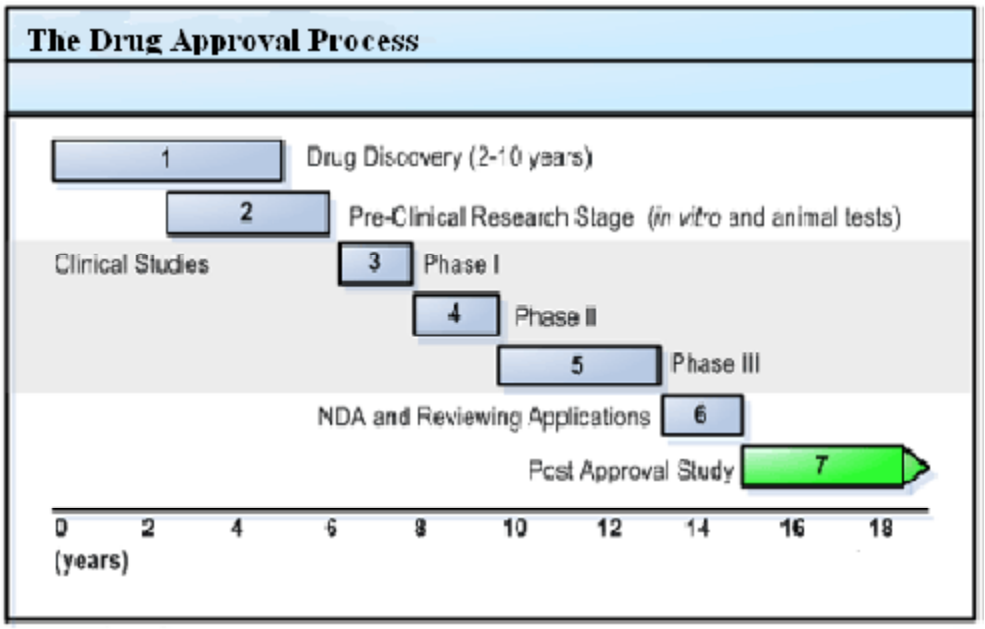

Figure 5: The drug approval process as a function of time

2. Requirements for permission of New Drugs Approval

The manufacturer/sponsor have to submit an application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945. The document design is as per the International submission requirements of Common Technical Document (CTD) and has five Modules.

Module I: **Administrative/Legal Information:**

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module II: **Summaries:**

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action and proposed clinical use. In general, the introduction should not exceed one page. The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It contains the CTD summaries for quality, safety, efficacy information. This module is very important, as it provides detailed summaries of the various sections of the CTD. These include a Quality overall summary, Non-clinical overview, Clinical overview, Nonclinical wrote and tabulated summaries for pharmacology, pharmacokinetics, and toxicology.

Module III: **Quality information (Chemical, pharmaceutical and biological):**

Information on quality should be presented in the structured format described in the guidance M4Q. This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products. It contains all of the quality documents for the chemistry, manufacture, and controls of the drug substance and the drug product.

Module IV: **Non-clinical information:**

Information on safety should be presented in the structured format described in the guidance M4S. The purpose of this section is to present a critical analysis of the non-clinical data pertinent to the safety of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative and should explain why and how the data support the proposed indication and prescribing information. It gives a final copy of all of the final nonclinical study reports.

Module V: **Clinical information:**

Information on efficacy should be presented in the structured format described in the guidance M4E. It gives clinical summary including biopharmaceutics, pharmacokinetics and pharmacodynamics, clinical pharmacology studies, clinical efficacy, clinical safety, synopses of the individual studies and final copy of detailed clinical study reports.**[7]**

3. Preparation of the quality information for drug submission for new drug approval

1) Drug substance (name, manufacturer)
2) Characterization (name, manufacturer)
   - Physicochemical characterization
   - Biological characterization
3) Drug product (name, dosage form)
4) Control of drug product (name, dosage form)
5) Appendices
   - Facilities and equipment (name, manufacturer)
   - Safety evaluation adventitious agents (name, dosage form, manufacturer).

II. MALAYSIA

DRUG APPROVAL SYSTEM IN MALAYSIA

Investigational New Drug application

1 Overview

1.1 Type of applicant of a clinical trial:

There are two types of the applicant of a clinical trial:

- An investigator
- An authorized person from a locally registered pharmaceutical company/sponsor/ Contract Research Organization (CRO) with a permanent address in Malaysia.**[8]**

1.2 Product required for clinical trial permission:

Before commencing any clinical trial involving product(s) that requires Clinical Trial Import License (CTIL)/Clinical Trial Exemption (CTX) and prior importation/ manufacturing product locally for the study, the investigator/sponsor shall be required to submit an application for CTIL/CTX to the NPCB.

The following products will require a CTIL/CTX

- A product including placebo which is not registered with the DCA and is intended to be imported for the clinical trial purpose.
- A product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form and when used for unapproved indication/when used to gain further information about an approved use for the clinical trial purpose.
- A traditional product with a marketing authorization with an indication for "traditionally used" when used for unapproved indication/therapeutic claims for the clinical trial purpose.
- An unregistered product including placebo manufactured locally for the purpose of the clinical trial.**[9]**

2 Procedure

The CTIL/CTX application process is shown in Figure 6 as below. **[10]**

3 Interview advice meeting

There is no special regulation for pre-meeting.

4 Review period:

Table 2. CTIL/CTX Application Processing Days and Submission Fee

Classification	Processing days	Submission fee
Phase I trial, Biologics, cell and gene therapy product as well as herbal product	45 working days	The CTIL application processing fee is RM 500.00 per product. Note: Foreign currencies are not acceptable. The processing fee is not refundable. Application for CTX is free of charge.
All products except those Products mentioned above.	30 workings days	

Under normal circumstances, all CTIL/CTX applications will be assessed within the following timeline:

Day 0 is the day of receipt of complete CTX/CTX application. During the evaluation phase, the evaluator may have query raised related to the application.

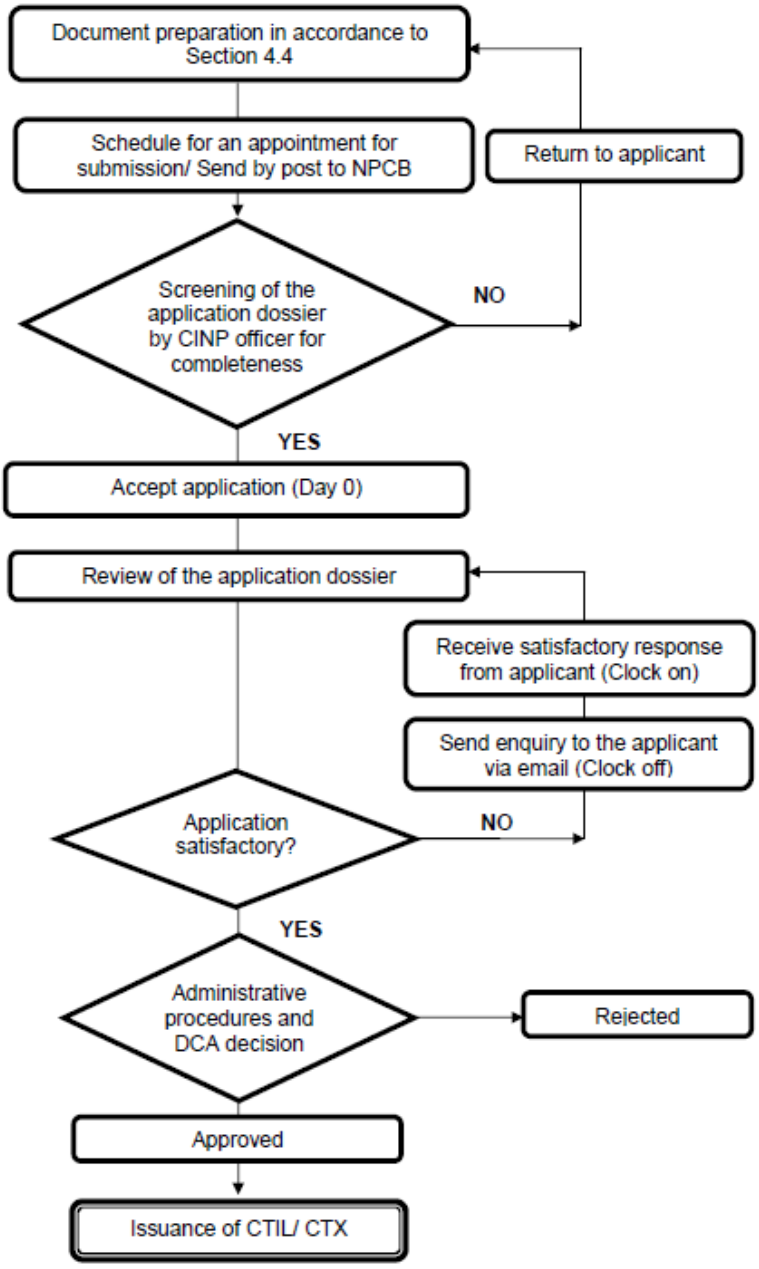

Figure 6. Flow Chart: CTIL/CTX Application Process

The clock will stop the day the query emailed to the applicant. The applicant is expected to respond to the query within 30 working days. Should the answer received to the query is found to be unsatisfactory, only additional 10 working days will be given for the applicant to give a satisfactory answer. Such CTIL/CTX application will be rejected if the NPCB does not receive satisfactory response/reply for the queries or information requested by the evaluator after the 10 working days.

5 Required dossiers

Required dossiers for CTIL/CTX application are shown in Table 3 as below:

Table 2. Documents to be submitted in a New Application for CTIL/CTX

Section	Description
1.	Cover letter
2.	CTIL/ CTX application form
	3.1 Processing fee (if CTIL, RM 500.00 per product)
	3.2 Company Registration Certificate, if applicable
3.	3.3 Applicant's Poison License Type A for pharmacist in private sector or Annual Retention Certificate for public pharmacist, whichever applicable
	3.4 Letter of Authorization, if applicable
4.	Opinion of the ethics committee
5.	Clinical trial protocol and protocol amendments
6.	Declaration by investigator/ PI
7.	Good Clinical Practice certificate and Curriculum Vitae for investigator/ PI
8.	Informed consent form
9.	Pharmaceutical data for all products that required CTIL/ CTX, Shelf life, and stability data, BE study
10.	Label(s)
11.	Certificate of Good Manufacturing Practice (GMP) or GMP Compliance Statement
12.	Investigator's Brochure
13.	Overall risk and benefit assessment
14	Other or additional documents

III. ALGERIA

Drug Registration Requirements in Algeria

The registration of all medicinal products with the Algerian Ministry of Health is the most important pre-requisite to be able to market or distribute any medicine in Algeria. Without registration, no medicine can be imported or distributed in Algeria It may, however, be noted that no registration formalities are required for non-medicinal equipment and hospital material etc.

The details of registration procedure are given below

Registration Process (Step I):

The revised registration process, initiated since 1996, involves making an application by the pharmaceutical company seeking to get registration for its pharma products in the prescribed format of Submission Sheet Products Pharmaceutical Registration year. It requires general information regarding the drug - its international name, form, and dosage, prices - in the factory, with taxes, and FOB/CIF, and the proposed price in Algerian market. It also requires information regarding how the medicine/drug is going to improve health situation in Algeria, and finally the market price in the country of origin and the prices in three other countries. After submission of this application, the Health Ministry would ascertain whether the particular medicinal product is required in this country and decide if the detailed dossiers for registration of this medicine/drug should be accepted or not.

The medicine to be registered should generally be listed in the Nomenclature National Medicines [available in a booklet form and can be procured from the Health Ministry]. However, if a particular medicine is not listed in this Nomenclature, then another application as per the format of form Therapy information for the registration in Algeria (was completed by the applicant) should also be filed in, which seeks more detailed information regarding characteristics, mode of administration, pharmacological properties, efficiency, evaluation of therapeutic risks, etc. of the medicine.

Registration Process (Step II):

Once the File submission is accepted, the concerned pharmaceutical company is required to make a detailed application in the form of a dossier as per detailed instructions contained in Procedures expertise analytical pharmaceutical application and products pharmaceutical[can be obtained from the Health Ministry] The dossier is required to be sent in triplicate - one containing all original documents and two dossiers containing copies, along with two samples for each dosage form submitted for registration. The samples (whenever necessary, should be sent in refrigerated conditions) must accompany analysis of the

(i) Basic raw material,
(ii) Intermediate products,
(iii) Finished products used in the drug.

The proforma price list of the samples and a certificate to the effect that the 'products being sent are for sample purposes only' should also be dispatched along with samples. Technical information regarding international and commercial names of the

product, quantity, lot manufacturer and expiry dates of the product provided as per medical free samples form would secure assistance from the Ministry of Health to expedite customs clearance in Algiers.

One lot of samples are then sent to the National Laboratory of Pharmaceutical Products control, which generally require 30 ampoule units for drugs of 5 ml/mg or above, and 50 ampoule units for drugs of 1 to 1.5 ml.

Decision of the Health Ministry

Generally, a period of 3 months or more is taken to evaluate the dossiers and conduct lab tests on the samples. However, if any particular product is found to be very competitive, Ministry of Health's registration can also be provided in a very short period.

A provisional registration valid for one year is granted by Health Ministry after scrutiny of dossiers by them. However, a longer duration registration valid for five years is granted by Health Ministry only after they receive a positive report on technical/laboratory evaluation of the samples. The provisional registration also entitles the specific product for marketing/distribution in Algeria.

General

The Algeria Ministry has suspended receiving applications for registrations for some time. They have not indicated as to when they would resume registration procedures.**[11]**

IV. GCC (Gulf Cooperation Council)

Registration procedure

Gulf cooperation council regulatory authorities Approved in May 1999 Located in the executive officer for health ministers, Riyadh, Saudi Arabia.

Drug registration

Two processes of drug registration
A. Centralized Procedure
B. Decentralized Procedure

A. Centralized Registration Procedure

The executive office of GCC-DR assumes the receipt of registration files after ensuring the fulfillment of registration requirements and upon duly filling the following forms: The drug companies registration form. A pharmaceutical chemical entity preparation registration form. Eight complete files for each chemical entity & 17 samples have to be submitted to the executive office and two samples shall be dispatched to each country along with registration file.**[12]**

B. Decentralized Registration Procedure

Registration regulations in major countries of GCC although there is a centralized and quite harmonized process for drug registration in GCC countries, the regulatory requirements of few big countries like Saudi Arabia and UAE are separate .these countries have their well-established regulatory system and its enforcement In this study we will discuss briefly the registration requirements of multi-source generic products of GCC countries Saudi Arabia, Bahrain, Kuwait, Oman, UAE.**[13]**

REGULATORY PROCESS OF KUWAIT

The most important goal of the Kuwaiti review process is to ensure that

A. The product is registered and marketed in countries with recognized and competent regulatory authorities for at least twelve months.
B. The product meets the desired, internationally recognized, quality standards to ensure that the product was manufactured for its intended use.
C. The product is stable for the entire proposed shelf life and for six months under the stressed conditions of 40°C/75% relative humidity.
D. The product price must be reasonable and affordable for local patients.

The Submission Phase

The review process starts with the local agent (or the sponsor) submitting the registration dossier along with a covering letter to the Director of Kuwait Drug and Food Control (KDFC) officially requesting the registration of the pharmaceutical product.

The Evaluation Phase

After entering the scientific review stage, the reviewer evaluates the Chemical and Manufacturing Control (CMC) data focusing on the following data,

- Product specifications and detailed methods of analysis of the finished products with the reference pharmacopeias.
- Full stability studies in tabulated form addressing the proposed product shelf life.
- Raw material specifications and their methods of analysis as well as the reference pharmacopeia.

The Authorization Phase

When the full assessment has been successfully completed, the final approval decision is made by the DRRS which is officially endorsed by the director of the authority.**[14]**

REGULATORY PROCESS OF OMAN

The regulatory review process in Oman comprises ten stages which are considered critical and have an impact on the approval time of medicines

The Submission Phase

The sponsor submits the product registration file to the authority. All documents must be completed for official acceptance. The following items are checked at the validation stage,

1. Legal status of the applicant/local agent
2. GMP status of the manufacturer
3. Organization of the registration dossier
4. Certificate of a Pharmaceutical Product (CPP) authenticated by the respective embassy or consulate general.

The Evaluation Stage

There is a formal record for the starting time of the scientific assessment. In the primary scientific assessment procedure, an internal reviewer in the drug control department completes a scientific product report, detailing the trade, generic names, indication and country of origin.

The Authorization Phase

The registration committee is responsible for granting the marketing authorization and pricing of the product after completion of the review process. **[15]**

REGULATORY PROCESS IN THE UNITED ARAB EMIRATES (UAE)

The regulatory review process in UAE consists of twelve critical stages that are considered essential and comprise a significant part of the review procedure.

The Submission Phase

The sponsor submits the registration dossier, which must contain all the required data to pass the validation stage and become accepted for review. An appointment is then arranged with the department's administrative staff to submit the product for registration and an appointment sheet and evidence of the manufacturing site registration must be presented at this stage.

1. Legal status of applicant/local agent
2. Patent/IP status of the active ingredients
3. Evidence of payment of the relevant fees

The Evaluation Phase

The dossier is split into the three sections; quality, safety, and efficacy; which are all reviewed together by the same appointed reviewer. The reviewer must complete a product evaluation template and print all the resulting requirements into one report for the sponsor.

The Authorization Phase

The higher registration committee is the committee that is responsible for granting the final approval for a product, which is of political and administrative rather than of technical membership. The registration committee reviews the scientific committee report and makes a decision to grant marketing authorization for a product accordingly.**[16]**

V. UKRAINE

New registration

Import, advertising, sale, medicinal use, and marketing of medicinal products are allowed only state registration (marketing authorization) of the product. State registration of all types of medicines is performed by Ministry of Health of Ukraine, as a result of the centralized expertise of safety, quality and efficiency of the product by State Expert Center of Ministry of Health of Ukraine.

The registration certificate is valid for 5 years from the date of its issue. Application for renewal of registration should be submitted not later than 90 days before expiry of the valid certificate.

Dossier

The application should be amended with registration materials formed in accordance with specified structure (registration dossier). Two types of registration dossier are applicable in Ukraine – CTD format (in general harmonized with EU) and "simple" format that is similar to NTA format. The applicant is free to choose the format for submission.

Depending on the status of the product (original, generic, fixed combination, well-established use, traditional etc.) relevant parts of the dossier should be formed. The dossier should be submitted in paper form in 4 copies. Some parts of the dossier require translation into the Ukrainian language. Additionally, registration dossier should contain specific materials prepared in accordance with Ukrainian guidelines:

- AND (summary on quality: composition, specification and control methods of finished product, package system, storage conditions, information on manufacturers;
- Package mock-ups (drawings of the primary and secondary package);
- Package insert (instruction for medical use of the product);

Expertise procedure

The procedure is initiated by submission of Application form with "micro-dossier" to State Expert Center. The expertise of full registration dossier starts only after payment of relevant state fees. State experts have the right to inquire additional information by official deficiency letters. Applicant has 90 days for an official reply to the questions; otherwise, product can be withdrawn from registration.

Laboratory analysis can start after the positive conclusion of the expert on chemical-pharmaceutical part of the dossier. Laboratory analysis requires import of samples of the finished product, reference standards and other products than can be required for evaluation of all control methods of the finished product. Import of the samples usually requires official import permission from Ministry of Health.

After positive conclusion from all experts and laboratory analysis product is adopted for registration in Ukraine on the session of State Exert Center. Within several weeks original registration certificate is issued and the product is included in State Registry of Medicines.

Timing

Expertise procedure is officially limited to 210 days, not including timing required by Applicant for answers on deficiency letters and timing of laboratory expertise.

Renewal of registration

Marketing authorization of medicinal product should be renewed each 5 years. Renewal of registration is a process that requires submission of Application and renewal materials (dossier for renewal), payment of state fees, detailed state expertise of materials, answering on deficiency letters till approval of the product for renewal. There is no laboratory analysis of the samples during renewal.

Renewal process itself is much easier than new registration, but:

- Registration certificate and its annexes should be updated according to up-to-date legislation requirements (for example – Braille should be applied to package drawings, PIL is usually should be updated with new safety data etc.);
- renewal process can include in-process variations to registration materials; each variation should be presented by separate Application and necessary justifications;

Timing

Submission of Application form with micro-dossier should be done not later than 90 days before expiry of the registration certificate. Official timing of state expertise is limited to 90 days, not including timing required by Applicant for answers on deficiency letters. Additionally, renewed registration certificate is issued only after signature of Minister of Health; that additional time is officially limited to 2 months. **[17]**

CONCLUSION

The registration processes in different countries/regions have critical differences. Most countries required additional documentation that is not part of Module 2-5 of the CTD, some of which might also be challenging to obtain. The primary challenges in drug registration process observed and some key recommendation for success in the region is Knowledge of the drug registration processes and submission content for a particular country is essential for the effective planning and execution of global regulatory strategy. Engaging regulatory professionals with expertise regarding the region early in the development phase of a candidate product is crucial. Experts can be internal or external to the company but must be, or have a strategic partnership with reliable regulatory professionals on the ground who are aware of practical regulatory nuances and expectations from Has, and who keep up-to-date with changes to the regulatory environment in the region to avoid delays or show-stoppers to the MA applications.

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