Model Business Process Flows for Registration of Medicines: A Guide for Establishing a Standardized Generic Version of SIAPS Pharmadex Software

Benjamin Kwame Botwe

April 2017

USAID FROM THE AMERICAN PEOPLE SIAPS

This report is made possible by the generous support of the American people through the US Agency for International Development (USAID), under the terms of cooperative agreement number AID-OAA-A-11-00021. The contents are the responsibility of Management Sciences for Health and do not necessarily reflect the views of USAID or the United States Government.

About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

Recommended Citation

Botwe B K. 2017. *Model Business Process Flows for Registration of Medicines: A Guide for Establishing a Standardized Generic Version of SIAPS Pharmadex Software*. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health.

Key Words

Pharmadex, medicines registration, drug registration, dossier assessment, medicines regulation, drug regulation, pharmaceutical information system

Systems for Improved Access to Pharmaceuticals and Services
Pharmaceuticals & Health Technologies Group
Management Sciences for Health
4301 North Fairfax Drive, Suite 400
Arlington, VA 22203 USA
Telephone: 703.524.6575
Fax: 703.524.7898
E-mail: siaps@msh.org
Website: www.siapsprogram.org

CONTENTS

ACRONYMS AND ABBREVIATIONS

ADEC	Australian Drug Evaluation Committee
API	active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical (Classification)
BP	British Pharmacopeia
CHMP	Committee for Medicinal Products for Human Use
COA	certificate of analysis
CTD	common technical document
EAC	East African Community
ECOWAS	Economic Community of West African States
EMA	European Medicines Agency
EU	European Union
FPP	finished pharmaceutical product
GMP	Good Manufacturing Practices
ICH	International Council for the Harmonization of Requirements for the Registration of Medicines for Human Use
INN	international nonproprietary name
MCC	Medicines Control Council
MSH	Management Sciences for Health
NMRA	national medicines regulatory authority
PSUR	periodic safety update report
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
USAID	US Agency for International Development
USFDA	US Food and Drug Administration
USP	United States Pharmacopeia
WHO	World Health Organization

ACKNOWLEDGEMENTS

I acknowledge with gratitude the support provided by the MSH SIAPS team led by Francis Aboagye-Nyame.

I am particularly indebted to Sameh Saleeb, Kim Hoppenworth, Wonder Goredema, and Kate Kikule for their relentless efforts in providing technical guidance, review, inputs and feedback during the assignment.

INTRODUCTION

Background

The overall responsibility of national medicines regulatory agencies (NMRAs) is to ensure that the populations living in their jurisdictions have medicines, vaccines, and related health technologies that conform to international standards of quality, safety, and efficacy that are accessible, affordable, available, acceptable, and cost effective, backed by a streamlined and efficient supply chain mechanism relying on internationally recognized standards.[1]

To this end, legislation stipulates that medical products be regulated, which includes product registration, inspection of products and manufacturing sites, quality control of medicines, pharmacovigilance, control of advertising, control of clinical trials, licensing and authorization of imports and exports, and licensing and monitoring of manufacturers, wholesalers, retail distributors, and professionals involved in all these processes and functions.

The process of medicines registration, also known as the granting of marketing authorization, is a pivot around which the medicines regulatory system revolves. The registration of medicines requires not only a good understanding of the scientific knowledge of these products, but also an understanding of the business flows and regulatory processes required for final approval for registration. A good medicine registration information system and its proper implementation results in:

- Efficiency in the use of regulatory resources
- Capture, storage, and utilization of data and information on medicine applications received by the NMRA
- Improved dossier archival and retrieval systems
- Efficient tracking of applications during the registration process
- Reductions in timelines for the registration of medicines and avoiding backlogs of unprocessed applications

Different countries have differing capacities to perform all necessary regulatory functions effectively. These include the well-resourced NMRAs, like the US Food and Drug Administration (USFDA), the United Kingdom Medicines and Health Products Regulatory Authority (MHRA), Health Canada, Swissmedic, the Therapeutic Goods Administration of Australia, among others. Other jurisdictions with limited capacities, particularly in sub-Saharan Africa and Southeast Asia, have suffered much from substandard and falsified medicines along with uncontrolled or illicit sale of medicines.

Strengthening pharmaceutical systems requires simultaneous strengthening of medicine regulatory systems, key among which is the process of medicine evaluation and registration.

Different guidelines exist for the registration of medicines, ranging from those issued by the ICH (International Council for the Harmonization of Requirements for the Registration of Medicines for Human Use), WHO, Pan American Health Organization, the Economic Community of West African States (ECOWAS), East African Community (EAC),[2] among others which are international in nature, to individual country guidelines and requirements. Although these requirements largely ask for similar information, the arrangements and modes of presenting data vary significantly. As a consequence, applicants, sponsors, and manufacturers of medicines who wish to register their products in different countries and regions have to contend with compliance to different guidelines and data presentation formats. In recent times, however, most of the guidelines available are in conformity with the ICH guidelines that are presented in modules or sections that deal with particular titles in the registration dossier as per the applicable guidelines.

The use of the common technical document (CTD) format for new medicines applications in the European Union (EU) and Japan became mandatory, and the recommended format of choice for new medicines applications submitted to the USFDA. This was the result of an agreement reached between regulators and industry players in these regions and countries to assemble all the quality, safety, and efficacy information in a common format (the CTD), which has revolutionized regulatory review processes and led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industry, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.

The CTD format is organized into five modules. Module 1 is region specific and modules 2–5 are intended to be common for all regions.

The business process for registration therefore needs to be clearly elaborated in conformity with the CTD format to facilitate a more efficient registration process by NMRAs.

As part of the regulatory systems strengthening efforts to improve management of these processes and to build the capacity of selected NMRAs, the USAID's Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program, implemented by Management Sciences for Health, and its predecessor program Strengthening Pharmaceutical Systems, developed software known as Pharmadex, which aims to assist NMRA staff in managing and improving business processes of key regulatory functions (with focus on the registration function) and to streamline the flow of documentation and communication (internal and external) with clients and providers.

The software application is web-based and uses mainly open source components like Apache and Java. It runs on Windows, Linux, and MacOS. The software has so far been implemented in Namibia, Ethiopia, Bangladesh, and Mozambique. In an effort to develop a model version of the registration module of Pharmadex, SIAPS solicited the development of a model set of business process flows. This scope will further build on past efforts as well as on the four versions of Pharmadex already implemented to define a generic version of Pharmadex.

Problem Statement

NMRAs need to have adequate institutional and human resource capacity to effectively and efficiently process the numerous applications for medicine registration. Low staff capacity in some countries, in terms of numbers and skills mix, leads to delays in processing applications and results in backlogs. Additionally, application processing delays have been attributed to non-compliance to registration requirements and long processing times after submission.

Assessment of the registration processes in many countries has identified the need to create a platform for effective communication between NMRAs and clients, identification of critical data input requirements, and documenting and archiving dossiers as major challenges.

Purpose

The introduction of Pharmadex has so far targeted individual country requirements. Currently, under the African Medicines Regulatory Harmonization initiatives, efforts are underway to adopt common and harmonized processes and communication platforms for medicine registration in regional economic communities, such as EAC, ECOWAS, and the Southern African Development Community.

The purpose of this report is therefore to describe the currently known processes in selected countries and develop a model set of business processes for medicine registration based on internationally accepted standards. These model business processes can then serve as the basis for establishing a model version of Pharmadex's registration module.

Specific objectives are to:

- Review existing medicine process flows in Australia, Bangladesh, Ethiopia, Ghana, Indonesia, Mozambique, Namibia, and South Africa
- Identify key medicine registration functions and review and develop clear business process flows for each step and options that could be followed by different NMRAs
- Propose optional and alternative functions/steps process flows corresponding to best practices for medicine registration and CTD requirements
- Identify required, optional, and alternate input and output documentation and products for medicine registration, such as registration forms, certificates of analysis (COAs), certificates of pharmaceutical products, reports, etc., in support of identified functions and processes

MEDICINE REGISTRATION PROCESS REVIEWS

A desk review of existing medicine registration process flows for Australia, Bangladesh, Ethiopia, Ghana, Indonesia, Mozambique, Namibia, and South Africa was performed. Existing documents on the implementation of Pharmadex software in Bangladesh, Ethiopia, Mozambique, and Namibia were obtained from the MSH technical team. The purpose of the desk review was to establish the similarities and differences in these systems so that a model medicine registration process could be described and used to develop generic medicines registration software. This was followed by identifying the critical steps in the model medicine registration process, and then comparing those steps to provisions made within the CTD of the ICH, and guidelines issued by the EU, WHO, West African Health Organization, and EAC in the CTD format. As per these international requirements, certain documents are required at different stages of the registration processes, and these were identified, including those for reregistration and variations of existing registration. The documents identified become the process inputs required, either at the beginning or in the middle of the registration process.

Each working draft that was developed was shared with technical staff at MSH to solicit feedback from them on the medicine registration business process flow and documentation before the report was finalized.

The same consultative process was used to finalize and document functions, process flows, and diagrams following consultative review.

Summaries of the reviewed processes from the individual countries, identified medicine registration steps, and inputs required and outputs expected at different stages of the process are described in the following sections.

Description of Business Flows in Selected Countries

The principles of application submission, screening, assessment, decision making and communication, and post-registration activities were found to be in common in most countries whose registration business flows were reviewed. It was also observed that different process flows and pathways existed for different categories of products. These include, but are not limited to, medicines for public health emergencies, public sector pharmaceutical procurements, donations, new chemical entities, complementary medicines including herbal medicines and supplements, and veterinary medicines. Depending on the public health importance and individual country priorities, abridged registration pathways are available with shortened timelines and with specific dossier requirements as may be necessary.

Australia

- At the time of submission, 75% of the fees are paid and the remaining 25% are paid after the application is accepted for processing; if the application is not accepted for processing, 10% of the fees are retained as an administrative charge.

- Evaluation of the dossiers is done by either internal or external reviewers, depending on the complexity and nature of the application.

- A pharmaceutical sub-committee reviews the quality part of the dossier before submission to the Australian Drug Evaluation Committee (ADEC).

- The non-clinical and clinical review reports are submitted by the reviewer to the sponsor or coordinator at the Therapeutic Goods Administration who prepares the final report and submits it to the ADEC.

- The ADEC then recommends for approval or otherwise.

- Reapplication and appeal mechanisms exist for rejected applications.

Bangladesh

- Pre-inspection report of the manufacturing premises is required as part of the registration process (figure 1) and therefore the inspection report needs to be captured before the process can begin.[3]

- A staff officer receives the application, verifies and screens it.

- The staff officer then forwards the application to a moderator who does further verification and assigns the dossier to reviewers and follows up on progress of the assessment.

- The reviewers upload their reports and relevant documentation and forward them to a moderator.

- The moderator then prepares a summary report and presents it to a committee.

- The committee's report is then entered into the registration system to change the status of the product based on the recommendations of the committee.

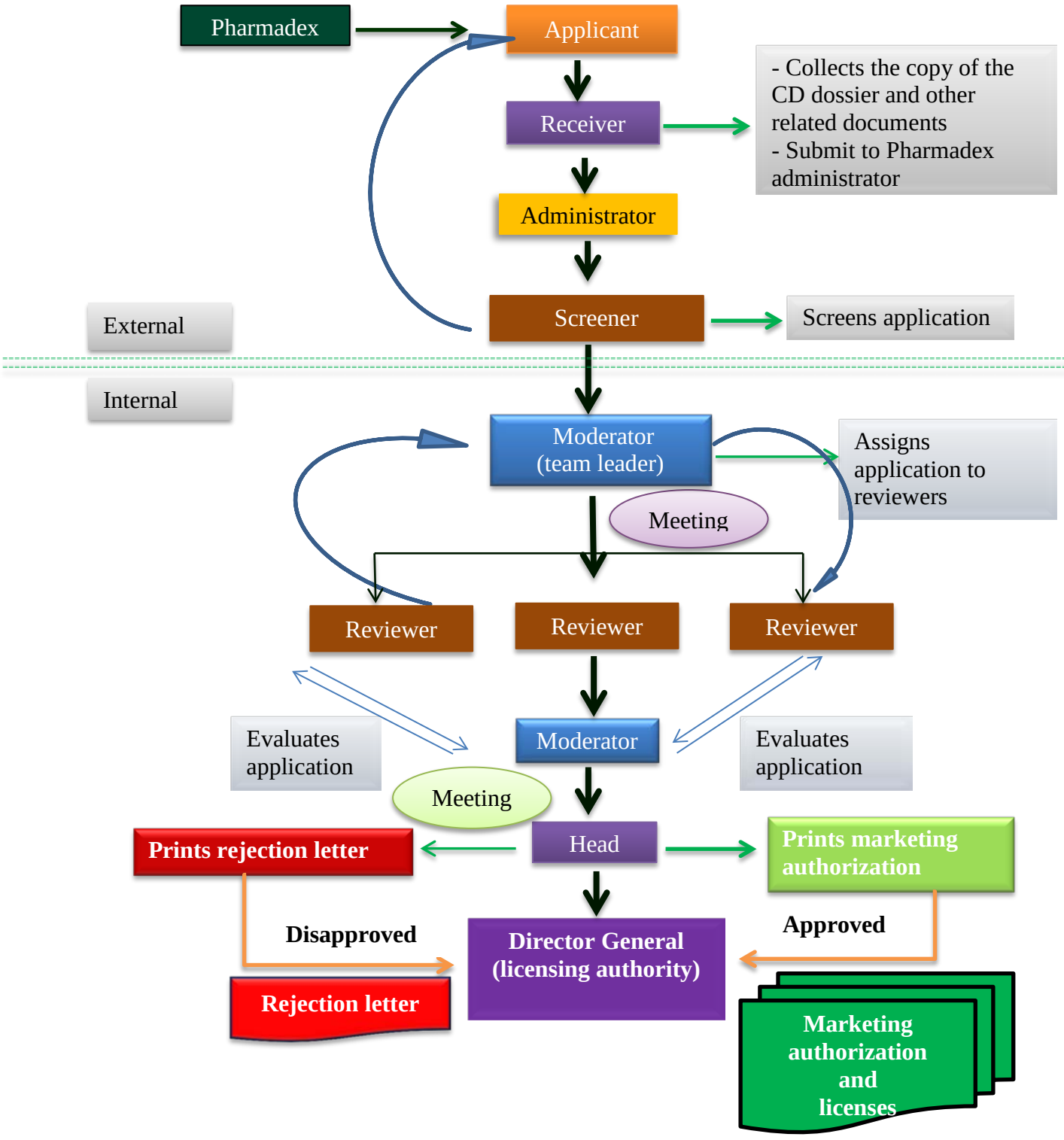


Figure 1. Bangladesh medicines registration process flow[4]

Ethiopia

- After the applicant information is captured, it goes to a customer service desk where it is screened for completeness.
- It is then forwarded to a registration team leader who schedules and distributes the dossier to assessors.
- After assessment, the dossier goes back to the team leader for review and approval of reports and, when necessary, requests are made for further information from applicants.
- The assessors then prepare certificates for the team leader to review and sign.
- The signed certificates are sent to the customer service desk for issue to applicants.
- No provision is made here for deferrals; rejected products will have to go through a resubmission process or an appeals system when necessary.

Ghana

In Ghana, Good Manufacturing Practice (GMP) inspection reports are required for all new applications and need to be submitted before the registration committee meeting at which the application is to be considered. The processing of applications follows the pathway described below.

- Receipt and screening of applications for completeness is done at the front desk office by regulatory officers who also ensure the payment of appropriate fees.
- The head of division then allocates cleared dossiers to internal assessors who are experts in medicines registration
- Registration pathways differ for medicines for public health programs, pediatric formulations, Ministry of Health tenders, post-approval variations, or renewal of registration.
- Evaluation reports are peer-reviewed, and the final reports are coordinated and presented to the Drug Registration Committee.
- When assessors issue queries, applicants have a limited amount of time to respond after which the application processing is terminated.
- Decisions of the committee are communicated to the applicant from the Office of the Chief Executive Officer through the front desk office.
- Processes exist for re-application and appeals of decisions.

Indonesia

Medicine registration applications are submitted to the head of the national agency. Manufacturing site inspection reports are required before submission of applications. The medicine registration process consists of preregistration and submission of the registration dossier (figure 2).

The pre-registration process is conducted to determine the application review and evaluation pathway which depends on the type of medicine application. The evaluation pathway is dependent upon whether the product is used to treat serious or life-threatening diseases, is an essential generic medicine for a public health program, or is a new medicine already approved in certain designated countries. Consultation on completeness of the registration dossier/document is established and the registration fee is paid at this stage. The result of pre-registration will be communicated to the applicant in writing and it is binding.

The second step includes the submission of registration documents for screening and the evaluation process. The documentation should include completed registration forms and the receipt of payment of evaluation and registration fees and the result of pre-registration.

The application dossier is then evaluated and the results submitted to the registration committee. The committee's approval or rejection is communicated to the applicant.[2]

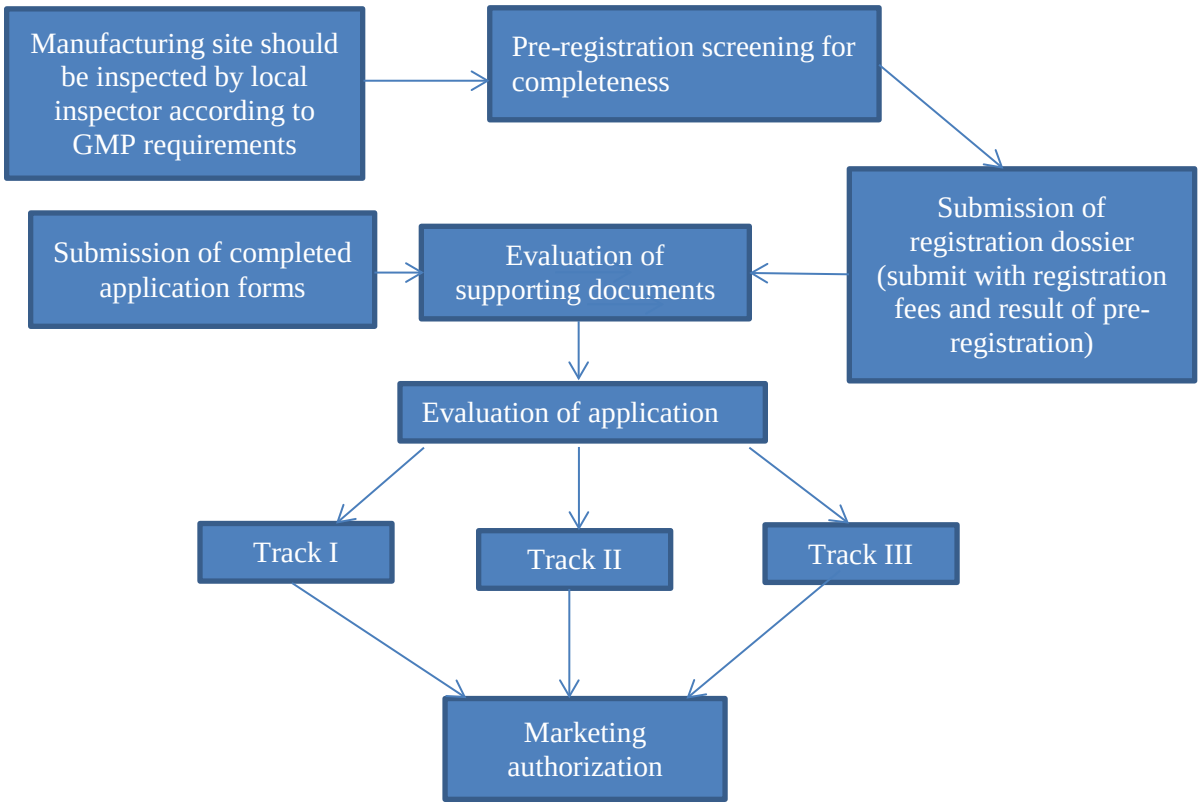


Figure 2. Medicine registration process in Indonesia (adapted from ref. 2)

Mozambique

- The registration department receives and reviews the application, including the payment of applicable fees.

- Dossiers are then assigned to experts for evaluation and report. The administrative and quality part of the dossier is reviewed within the department while the non-clinical and clinical parts of the dossier are reviewed by external experts. Registration samples are submitted independently to the quality control laboratory for analysis.

- Reports from dossier evaluation and quality control laboratories are submitted to a registration committee for peer review.

- Decision making on the final status of the application is based on recommendations of the committee.

Namibia

- The Namibia process is for both paper-based and electronic submissions.

- Medicine application dossiers are screened for completeness and that application fees have been included.

- Data on the dossiers is entered into the registration database; an application number is assigned and information communicated to the applicant.

- The dossier is scheduled for evaluation by the staff of the registration section. Dossier assessment is performed by medicine regulatory staff who are trained to assess the quality, non-clinical, and clinical modules of the dossier. A detailed evaluation report is generated. Deficiencies, missing information, etc., are communicated to the applicant, and the deadline to respond to queries outlined.

- Completed dossier reports and recommendations are forwarded to the Pharmaceutical and Analytical Committee of the NMRC.

- Products approved by the NMRC based on the recommendations of the Pharmaceutical and Analytical Committee are assigned a registration number and gazetted. The product is then entered into the medicines register.[5]

South Africa

- All new medicine applications are submitted to the Medicines Control Council (MCC).

- The MCC screens the application and dossiers for completeness.

- Uncompleted dossiers are returned to the applicant to deal with any queries, and then the dossiers are resubmitted to the MCC.

- Complete applications are referred to appropriate committees for review. These committees include the Pharmaceutical and Analytical Committee and the Clinical Committee.

- Responses received are resubmitted to the appropriate committees for final assessment and recommendations on approval or otherwise of the application.

European Medicines Agency

The 31 members[*] of the European Medicines Agency (EMA) use the following versions of a standard procedure:

1) Centralized
2) Decentralized
3) Mutual recognition
4) Nationalized

The procedures are well described in a review article.[6] To market a medicine in the EU, it must pass a medicine clinical trial application and a marketing authorization application. (This process is similar to how it's done in the United States). Clinical trials must be approved by the member states, and marketing authorizations must be approved by the member state and at the central level.

In general, the EMA takes approximately six months longer than the USFDA to approve a new medicine.[7] This time lag is caused by "stopping the clock" (when an application is returned to the applicant to answer queries) and the delay between getting a good opinion from the Committee for Medicinal Products for Human Use (CHMP) and approval from the European Commission (figure 3). Also note that, in the United States, most cancer medicines are considered a priority over other medicines and that accelerated assessment is rarely used by EMA.

[*]Member countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and United Kingdom

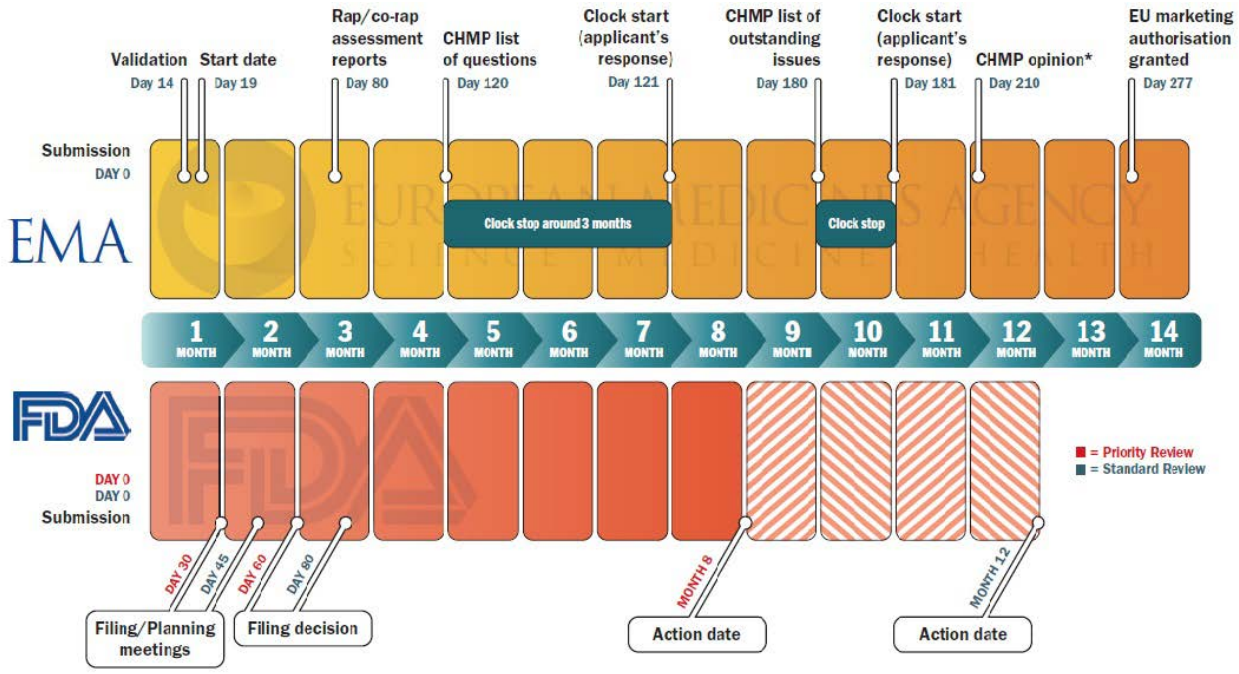


Figure 3. Comparison of USFDA and EMA timelines for medicine approval[7] (*occurs on day 150 for accelerated assessment; Rap, rapporteur)

Centralized Procedure

The centralized procedure (figure 4) must be used when medicines are:

- Derived from any biotechnology processes, such as genetic engineering
- For the treatment of cancer, HIV/AIDS, diabetes, neurodegenerative disorders, autoimmune diseases, and other immune dysfunctions
- Officially designated as orphan medicines (medicines used for rare diseases)

During the marketing authorization phase, the application is evaluated by an assigned rapporteur. The EMA's opinion is issued within 210 days, and the application is submitted to the European Commission for final approval. Once the marketing authorization is obtained, it is valid throughout the EU, Norway, Iceland, and Liechtenstein.

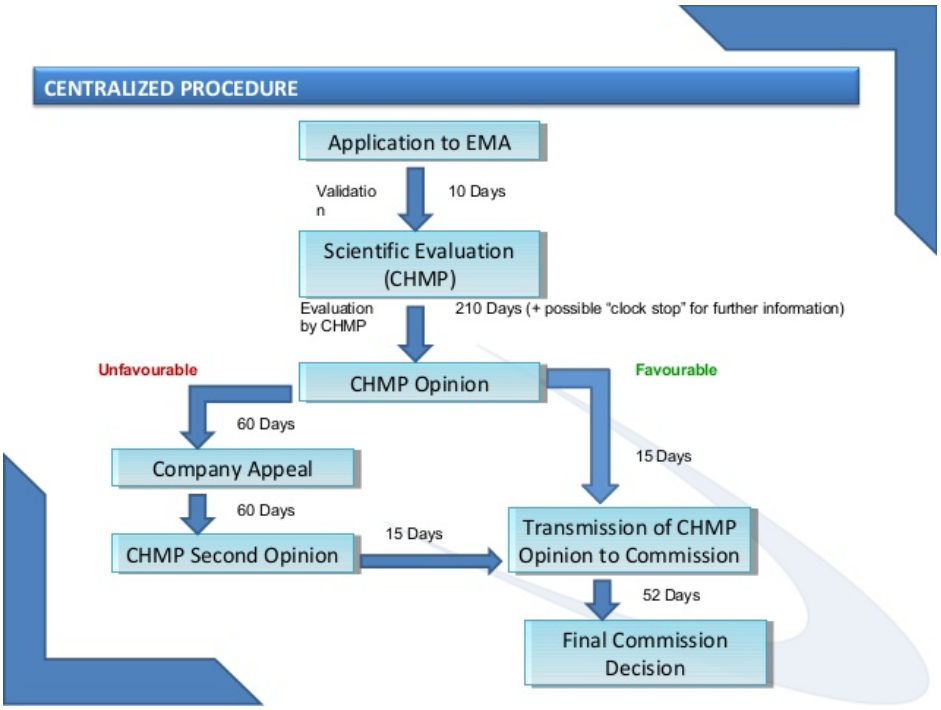


Figure 4. Flowchart of centralized procedure (source: https://www.slideshare.net/pradeepgangavaram/eu-regulatory-evaluation-process)

Decentralized Procedure

For products that have not been authorized in any EU country and that do not fall within the guidelines of the centralized procedure, the decentralized procedure can be used to apply for authorization simultaneously in more than one EU country (figure 5).

When one member state decides to evaluate the product, it becomes known as a reference member state (RMS). The RMS notifies the other states to which applications have been submitted of its decision; these states now become known as concerned member states (CMS).

The RMS prepares an assessment report on the basis of its own findings. Marketing authorization is granted in accordance with the decision taken by the RMS; any comments made by the CMSs are also considered. The process generally takes approximately 210 days.

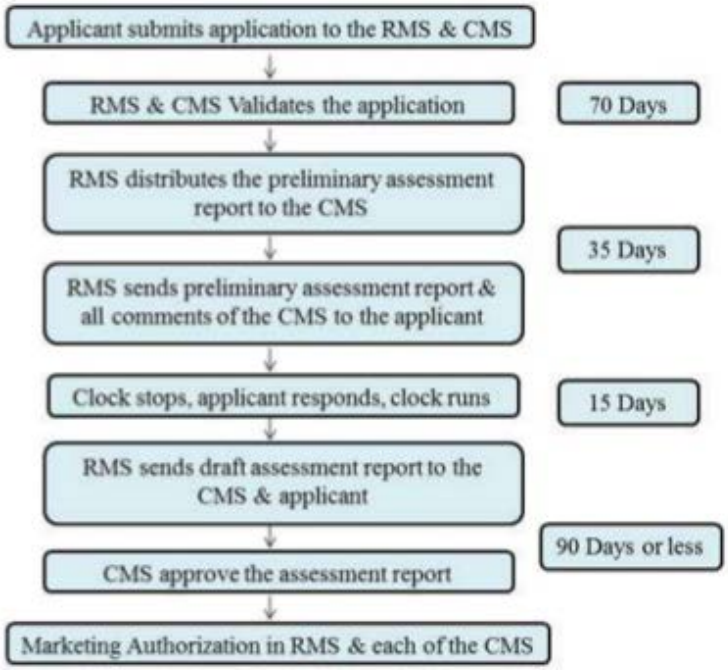


Figure 5. Flowchart of decentralized procedure[6]

Mutual Recognition Procedure

The mutual recognition procedure can be used to obtain marketing authorization in CMSs other than the RMSs that have already approved the medicine. This process is usually used by the generics industry and takes approximately 390 days.

- Applicant submits identical dossiers to all EU member states in which they want marketing authorization.

- As soon as one state decides to evaluate the product (at which point it becomes the RMS), it notifies the other states to which applications have also been submitted (which at this point become CMSs).

Nationalized Procedure

The nationalized procedure allows applicants to obtain a marketing authorization in only one member state. New substances that do not fall under the criteria set out in the centralized procedure can obtain approval under this procedure. The timeline for approval is approximately 210 days.

Details of the EMA Procedures

All applications are electronic following the standards described in eCTD. The steps (and approximate timeline prior to submission) are:

1) Submission of eligibility request (18 months at the earliest and 7 months at the latest in advance of submission)

2) Notification of intention to submit an application (7 months in advance of submission)

3) Appointment of rapporteurs (7 months in advance of submission)

4) Pre-submission meeting. (7 months in advance of submission)

5) Submission of the application

6) Scientific evaluation (210 days of assessment)

7) CHMP issues its scientific opinion

8) European Commission decision on the marketing authorization

EMA Post-Marketing (Variations)

EMA has a set of minor (types IA and IB) and major (type II) variations. A comprehensive guide is also available that describes all variation definitions and requirements (30 August 2017, EMEA-H-19984/03 Rev. 74 Human Medicines Evaluation Division, European Medicines Agency post-authorization procedural advice for users of the centralized procedure or http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003981.pdf).

Comparison Matrix of Medicines Registration Processes

With the identification of various process parameters during the above review, table 1 was developed to compare and contrast their existence or otherwise in the various jurisdictions. The countries in which Pharmadex had been implemented were selected for this comparison. Additionally one NMRA each from sub-Saharan Africa and South-East Asia were selected. The standard practice represents a compilation of practices in well-endowed regulatory agencies and regions as well as WHO. The inclusion of Pharmadex is to showcase the dominant processes in the four countries in which the software has been rolled out. The gaps identified and the deviations observed are to be considered in the development of the model Pharmadex software.

Table 1: Comparison matrix of medicine registration processes in different countries

Process parameter		Bangladesh	Ethiopia	Mozambique	Namibia	Ghana	Indonesia	Australia	EMA, Europe	Standard practice	Pharmadex model
Presubmission	Eligibility request	X	X	X	X	X	X	X	√	X	X
Application submission	Preinspection report	√	X	X	X	X **D**	X	X	X	X	X
	Applicant information	√	√	√	√	√	√	√	√	√	√
	Fee payment	√	√	√	√	√	√	√	√	√	√
	Application form	√	√	√	√	√	√	√	√	√	√
	Dossiers	√	√	√	√	√	√	√	√	√	√
	Samples	√	√	√	√	√	√	√	√	√	√
Screening/EMA presubmission	Application coding	√	√	√	√	√	√	√	√	√	√
	Payment confirmation	√	√	√	√	√	√	√	√	√	√
	Product information	√	√	√	√	√	√	√	√	√	√
	Category of distribution	√	√	√	√	√	√	√	√	√	√
	ATC classification	√	√	√	√	√	√	√	√	√	√
	Addresses	√	√	√	√	√	√	√	√	√	√
	Declarations	√	√	√	√	√	√	√	√	√	√
	Dossier content	√	√	√	√	√	√	√	√	√	√
	Recordings & data capture	√	√	√	√	√	√	√	√	√	√
	Acknowledgements	√	√	√	√	√	√	√	√	√	√
Dossier assignment and assessment (EMA scientific evaluation)	Assessors data	√	√	√	√	√	√	√	√	√	√
	Distribution records	√	√	√	√	√	√	√	√	√	√
	Internal assessors	√	√	√ **Q**	√	√	√	√	√	√	√
	External assessors	√	√	√ **C**	X	√	√	√	√	√	√
Decision making/ communication	Assessors data	√	√	√	√	√	√	√		√	√
	Technical Committee	√	X	√	√	√	√	√	√	√	√
	Head/director of registration	X	√	√	X	X	X	X	X	X	X
	Head of agency	X	√	√	X	X	X	X	X	X	X
Post-registration	Appeals	√	√	√	√	√	√	√	√	√	√
	Deferrals	√	√	√	√	√	√	√	√	√	√
	Quality and PSURs	√	√	√	√	√	√	√	√	√	√
	List of registered products	√	√	√	√	√	√	√	√	√	√
	Applicants' database	√	√	√	√	√	√	√	√	√	√
	Manufacturers' database	√	√	√	√	√	√	√	√	√	√
	Dossier tracking records	√	√	√	√	√	√	√	√	√	√
	Dossier archiving records	√	√	√	√	√	√	√	√	√	√
Preregistration	Laboratory analysis	X	X	√	X	√	X	X	X	X	X
Application type (pathways)	Variation	√	√	√	√	√	√	√	√	√	√
	Renewal of registration	√	√	√	√	√	√	√	√	√	√
	New chemical entities	√	√	√	√	√	√	√	√	√	√
	Generics	√	√	√	√	√	√	√	√	√	√
	Complementary medicines	√	√	√	√	√	√	√	√	√	√
	Herbal medicines	√	√	√	√	√	√	√	√	√	√
	Public health products	√	√	√	√	√	√	X	X	√	X
	Veterinary	√	X	X	X	√	X	X	√	√	√

Key:
√ – the parameter is included in the country registration process
X – the parameter is not included in the country registration process
Q – internal assessors for quality part of dossier
C – external assessors for clinical part of dossier
D – required at decision making for new applicants only

PROPOSED STEPS FOR A MODEL PROCESS FLOW FOR REGISTRATION OF MEDICINES

From the analysis of the registration business flows in Bangladesh, Ethiopia, Ghana, Indonesia, Mozambique, Namibia, and South Africa as well as the comparison of the registration process parameters in the table above, the following key medicine registration functions have been identified. They have been fully described, and input and output parameters have been outlined. These are to be considered in the model software development process.

Submission and Receipt of Application

The process involves the submission of applications in line with the appropriate regulations and guidelines at national, regional, and international levels as the case may be. Based on requirements, two hard copies of the dossier are usually submitted. Electronic submissions are permitted in many jurisdictions. An application form, which is usually a summary of the content of the dossier, is required to be submitted along with the dossiers. Whichever form it takes, the submission is accompanied by a cover letter and samples usually in the package that will be on the market after approval. In most cases, fees are paid either online or at the time of submission of the dossiers. Receipts of payment are required for verification before moving to the next stage of the registration process.

The receiving officer must be qualified and trained with the skills required to screen medical product applications. The NMRA shall maintain a database on such persons to ensure uniformity in applying standard operating procedures (SOPs) for receipt of applications.

Screening of Applications

The process of screening applications involves step-by-step examination of all the documents and samples received (figure 6). Usually NMRAs are required to develop SOPs for screening. The purpose is to ensure that the procedure is done the same way for all applications and that the submission is complete and all documents and other requirements have been fully submitted. This will avoid delays and minimize issuance of queries during the assessment process. The following requirements apply.

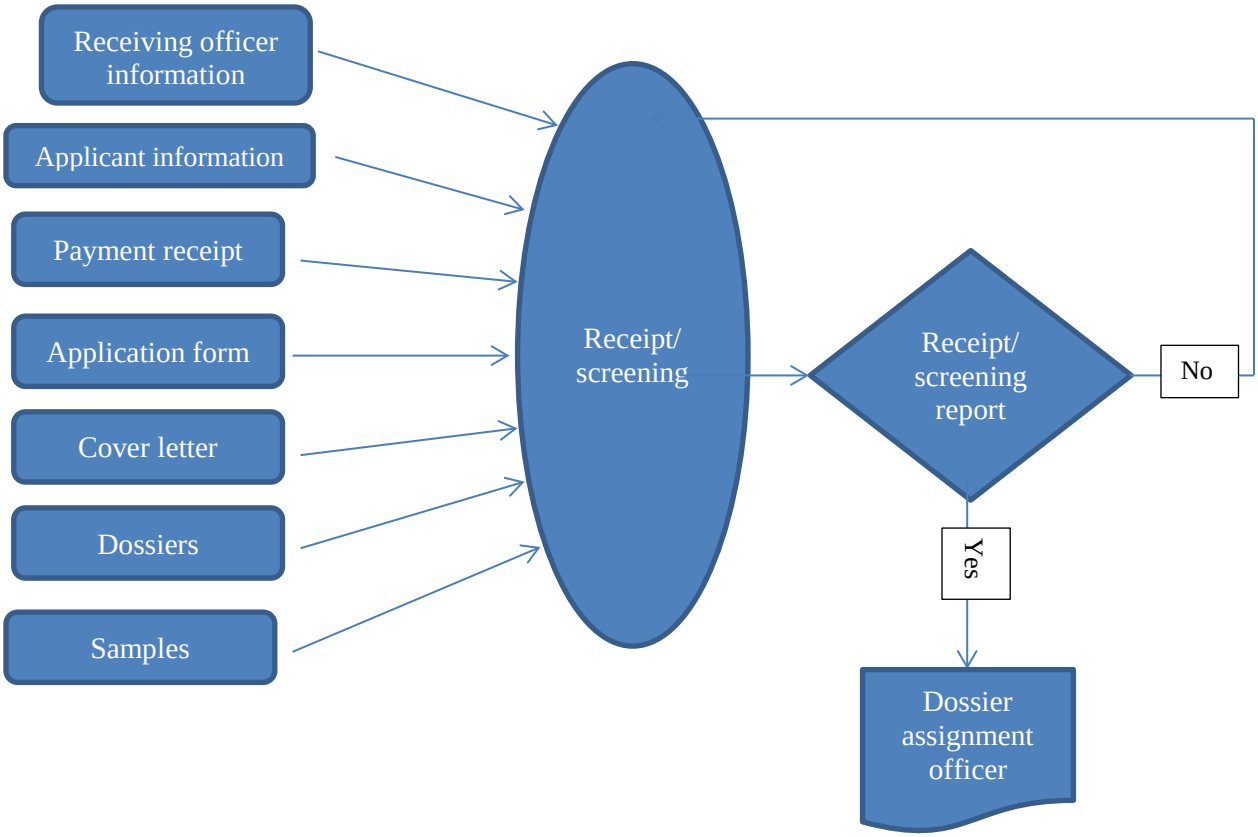


Figure 6. Application management

Cover Letter

The application should be submitted with a cover letter. A typical cover letter should be on the letterhead of the applicant company and should contain:

- Name and full premises and postal address of the applicant
- Date of submission of application
- Name and address of the receiving NMRA
- Subject of the submission, e.g., Application for the Registration of XOX 50 mg Tablets
- List of items in the submission and annexes
- Name and address of local agent (if required by the NMRA)
- Details of samples accompanying the submission
- Amount of registration fees
- Name and signature of authorized person (s)
- List of persons or agencies that are copied (when applicable)

Application Form

The filled application form should be screened by the receiving officer to ensure completeness. The application form is usually in different sections and the screening is done according to information provided in each section.

Assign a Dossier Reference Number

The officer receiving shall assign an application number to the submission which should be coded and will serve as the identification reference throughout the registration life cycle of the application. This is to avoid mix-ups of dossiers and samples as the application moves from one stage to the next within the registration process. That code number will be used when assigning the dossier to assessors, collating the assessment reports, and preparing them for various technical and registration meetings.

General Product Information

1) Proprietary name: This is the name given by the applicant, which may be an exclusive brand name or a branded generic name. In this case, most jurisdictions require that it not appear similar to a previously registered product in terms of spelling and pronunciation. For generic products, the name is usually the internationally accepted generic version.

2) Approved name: The international nonproprietary name (INN) as included in the WHO list.

3) Dosage form: The pharmaceutical form in which the product is presented. It may be a tablet, capsule, syrup, powder, injectable, suppository, or other form.

4) Strength: The strength is the quantity of active ingredient or its chemical equivalent per unit dosage form (example: paracetamol 500 mg means each tablet contains an average of 500 mg of paracetamol).

5) Color: The color in which the final medicine product is presented before it is put into its primary package.

6) Pack size/commercial presentation(s): Commercial presentations are the pack sizes in which the product is or would be available on the market (example: 10 tablets × 3 means each pack contains 3 strips each of which has 10 tablets or capsules as the case may be.)

7) Country of manufacturer/origin: The country of origin is the country in which the product is manufactured. In situations where there are multiple sites for the manufacture of the product, the country in which the final stage of production takes place becomes the country of manufacture. NB: the dossier will have to include all other manufacturing sites.

Category of Distribution

Medical products are generally classified on the basis of the levels of health care provision and distribution. For some products, prescriptions are required from a qualified health care provider to permit the dispensing of such products. They are usually termed prescription only medicines (POMs). Others are dispensed from pharmacies with or without prescriptions and are referred to as pharmacy initiated medicines (P). There is also a general category of medicines which are permitted for sale in non-pharmacy premises, including supermarkets. They are sometimes referred to as exempted or over-the-counter (OTC) medicines. In other jurisdictions, the

classification is made as schedules (A, B, C, etc.). In whatever form it takes, they are usually backed by law, and the law in the country in which the application is being made applies.

Pharmacological Classification

The classification of the active pharmaceutical ingredient (API) where required by the applicable guidelines of the country's NMRA should be according to the Anatomical Therapeutic Chemical (ATC) Classification System. This system classifies APIs according to the organ or body system they act upon and their pharmacological, therapeutic, or chemical properties.[8] The appropriate classification is to be assigned by the applicant on the application form.

Addresses

The names, premises, postal addresses, phones, faxes, and e-mail addresses of the applicant, manufacturer, and local agent are required to be detailed on the application form. When manufacturing takes place at multiple sites, the information above shall be provided for each site.

Declaration

A declaration that all information contained in the dossier is correct and true, indicating the name, position, signature, date, and official stamp of the authorized person submitting the application is required. This facilitates communication during the application processing cycle.

Requirements for the Submitted Dossier

Depending on the specific guidelines being used, the required hard copies of dossiers for each application are to be submitted in a well-bound document to avoid loss of pages during the processing, handling, and intra- and interdepartmental transfers of the application. Electronic submissions are verified to confirm accessibility and clarity of the soft version of the document and the availability of all the modules required by the applicable guidelines or CTD. Dossiers submitted electronically are submitted in both pdf and Word formats, the latter for ease of review and insertion of comments by the assessors.

Requirements for Submitted Medicines Samples

The required quantity of samples as per guidelines must be submitted. These samples should not have expired at the time of submission. They should bear lot/batch numbers and COA numbers. Samples submitted should be in the same package and presentation as would be made available on the market once the marketing authorization is granted. The sample must also include the patient information leaflet.

Updating the NMRA Medicine Database

A register of all applications should be kept and should indicate the following particulars:

- Application number

- Name of product (generic, proprietary, branded generic)
- Dosage form and strength
- Date of submission
- Fee paid/receipt number
- Action taken (accepted or returned to applicant to make corrections and then resubmit the application)
- Name and signature of receiving officer

Issue Acknowledgement Letter

At this stage, an acknowledgement letter should be issued to the applicant, indicating the results of the screening and next steps to be taken on the application (this could be generated automatically).

- Accepted
- Rejected with the list of documents/items to be submitted later with time lines

Assignment of Dossiers

Role of the Assessors

The NMRA shall keep a database and curriculum vitae of all assessors. This will enable the NMRA to identify the specializations of all assessors and assign appropriate segments of the dossiers to them for technical review. For a number of NMRAs, officials have been trained to undertake general dossier assessment covering all the modules, especially for generic applications whereas in other cases, different experts are assigned different sections of the dossier for assessment. The assessors may be NMRA staff or may be external/independent from academia, research, or private sector institutions. In cases where the assessors are external, a contractual agreement between them and the NMRA is needed to spell out issues of confidentiality and conflict of interest.

Criteria for Assigning Dossiers

The assignment of dossiers to assessors is based on the expertise of the assessors, their availability, and risks associated with the product. For a certain category of products, particularly those for public health emergencies, expedited, fast-track actions are required. These may be assigned directly to specific experts or technical working groups with timelines. A record of the application number, name of assignment, date of assignment, name of assessor, and the expected date of submission of the report is to be kept in order to track and trace all dossiers. These documents would have to be duly signed by the assigning officer as well as the assessor.

Technical Assessment/Review of Dossier

Assessment of the General/Regional information

Administrative Information

- Dosage form
- Strength
- Commercial presentation(s)
- Proposed shelf (months)
- Storage conditions
- Primary container
- Indication
- Country of origin
- Category of distribution
- Applicant's name and address
- Manufacturer's name and address
- Local's name and address

Assessment of the Quality Modules for Medicine Substance and Drug Product (Finished Pharmaceutical Product [FPP])

General Information about the APIs

- Signed declaration
- Reference specified: British Pharmacopoeia (BP), United States Pharmacopoeia (USP), European Pharmacopoeia (Ph.Eur.), International Pharmacopoeia (Ph.Int.), or in-house specifications; also specify type/source/number/version
- Nomenclature and structure
- General properties of the APIs
- Manufacturers and valid manufacturing authorization/certificate of GMP compliance

Process-Related Information

- Description of manufacturing process, process controls, and process validation
- Control of materials used in manufacture of API
- Control of critical steps and intermediates
- Elucidation of structure and other characteristics, including stereochemistry and isomerism
- Control of the APIs (impurities, residual solvents, analytical methods, batch analysis, forced degradation)

- Reference standards or materials of the APIs
- Container closure system of the APIs
- Stability of the APIs

General Requirements of the FPP

- Certificate of pharmaceutical product
- Certificate of registration (if registered by another NMRA)
- Contract agreements
- Manufacturing license
- Other certificates (COAs, asbestos-free, transmissible spongiform encephalopathy/bovine spongiform encephalopathy)

Process Requirements

- Specifications (active raw materials, FPP, and packaging materials)
- Process validation
- Analytical procedures for FPP (BP/USP/Ph. Int./Ph.Eur./in house)
- Analytical method validations (API, impurities and related substances)
- Batch manufacturing records and batch packaging records
- Stability studies

Assessment of Safety Information

- Animal studies (pharmacology and pharmacokinetics)
- Human studies (pharmacology and pharmacokinetics)
- Toxicology
- Literature reference

Assessment of Efficacy Information

- Bioavailability studies (bioequivalence and dissolution studies)
- Pharmacology
- Summary product characteristics

Final Steps of the Assessment Process

Compiling the Evaluation Reports

The evaluation report is to be produced by the assessors using a recommended assessment form/format, which may be manual or electronic. The elements in the reporting format shall include, but are not limited to, the name of the product, the INN, conformances/non-

conformances to specifications, the specific section of the application dossier that was assessed (where applicable), date of receipt of dossier, date of completion of assessment, assessor's overall comments/recommendations and conclusion and it must be appropriately signed and dated. At this point, a report on compliance to GMP, PSURs, and quality monitoring may be included.

Technical Meeting/Decision Making

The report and recommendations of assessors shall be presented to a centralized database that is accessible by authorized persons. The evaluation reports are subject to the final technical review that may be done by a technical/registration committee or by the technical head of the agency as the case may be.

The decision of the assessment will be based on the recommendations and comments on the quality, clinical and non-clinical information submitted, product label and package insert, and other product information provided in the dossier and duly assessed. The assessor's recommendations on GMP compliance, PSURs, and safety and quality monitoring may be considered in the final decision.

The overall conclusion needs to be one of these three:

- Approval/acceptance of dossier application
- Deferral of dossier application with recommendations for further clarification or submission of additional documents
- Rejection of dossier application

Approval/Acceptance of Dossier Application

Letter

When the decision is to give approval and market authorization to the product application, an approval letter of registration shall be issued. Its contents shall contain the name of the company, name of the product, unique and coded registration number, a validity period, and further restrictions and conditions of registrations, including those pertaining to advertising and safety monitoring.

Certificate

The final certificate of registration is issued after all conditions of registration as per the guidelines have been fulfilled. The certificate shall specify the names of the marketing authorization holder, the manufacturer, the local agent where applicable, and the product; the list of active ingredients; pharmacological class; product registration number; certificate number; and validity period. The certificate should be duly signed by an authorized officer of the NMRA.

Deferral of Dossier Application

Some applications may be deferred because further clarifications or submission of additional documents are needed. A letter that specifies the modules/areas that need clarification, additional documentation needed, and time lines for resubmission should be sent.

Rejection of Dossier Application

In the event that a dossier application is rejected, a letter shall be written with the various key subject areas and reasons for rejection, items rejected, and time lines for resubmission, if applicable.

Appeals against Decision

In many jurisdictions, a decision to reject a registration application on stated grounds can be appealed, either to a higher authority such as the minister responsible for health or the head of the NMRA. This appeal must contain justification and the necessary documentation. In such situations, the application will be subject to reassessment and appropriate recommendations made.

Post-Registration Activities

Variation of Registration

Within the period of validity of the certificate of registration, an application may be made for the variation of some product information or conditions of the approval. These may include:

- Change of site(s) of manufacture
- Additional indications
- New indications
- Change of manufacturing process
- Analytical methods
- Sources of raw materials
- Other

Full justification in terms of the effects of the variables on the quality, safety, and efficacy of the product shall be submitted for assessment and decision making.

EMA specifically considers major variations (type II), minor variations (types Ia and Ib), and unforeseen variations.

Periodic Safety Updates

PSURs are pharmacovigilance documents that play a part in evaluating the risk-benefit characteristics of medicinal products.[9] Marketing authorization holders need to submit them at a defined interval, such as every five years.

Renewal of Registration

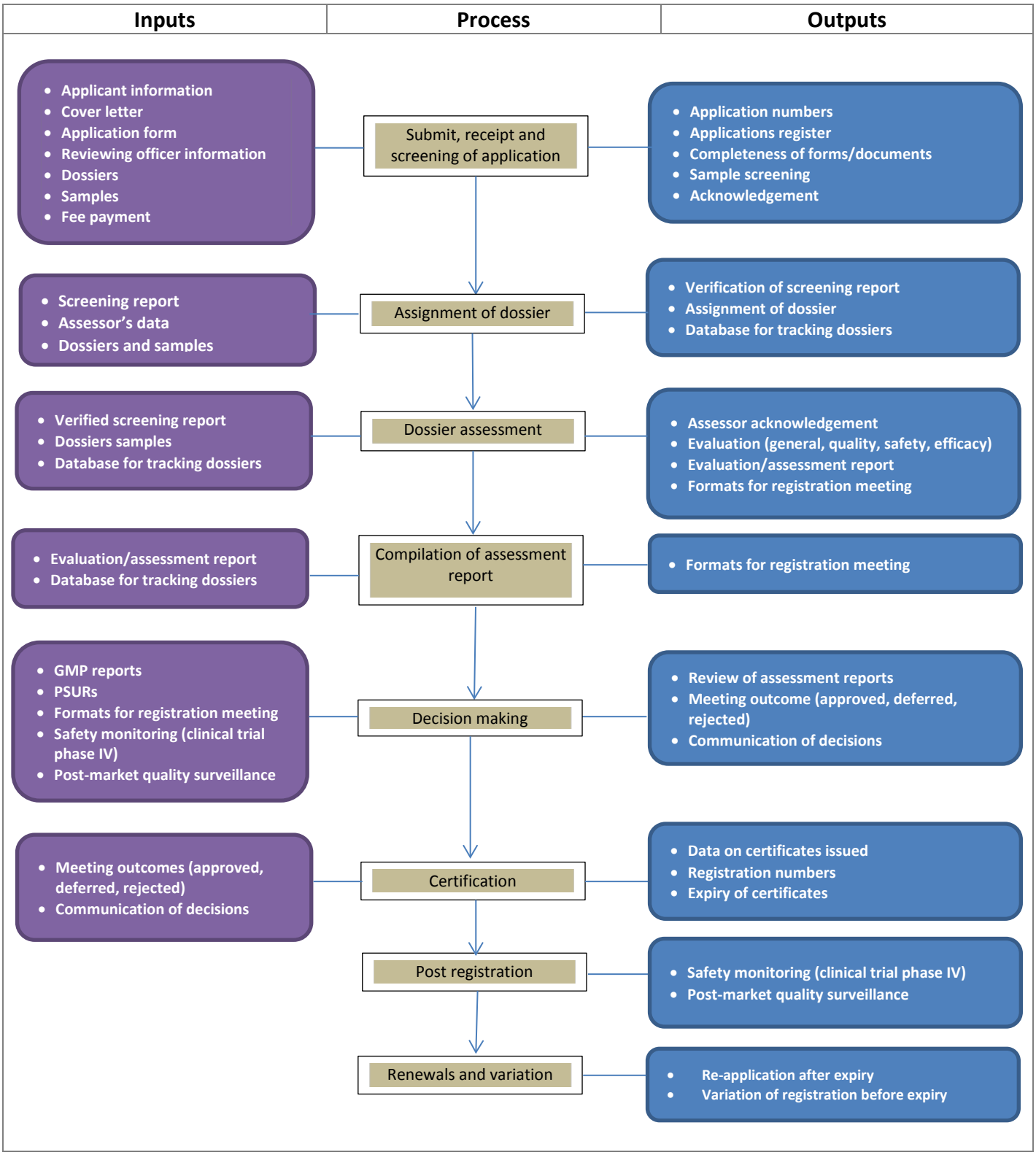
When the certificate of registration expires, which varies between three and five years, the application can be renewed by going through the reregistration process. As part of the renewal process, information should be provided on any changes that have occurred since the last registration application, which might have been dealt with as a variation before the expiry, covering all the modules of the applicable guidelines. Additionally, post-registration safety and quality updates and any other administrative directives, such as product recalls and reasons for the recall if any, shall be provided. Applicable guidelines should be complied with and submitted to go through the application processing tree.

Cessation/Suspension and Withdrawal of Registration

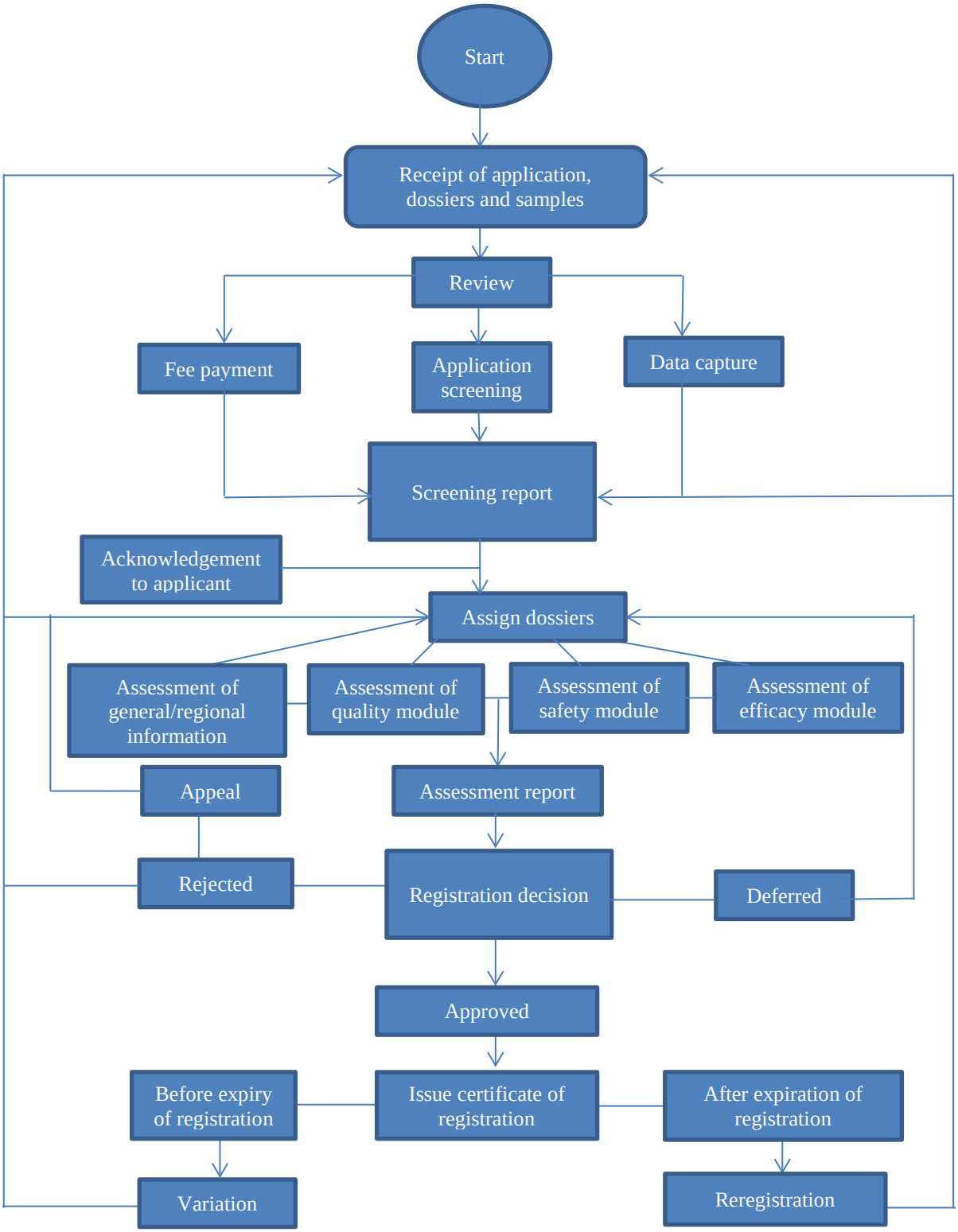
There are several ways whereby a pharmaceutical product will not be available on the market for various periods of time.

1. Withdrawal (e.g., confirmed safety risk)
2. Suspension (e.g., safety investigation or non-payment of fees)
3. Cessation (e.g., marketing authorization holder removes the product from the market)

PROPOSED INPUT, PROCESSES, AND OUTPUTS FOR MEDICINE REGISTRATION



PROPOSED MEDICINE REGISTRATION FLOW CHART MODEL



GUIDANCE ON DEVELOPING AND IMPLEMENTING PHARMADEX

The development and implementation of any medicine registration information system requires a stepwise approach and continuous feedback from clients and industry practitioners (who need to upload documents as part of the electronic submission/registration process) to ensure ownership and appropriate use in order to make it fit for purpose. The developer will have to work in close collaboration with the client to achieve the objectives of reducing the registration life cycle, training critical staff, efficient use of regulatory resources, transparency, and eventual improvement in timely access to essential medical products. The steps involved in the information system implementation process include but are not limited to the following.

Map and Optimize the Registration Process

This document clearly maps out the model registration process which involves:

1) Requirements for submission of applications
2) Availability of written procedures and work instructions
3) Application receipt system
4) Application screening and assignment process
5) Technical assessment of dossiers
6) Preparation of reports
7) Decision-making process
8) Post-registration activities

The input and output requirements for each of these stages are identified and should be taken into consideration. Other requirements, such as quality control, inspection reports, and a system to track and trace them along the processing cycle, should be addressed. Timelines for assessment of applications and an internal tracking system should be established to follow the targeted time frames. Archiving and retrieval of registration documents after completion of the registration process should also be incorporated into the system.

Set Up a Technical Working Group

The NMRA would have to set up a technical working group (TWG) to spearhead establishment of the new information system to be implemented within the Registration Department. The TWG should be chaired by a representative of the top management team and have representatives from the Registration, Information Technology, Quality Management, and Planning Departments, among others. The team will work in close collaboration with the system developer to ensure full validation and adaptation, implementation, testing, launching, and use of the system. The TWG shall draw up plans for the identification of the appropriate staff to be fully trained on the software to ensure effective data entry and management as well as reporting. It will be responsible for drafting and reviewing software transfer agreements and liaising with the developer for authentication and signing.

Share the Initial Version of the Software with the Client

The implementation process begins when the initial version of the developed software is shared with the client (represented by the TWG). Online demonstrations may be required and, when necessary, face-to-face meetings may be held to facilitate direct interactions and agreements. When necessary, a dossier submitted to the NMRA could be used as a sample to demonstrate the software, which could also be a capacity-building tool and process for the client.

The client, led by the TWG, may then independently work with a set of application dossiers as a test case using the approved and validated processes and work instructions. The input of data, issuance of letters, retrieval of reports, certification, and post-registration activities should all be monitored at this stage. All troubleshooting events and challenges faced in the roll-out of the system must be documented and sent to the developer. This feedback is of utmost importance to enable the developer to update the software to meet the agreed term of engagement to enrich the registration software and process. These exchanges may be repeated until the client finally accepts the product for implementation.

Deploy the Software

The finalized version submitted by the developer after incorporating all the feedback could then be deployed for use by the NMRA. However, in-use challenges must be identified and documented together with other information that may be useful in the future when a new version of Pharmadex is to be developed. Continuous training of other registration staff, assessors, and data management staff by the trained TWG members is critical to ensure efficient use of the software. Any other issues, including fixing bugs, glitches, etc., must be resolved at this stage.

To make applicants and clients of the NMRA and the general public aware of the quicker access to essential medical products and reduced registration lifecycle, the product should be officially launched at a public ceremony. All stakeholders including the developer and the press are to be invited to the ceremony, which should include a demonstration of the software.

Technical Requirements and Specifications

The software should include internal standards and terminology like INN, ATC, SNOMED, or comparable. It should also be available in multiple languages with priority on English, French, and Spanish.

Suggested features should include 3D-imaging of medicines and packs, patient information leaflets, and multiple checklists for both standard procedures and items that need to be fast-tracked.

The following tables describe hardware and software required for the main server and the client/user.

Server		
Component	**Minimum required**	**Recommended**
Hardware		
CPU	Intel Xeon, produced after 2012, 2 cores	Requirement unlikely to increase
RAM	8 GB	16 GB would be beneficial in the long run
HDD or SSD	100 GB	200 GB would be beneficial in the long run
Internet connection		
Provider	Internet exchange point (IXP) or connection to the national IXP at least 100 MB/S symmetric	Periodically test the provider's Internet connection from geographical locations of selected Internet users; consider changing the provider if connection tests from many endpoints and using various providers are constantly slow or unstable
Speed	10 MB/S to the provider, SDSL	Pharmadex does not impose significant loads on the Internet connection. Clients interact with the system by issuing HTTP POST queries. In addition, file uploads are required. Therefore, SDSL 10MB/S or ADSL with at least 10MB/S outgoing is the minimal requirement. Consider upgrading the Internet connection speed only if many Internet users complain about Pharmadex's response times and other ways to fix it do not work.
Software	**Details**	
Windows Server 2008 or Linux Server	There are 2 options for the platform/server installation: 1. Windows server (tested and working well) 2. Linux server (not tested but the architecture theoretically should work) The choice will probably depend on the MIS IT strategy currently under development.	
Java JDK 7.79	http://www.oracle.com/technetwork/java/javase/downloads/jdk7-downloads-1880260.html	
MySQL	http://dev.mysql.com/downloads/mysql/	
Additional Microsoft software for MySQL workbench; does not apply to Linux	https://www.microsoft.com/en-us/download/details.aspx?id=17113 https://www.microsoft.com/en-us/download/details.aspx?id=40784	
Database toolkit	Will be provided by MSH	
Tomcat application server	Preconfigured software will be provided by MSH	
Pharmadex application	Will be provided by MSH	
Apache HTTPD	Preconfigured software will be provided by MSH	

Client		
Hardware	**Minimum required**	**Notes**
PC (laptop or desktop)	I3 processor, SSD, 4 GB RAM, RJ-45 and/or WiFi, 14" screen	Has been tested in Chrome and Internet Explorer browsers

RECOMMENDATIONS AND PROPOSED WAY FORWARD – PREPARATIONS FOR SOFTWARE DEVELOPMENT

A system requirements specification will be developed on the basis of this report that will lay-out the details of all features for the Pharmadex generic medicines registration system.

REFERENCES

1) Goni MC. Accelerating Regulatory Approvals through WHO Collaborative Registration Procedures. Pharmaceutical Policy and Law 2016;18:109-120

2) Ravi G, Reddy RM, Reddy DK, Gupta NVK. Comparison of Marketing Authorization and its Requirements for Brunei Darussalam and Indonesia. Journal of Clinical Study 2015;7(1), 39-40

3) Kim EM, Srivastava U, Thumm M. CTDs and Pharmadex Trip Report, Dhaka, Bangladesh, March 2014; document number SIA-2014-00-241.

4) Directorate General of Drug Administration. Standard Operating Procedure: Standard Procedure for Evaluating Dossiers in Pharmadex (DGDA Staff).

5) Medicines Registration Overview, Namibian Medicines Regulatory Council, 2015; www.nmrc.com.na/productreg

6) Vishal P, Rahulgiri G, Pratik M, Kumar BJ. A Review on Drug Approval Process for US, Europe, and India. International Journal of Drug Regulatory Affairs 2014;2(1):1-11; ISSN 2321-6794

7) CDER 21st Century Review Process (www.fda.gov); User Guide for Micro, Small, and Medium-Sized Enterprises (www.ema.europa.eu); http://cancerworld.net/cutting-edge/approval-rating-how-do-the-ema-and-fda-compare/

8) WHO Collaborating Center for Drug Statistics Methodology, Guidelines for ATC Classification and DDD Assignment 2013. Oslo 2012.

9) http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000041.jsp&mid=WC0b01ac0580023e7d