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Dr. Josephine Aimiuwu

August 2016

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Systems for Improved Access to Pharmaceuticals and Services
Pharmaceutical & 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

API	Active Pharmaceutical Ingredient
BAPI	Bangladesh Association of Pharmaceutical Industries
CTD	Common Technical Document
DCC	Drug Control Committee
DG	Directorate General
DGDA	Directorate General of Drug Administration
GMP	Good Manufacturing Practice
GRP	Good Review Practice
ICH	International Conference on Harmonization
KOICA	Korea International Cooperation Agency
MFDS	Ministry of Food and Drug Safety
MOHFW	Ministry of Health and Family Welfare
MSH	Management Sciences for Health
NRA	National Regulatory Authority
PMS	Post-marketing Surveillance
PV	Pharmacovigilance
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
TORs	Terms of Reference
USAID	United States Agency for International Development
WHO	World Health Organization

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EXECUTIVE SUMMARY

Background

The Directorate General of Drug Administration (DGDA) is Bangladesh's national regulatory authority (NRA) and is responsible for regulating all medicines and other health products in the country. Presently, the medicines that are registered in Bangladesh have not been sufficiently evaluated for quality and performance, because manufacturers have not been required to provide sufficient technical data to demonstrate that their products are safe, effective, and of good quality. Although the DGDA has been putting their efforts into improving their medicine regulatory practices, it still faces challenges due to their limited technical capacity, human resources, and budget.

Interventions and Accomplishments

SIAPS has been providing technical assistance to DGDA to improve its regulatory function by helping them adopt international standards for medicine registration based on a common format proposed by the International Council for Harmonization for Technical Requirements for Pharmaceuticals for Human Use (ICH), known as the Common Technical Document (CTD). The use of the format has advantages for both country regulatory authorities and pharmaceutical manufacturers because only one technical data set that is accepted in different countries and regions is generated, thereby reducing the amount of human and animal experimentation. This standardization also provides common regulatory standards for evaluations and inspections and facilitates regulatory communication and information sharing that ensures that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. Furthermore, in the case of Bangladesh, adoption of the CTD may enhance the perception that products manufactured and registered in the country meet the quality and safety standards acceptable for export to other countries, providing faster access to medicines of high public-health value.

As a first step, SIAPS worked with DGDA to develop the Bangladesh CTD guidelines and associated templates and is in the process of integrating their use within the directorate. This will allow medicine dossiers submitted to DGDA to be aligned with international standards for medicine registration and ensure the quality of the products registered. At the same time, SIAPS has worked with DGDA to ensure that the process of revision is better structured and organized in terms of roles and responsibilities among the staff and establishing adequate terms of reference (TORs).

Second, SIAPS continues to build the capacity of DGDA officers and the staff of pharmaceutical manufacturers for submitting and reviewing applications for registration following the international standards of the medicine registration process. The training includes the concept of CTD, how to prepare and review CTD-based dossiers, and presentation of case studies. Master trainers (MTs) have also been established within both groups. Additionally, to sustain the technical capacity-building activities for CTD guidelines, SIAPS has facilitated a three-year

partnership between DGDA and the Korea International Cooperation Agency (KOICA). This will permit DGDA staff to participate in a long-term capacity-building program tailored for Bangladesh needs offered by the Ministry of Food and Drug Safety (MFDS) of Korea.

Third, SIAPS has tailored its online drug registration management system (Pharmadex) for the specific needs of Bangladesh and according to the new CTD guidelines for automated registration. Pharmadex will be used as a platform for implementation of the CTD format through the embedded data-requirement checklist and review templates and for tracking the overall progress of medicine registration. In September 2016, Pharmadex will be piloted in DGDA with a few selected pharmaceutical companies and more training will be provided for applicants.

Lessons Learned

It is important for full, early-on, and strategic engagement and buy-in of stakeholders including the DGDA, the Ministry of Health and Family Welfare (MOHFW), and pharmaceutical manufacturers after the initial assessment before any intervention areas are identified. The DGDA should be orientated so that they have a clear understanding of their technical needs and the complexities that might arise, such as the significant shift from their current minimal standard and all paper-based structure. In addition, improving the registration function of the DGDA is quite a slow process because of the challenges in the technical capacity of the DGDA to assess the scientific information in the medicine dossiers. Automation of the product registration process should take place after introducing some form of electronic database that contains legacy data. In addition, the administrative approval process and technical capacity of the organizations must be improved, including changes to their regulatory framework, such as guidelines and standard operating procedures (SOPs), which take a significant amount of time to develop.

The Way Forward

Continuing support is needed to facilitate capacity building for DGDA officers and pharmaceutical manufacturers on international standards of the medicine registration process, including established MTs. To improve the sustainability of the registration review process, it is highly recommended that DGDA network with other NRAs to learn their practices in order to implement needed changes in their own practices. Automation of the medicine registration process, including embedded review reports, will help reviewers improve transparency and the quality of the review only when they have improved their review practices. This includes strengthened data requirements, such as CTD-based dossiers and the ability to conduct rigorous reviews on the basis of their improved technical capacity. To fully meet the requirement for effective implementation, advocacy for resource mobilization and reassignment of officers is continually needed.

BACKGROUND

The DGDA was established in 1976 under the MOHFW, originally known as the Directorate of Drug Administration (DDA). In 2010, the DDA was upgraded to the status of Directorate General (DG), in an attempt to raise its profile and improve its capacity to serve essential regulatory functions, such as registration, licensing, inspection, quality control, post-marketing surveillance (PMS), and pharmacovigilance (PV). The DGDA is therefore mandated to guarantee access to quality medical products and protect Bangladesh's public health. In addition, the DGDA is the licensing authority for the manufacture, distribution, export, import, and sale of medicines and vaccines. This upgrade from DDA to DG was a result of a number of high-profile regulatory failures, some of which cost lives and others estimated to have had a severe financial impact on the industry. However, the higher profile of the DGDA, while beneficial in many regards, has not resulted in stronger regulation to prevent the circulation of fake, substandard, and expired medicines. In addition, there are limitations in its decision-making autonomy, both in terms of human resources and financial independence, and this hampers the DGDA's operational effectiveness. The DGDA has to rely on the MOHFW's bureaucratic architecture and financial limitations to recruit staff.

The existing laws and regulations for medicines in Bangladesh are outdated and are not in convergence with current pharmaceutical legislation in other countries. In particular, technical and regulatory requirements for medical products and devices, mandates on clinical trials, control of prescribing, regulatory instruments for biosimilars, and requirements for bioequivalence, bioavailability, and PV are inadequate. The Drug Acts and Rules 1946 to 2006 and the National Drug Policy 2005 herein together referred to as the 'Act' provide the legal basis and outline the criteria for registration of medical products on the basis of safety, quality, efficacy, and usefulness.

At present, DGDA has two types of application forms (DA-2/88 and DA-1/88) that are used to register medical products in the country. The forms require the applicants to provide summary information regarding the medicines that are being registered; even then, this is usually not submitted to DGDA in its entirety. DA-2/88 is used to register products that are the first generic versions in the country, and are termed "unintroduced drugs" according to the Act. Accordingly, to register an unintroduced drug, a technical sub-committee within DGDA reviews the summary report submitted by the manufacturer, and then the Drug Control Committee (DCC; which meets approximately every six months) formed by the MOHFW makes recommendations to the DGDA on whether to register new products in Bangladesh. Conversely, DA-1/88 is used to register products that are not new generic versions, that is, they already exist in the country because they have already been registered by another pharmaceutical company. This is termed "introduced drugs". Subsequently, the registration of a product that is already available in the country is reviewed by an internal committee in the DGDA that meets every month and approves the application without further approval from the DCC.

Given the inadequacy of the current forms that are used to collect information on the medicines that are being submitted for registration, the DGDA is relying on very limited data on which to make a decision whether the product is safe and effective and of expected quality. The DGDA is

therefore confronted with systemic challenges to fully fulfill its mission. Such weaknesses have contributed to backlogs of applications, and the questionable quality of products manufactured and marketed in the country. As a result of the 1982 Drug Control Ordinance that restricted imported drugs, Bangladesh has experienced a strong growth in the pharmaceutical sector over the past few years with more than 95% self-sufficiency[1], and the market was therefore flooded with medical products. However, regulation of the sector has not improved in parallel to provide the necessary controls to ensure quality and safety. Additionally, policies on ensuring access to medicines have not kept up with the rapid advancement of the pharmaceutical industry.

An assessment of the regulatory capacity of DGDA was conducted by SIAPS in November 2012 at the request of DGDA.[1] Some of the findings related to the registration function of DGDA are:

- Infrequent and irregular scheduling of meetings of the DCC, a technical sub-committee that considers efficacy, safety, usefulness, and quality of newly introduced medical products in Bangladesh

- Outdated application forms that enable submission of inadequate technical information for the registration of medical products; in addition, the information collected is not in compliance with the CTD format for international standard of medicine registration

- Inadequate human resources to process the number of applications and to cover the overall functions at DGDA

- Inadequate registration fees to support the operation of the directorate and the resources are controlled by the Government of Bangladesh, with annual budgetary allocations to DGDA; the budget allocation is insufficient to fund DGDA

- No electronic information management system to keep and update the register, especially in the case of licensing registered products and retail and wholesale pharmacies.

- Significant shortage of inspectors and inadequate knowledge on how to conduct proper inspections according to Good Manufacturing Practices (GMP) that can ensure the quality of medical products during design and manufacture before marketing authorization is granted by DGDA

[1] Nwokike, J., H. L. Choi. Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh. Arlington, VA: SIAPS; 2012.

GOAL

This report focuses on improvement of the regulatory capacity of the DGDA in regard to the registration process to ensure that the products manufactured or circulating in the country are of good quality and effective and safe for human use. The two main objectives aligned with regulatory system strengthening are to:

1. Build the capacity of DGDA officers and major stakeholders to improve the review of medicines for registration, to adopt the CTD format for registration, and to move the DGDA toward practices more consistent with international standards

2. Implement an online drug registration management system (using Pharmadex) to effectively track the process of drug registration, including licensing, inspection, and overall regulatory management at DGDA

IMPROVING THE REGISTRATION FUNCTION OF THE DGDA

The medicines that are currently registered in Bangladesh have not been sufficiently evaluated for quality and performance to ensure that they are safe and effective. The registration process is quite simple and low cost and does not include any scientific data or document submission to adequately assess the products. The lack of rigor in the medicine registration process has led to the establishment of about 275 pharmaceutical companies and more than 26,000 products on the market. To move DGDA toward adopting international standards for the registration of medicines, SIAPS provided technical assistance to DGDA to improve and upgrade their regulatory functions through a series of strategic steps and processes. The work involved two categories:

Category 1: Improving and standardizing the review and medicine approval process of pharmaceutical products

Category 2: Automating the process by using Pharmadex tailored to the Bangladesh context

Due to the complex nature of introducing the CTD format and an electronic system, the DGDA requested that the change in the registration process occur in a step-wise manner. This would allow the DGDA staff to become proficient with the process and also allow the pharmaceutical industry to adjust their dossiers to comply with the changes in requirements.

Category 1: Standardizing and Streamlining the Review and Medicine Approval Process

To establish international documentation and Good Review Practices (GRP), SIAPS proposed the adoption of the recommended format from the ICH for the CTD. This was expected to make the process of registration more fluid and efficient while complying with recognized international standards. The generic CTD is a common format for technical documentation that significantly reduces the time and resources needed to compile applications for registering human pharmaceuticals. It will also make regulatory review and communication with the applicant more efficient and provide an avenue for simplified exchange of regulatory information between authorities.[2] Using the CTD format was also expected to ease the preparation of electronic submissions.

According to the CTD format, each application is a collection of documents grouped into five modules. Module 1 consists of the administrative and prescribing information; the administrative information is usually specific to the region. Module 2 contains the summaries and overviews of the quality, nonclinical, and clinical sections of the dossier; the module begins with a general introduction to the medicine, including its pharmacological class, mode of action, and proposed clinical use. Module 3 focuses on the chemical, pharmaceutical, and biological data, which

[2]International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use. Geneva: ICH; 2016; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R4_Organisation/M4_R4__Granularity_Document.pdf

includes the data and process of the manufacture of the active pharmaceutical ingredients (APIs) and raw materials and the finished pharmaceutical products relevant to the application. Module 4 pertains to the nonclinical (pharmacotoxicological) data relevant to the application. Module 5 contains the clinical data to establish bioequivalence/bioavailability, safety, and efficacy of the medicine across an international patient population.[3] Module 4 is currently not applicable to Bangladesh because almost all the products that are locally manufactured are generic versions of brand name products and therefore do not require nonclinical studies (in-vitro and in-vivo). Additionally, because of the complexity in adopting this international standard, DGDA decided to defer the request for clinical studies (module 5) to focus on implementing modules 1 to 3. Even then, in rare cases concerning well-known APIs, the DGDA may be able to grant exemption from the submission of bioequivalence study data/reports, in module 5. Improving current processes for registration involved the following activities.

Sensitization of DGDA Officers

To create a supportive environment for the adoption and implementation of the CTD formats, SIAPS organized several short sessions with DGDA management officers. The positive implications of adopting CTD formats for the registration of medicines in Bangladesh were discussed. SIAPS also followed these sessions with one-on-one coaching sessions with senior officers of DGDA on CTD content and guidelines; the assumption is that if the managers of CTD operational processes in DGDA have a clear understanding of the module, they should be able to effectively communicate this knowledge to other DGDA officers under their supervision.

Establishing a Taskforce in DGDA

At the request of SIAPS, the DGDA created a taskforce as the group of champions who will lead the change and be direct counterparts to the SIAPS team. The DGDA assigned six members of the senior staff (one director, two deputy directors, one assistant director, and two superintendents of drugs) to be part of taskforce. This taskforce had clear TORs to oversee the full implementation plan to adopt CTD-based formatting and the implementation and launch of Pharmadex. The taskforce also designated the new structure for the staff that would review applications for registration.

The taskforce continue to work on an ad hoc basis and met at least once a week during the intensive development of the CTD guidelines and early implementation. They were responsible for reviewing and providing their inputs to the CTD guidelines and modules 1, 2, and 3 for finalization. They modified the flow of work (newly proposed steps for drug registration) within the DGDA.

The taskforce devised the structure of the review teams and their functions by assigning an officer as the head of the team and others as moderators for particular medicine groups, reviewers of dossiers, and screeners of CTD-based dossiers. The establishment of teams allows for parallel review of drug applications by multiple reviewers who are trained to evaluate

[3] SIAPS. Guidelines for the Submission of Bangladesh Common Technical Document: General Guidelines and Modules 1–3. Arlington, VA: SIAPS; 2015; http://siapsprogram.org/publication/guidelines-for-the-submission-of-bangladesh-common-technical-document/

specialty areas (saving time and increasing technical capacity). This is, in turn, expected to improve efficiency. The designated expert reviewers were trained to review specific modules of dossiers. This configuration allows for a clear guidance of what to review and how to review it, according to a review checklist and following GRP. It also helped to improve transparency and predictability. The taskforce was also instrumental in providing feedback on how to tailor Pharmadex to the Bangladesh context. Hands-on training on Pharmadex was provided to the taskforce and feedback requested on potential areas for developing and improving the system, understanding application process flow, and further orienting them on the functionalities of Pharmadex. A summary of the TORs for the taskforce is shown here.

TORs for the Taskforce Members

- Identify the structure of the review team, flow of work for medicine registration, and provide recommendations to the DGDA officers that would be designated for each category of work, e.g., the deputy directors were assigned as moderators and assistant directors as reviewers.

- Provide further feedback for improvement of Pharmadex, once it has been tailored to suit the new forms and flows

- Provide inputs and feedback in the development of the Bangladesh CTD guidelines and other documents, including SOPs, user manuals, etc.

- Continue to oversee the overall adoption of CTD and implementation of Pharmadex

Preparation of Bangladesh CTD Guidelines

As a first step to facilitate adoption of the CTD format for medicine applications, Bangladesh-specific CTD guidelines for modules 1, 2, and 3 were developed. At the initial stage, the taskforce and SIAPS teams confirmed that the guidelines should align with the existing rules, policies, and regulations of Bangladesh regulatory authority. The guidelines developed provided detailed information about the contents of an application, the bulk of the documentation needed, and any additional data needed that was to be included as addenda, including additional expert comment that may be provided as a supplement or overview. The Bangladesh CTD guidelines will serve as a resource to both DGDA and the pharmaceutical companies on how to properly organize and submit product dossiers that are consistent and in alignment with the ICH recommendations. Adoption of the CTD guidelines is a significant step in the strengthening of the drug regulatory system of Bangladesh, as the previous formats and procedures contributed to the lack of uniform requirements. This approach to develop country-specific CTD guidelines for medicine registration could be used for all SIAPS regulatory support platforms in other countries. The guidelines have been uploaded on the DGDA website.

Development of Bangladesh-Specific Official Templates

To continue to provide DGDA with the necessary tools and resources to strengthen their drug regulatory system, two sets of templates were developed: one focused on administrative documents for processing applications and the other on technical review templates for

registration of products. DGDA officers provided input to modify and customize the templates on the basis of Bangladesh-specific needs.

Templates related to administrative processes included:

a) Acknowledgment letter that the applicant receives when the application for registration of a product is submitted. The letter provides an estimated date that the review will be completed. Once the process is fully automated with Pharmadex, this letter will be automatically issued once the completed application has been submitted online.

b) Dossier screening deficiency letter lists the needed information or documentation that might be missing from the application and dossier submitted after screening has been done by the DGDA. The letter requests the applicant to resubmit the information within a stipulated time before further evaluation is done. As in the previous case, once Pharmadex is fully deployed and the screening process is conducted, this letter can be automatically issued. The format of the letter was standardized with input from DGDA officers.

c) Review deficiency letter lists the deficiencies identified during the evaluation of the dossier by DGDA reviewers. The letter requests that the applicant submit information that may refute or answer the deficiencies as an amendment before further evaluation is done. As in the previous case, once Pharmadex is fully deployed, the review process will be conducted online and this letter can be automatically issued. The format of the letter was standardized with input from DGDA officers.

d) Drug marketing authorization letter[4] is the official document that will be issued by DGDA authorizing the marketing or free distribution of a product after the evaluation for safety, efficacy, and quality has been completed. It contains the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using international nonproprietary names or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g., "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence."). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products—the register—and is often said to be "registered" or to "have registration." Market authorization may occasionally be referred to as a license or product license. On the basis of these criteria, a Bangladesh version of the drug marketing authorization letter was developed with input and final conformity of the DGDA officers.

e) Rejection notification letter is the official document that will be issued by DGDA rejecting the application for registration of a product. The evaluation has been completed, but significant deficiencies and other problems warrant rejection of the application. In this case,

[4] WHO. Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: A Manual for National Medicines Regulatory Authorities. 2nd ed. Geneva: WHO; 2011; http://www.who.int/medicines/areas/quality_safety/regulation_legislation/blue_book/en/

the applicant should submit a new application and CTD-based dossier, if they wish to try again.

Technical Review Templates

To facilitate the process of GRP, technical review templates were produced to:

- Screen the dossier
- Assess administrative and labeling information
- Assess the quality of the product

These templates were based on reviewers' concerns to ensure that the different requirements have been completed. These were expected to make the review of the dossier more efficient.

GRP is a documented best practice that discusses any aspect related to the process, format, content, and/or management of a product review.[5] These templates were developed as superior best practices based on SIAPS' collective experience to ensure that DGDA adopts standardized procedures that will provide consistency to the overall review process, especially in the pilot phase of CTD adoption. The GRP templates that were developed for DGDA will improve the quality, efficiency, clarity, and transparency of reviews and review management. The fundamental values for all GRP templates are[5]:

- **Quality**–consistent implementation of GRPs by the review staff enhanced by the use of templates will improve the quality of reviews, the review process, and the resultant regulatory action

- **Efficiency**–applying GRP will improve efficiency through standardization

- **Clarity**–GRP templates will support clarity and decision activities that must be completed before regulatory decision or marketing authorization can be granted by DGDA

- **Transparency**–GRP ensures that the review processes are readily available on Pharmadex to all DGDA officers

- **Consistency**–templates will help reviewers achieve a consistent approach, with occasional deviation when appropriate

Capacity-Building Activities on CTD and the New Review Process for Applications

To build the capacity of stakeholders on the new review process and the actual review of CTD-based dossiers, SIAPS offered several trainings and workshops for DGDA officers and

[5]FDA. Good Review Practices. MAPP 6025.1. Silver Spring, MD: Center for Drug Evaluation and Research; 2012; http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082016.pdf

pharmaceutical company representatives. The structure of the training emphasized the critical areas to be assessed for registration of medicines and how to prepare complete CTD-based documents according to the CTD guidelines. The trainings were intended to further strengthen regulatory systems, deepen knowledge, and improve DGDA staff's ability to adequately assess CTD-based dossiers. The sessions also emphasized adoption of the principles of GRP.

Understanding and Reviewing the CTD Format and Guidelines

SIAPS facilitated two sessions of the intensive training program that would aid in the efficient adoption of the format in Bangladesh. The first set of training sessions was conducted in August 2014 for three days off-site by an international CTD expert for 26 DGDA officers that make up the medicine registration team. In February 2016, a second set of training session was held for four days for representatives from 40 pharmaceutical companies and 25 members of the DGDA registration team. Training on basic CTD topics was also conducted for the DGDA officers based in the field, so they could have an overview of the new registration procedure that is being introduced in the directorate. The primary goal of the training program was for the trainees to understand the registration review process of CTD-based dossiers and to explore how the current DGDA drug registration process will be transformed following full adoption of the CTD. The following objectives were met in both sessions:

1. The concept of CTD and the relevance of its different modules to supporting the label claims of registered products, such as generic and biological products, were discussed. The development of the CTD from its beginnings to its value as an international core dossier was also addressed.

2. Medicine manufacturers were trained on how to prepare CTD-based dossiers for submission to regulatory authorities.

3. DGDA reviewers learned what information they need to evaluate medicine dossiers, how dossiers should be reviewed, and the principles of GRP.

4. Practical insights were given to DGDA reviewers to facilitate their evaluation of dossiers.

5. Potential MTs were identified from the DGDA officers and pharmaceutical company representatives.

The training has further strengthened the regulatory systems and capacity of DGDA, and the participants understood the regulatory components of each module of the CTD guidelines.

How to Review the Quality Module of CTD-Based Dossiers of Medicine Registration

The quality part of a product dossier is one of the most challenging sections of the evaluation process; therefore, as a follow-up to the intensive training, SIAPS conducted a workshop in October and December 2014 for a combined total of 39 DGDA officers in small groups. The training focused on how to review the quality module of CTD-based dossiers. The training outlined the requirements and data that DGDA needs to assess the APIs and the finished

pharmaceutical products. The structure of the exercise emphasized the most critical area to be assessed for registration of medicines to ensure that they are of good quality and are effective. The quality reviewer template was also used during the practice session.

Collaboration with the Korea MFDS for Building Capacity of DGDA Staff

To fully build the capacity of DGDA staff will require a long-term commitment, as procedures of review for different types of products cannot be learned in a short period of time. Given that the SIAPS Program is ending, it was considered advisable to look for other potential collaborations and donors to provide longer-term capacity building to improve the regulatory function of the DGDA. SIAPS has facilitated a formal partnership between the Bangladesh DGDA and KOICA, which in turn engaged the Korea MFDS to provide a long-term training program for DGDA. SIAPS successfully coordinated two meetings with DGDA, KOICA, MFDS, and WHO Bangladesh, who are the primary stakeholders in the country, to maximize the technical assistance provided to DGDA by each organization and to avoid any duplication. In addition, the training outline for each organization was informally mapped out, including trainings for those in and outside the country. Consequently, a multi-year capacity-building program has been established between the DGDA and MFDS, which will foster knowledge exchange and information sharing. The first year of the training was completed in November 2015 and the second year is underway. The objectives of the training for each year are given in table 1.

Table 1. Objectives of the MFDS Training

Year	Theme	Objectives	Main contents
1	Bio-pharmaceuticals (I)	Increase understanding and capacities of trainees on the approval, evaluation, and GMP inspections of bio-pharmaceuticals	• Product marketing authorization procedure for biopharmaceuticals (biologics, gene recombinant product, biosimilars, and cell and gene therapy products) • GMP inspection of biopharmaceutical products • National lot release system of MFDS
2	Bio-pharmaceuticals (II)	Build capacity of trainees on PMS, clinical trials, and quality assurance of biopharmaceuticals	• PMS (PV and traceability) • Managing clinical trials of biopharmaceuticals • Quality assurance and reference standards for biopharmaceuticals • Developing and managing national standard products • Quality assurance system, equipment validation, laboratory operation
3	Pharmaceuticals	Improved surveillance and safety management of biopharmaceuticals	• Product marketing authorization procedure of general medicines • Bioequivalence and bioavailability studies of generic medicines • PMS (PV and traceability)

Consultative Meetings with Pharmaceutical Company Representatives and Senior Management on Adopting CTD-Based Dossiers for Medicines Registration

There has been strong growth in the pharmaceutical sector over the past 20–30 years, since the 1982 Drug Control Ordinance was passed, which lay the foundation for the development of the local pharmaceutical industry.[6] This legislation intended to clean up the pharmaceutical sector by restricting the importation of non-essential and harmful medicines; supporting industrial policy, for example, by introducing clauses limiting manufacturing and sales by foreign firms; and promoting self-sufficiency of essential drugs at affordable prices for the citizens of Bangladesh. Despite the immense potential of this sector and these regulatory measures, some problems and anomalies persist as a result of the limited barriers to entry due to weak regulation. Consequently, medicine registration is easy and low cost because it does not require adequate scientific data or document submission to assess the quality and efficacy of products.

Because of the indigenous nature of the pharmaceutical industries in Bangladesh, it was imperative to engage pharmaceutical stakeholders at the early stages of the move toward adoption of CTD guidelines for international standard of medicine registration. Therefore, consultative workshops were held in November 2014 and February 2015 for representatives from the top 40 pharmaceutical companies, including representatives of USAID and the Bangladesh Association of Pharmaceutical Industries (BAPI), to create an environment for early engagement to adopt a stringent medicine registration process in the country. At the end of the sessions and, based on the questions, comments, and the workshop evaluation analysis (figure 2), it was confirmed that the initiative taken by the DGDA was well received and encouraged by the majority of industry representatives. The group identified some key points and suggestions on how DGDA can proceed, with the continued technical assistance of SIAPS (table 2). The most critical request was that the launching of CTD should be in phases, beginning with certain therapeutic classes of drugs and that a grace period be allowed so that the manufacturers could prepare better.

[6] Lombe Kasonde and Hui Si Teo, World Bank Report. August 2014: Overview of the Pharmaceutical Sector in Bangladesh (draft).

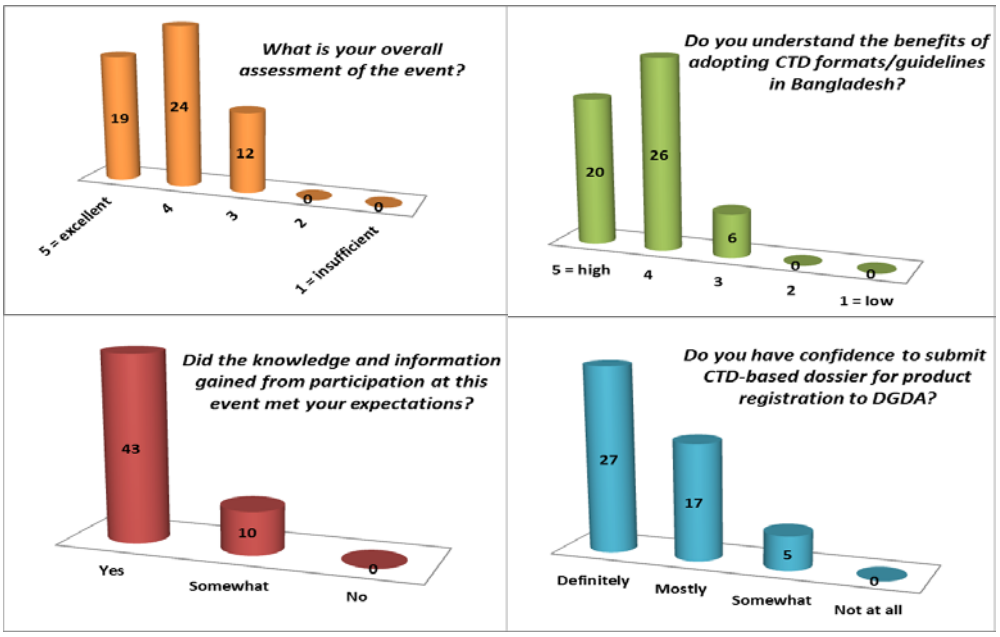


Figure 3: Analysis of key parameters from workshop evaluation and feedback reports from pharmaceutical company representatives

To further solidify buy-in from companies, the DG of DGDA requested that the executives, such as managing directors and chief executive officers of the top 40 pharmaceutical companies, attend a consultative meeting in February 2016. The DG emphasized his commitment to start this new initiative and process. The majority of executives responded positively, and they supported adoption of CTD-based dossiers for the registration of medicines.

Table 2: Comments/Recommendations from Pharmaceutical Companies Representatives

Pharmaceutical Companies Representatives	Responses by SIAPS and DGDA
General Comments	
MTs should be developed within the pharmaceutical industries.	SIAPS will work with BAPI. From the consultative and sensitization workshops, SIAPS has identified potential MTs from the manufacturers.
Multiple trainings on CTD need to be facilitated for the pharmaceutical manufacturers.	SIAPS will work on this.
Develop CTD guidelines within Bangladesh context.	Bangladesh CTD guidelines are already country specific.
In the first phase of implementation, comparative studies on dissolution/drug release were not included, but were grouped with bioavailability/ bioequivalence studies to be initiated in the second phase. However, the representatives requested that it be a part of the current phase of implementation, as this will allow the companies	Same request from the consultation meeting. Therefore, a dissolution guideline needs to be developed. In addition, not all the products in Bangladesh would require bioequivalence studies (this will be defined during bioavailability/ bioequivalence guideline development in the second phase).

Pharmaceutical Companies Representatives	Responses by SIAPS and DGDA
to prepare CTD-based dossiers that will be complete for submission to many other countries that always require dissolution/drug release data for product registration and approval.	
Clinical data needs to be submitted to DGDA before any drug is approved.	DGDA may not be able to handle all CTD requirements right now. As such, clinical data will be requested later. However, DGDA can also make a decision and request clinical data with regard to certain products, e.g., anticancer drugs, for a start.
Specific Questions	
What is the plan for new products or previously registered products with regard to adoption of CTD?	DGDA stated that CTD adoption will be focused on new product registration and not previously registered products. The reason is that DGDA currently has over 26,000 registered products in the country, and it will be quite difficult to retroactively request submission of CTD-based dossiers for such products.
If any data is wrongly posted while registering a product, can the company re-register for the same product with correct information?	If the application has not been submitted, changes can be made. However, if it is already submitted, DGDA has to be notified before any modification.
There are no details on bioequivalence studies on the highest strength of a product and waiver for the lower strength in module 1.	This will be part of the Bangladesh bioequivalence guidelines, which will be developed later.
Does DGDA currently have the capacity to review all the documents that are requested based on CTD formats?	With the help of SIAPS, DGDA is building its technical capacity. DGDA officers have been selected to act as screeners, reviewers, and moderators to aid the dossier evaluation process.
How can API quality be ensured? There was concern that CTD-based dossier requirements for APIs (mostly procured from other countries, e.g., India) will incur more cost and another challenge is to find a way to ensure the quality of APIs.	The sponsor should discuss the new Bangladesh requirements with the API manufacturer and request the quality control documentation from them. DGDA informed the participants that based on the volume of raw materials procured by manufacturers, a negotiation can ensue between the two manufacturers to address the problem.
Characterization of impurities is critical for ensuring the quality of a drug product and might delay registration, especially if the impurities are non-compendia. In addition, if it is a novel	Literature searches; ICH guidelines on impurities; companies can also develop their own standards, with adequate justification and discussion on the method and analysis

Pharmaceutical Companies Representatives	Responses by SIAPS and DGDA
impurity, how can the standard to characterize be obtained?	submitted in the dossier
How can DGDA control the amount of inactive ingredient in vitamins and mineral products?	Presently, DGDA is regulating only drugs. Minerals and vitamins fall under food regulation, which is not regulated in the country.

Category 2: Automating the Registration Process using Pharmadex Tailored to the Bangladesh Situation

Pharmadex is a web-based integrated information solution that facilitates management, documentation, dissemination, and sharing of regulatory information within NRAs and their major stakeholders. Pharmadex aids in the submission of medicine applications online from pharmaceutical companies, registration of medical products, licensing, amendments, inspections, and the overall management of functions for an NRA. It can capture and track whether the dossier requirements for medicine registration submitted by a pharmaceutical company are based on CTD formats. In addition, Pharmadex is useful for the NRA to review submitted applications and evaluate the dossier, which improves efficiency for applicants by eliminating unnecessary submission delays, as well as optimize the process of medicine registration and approvals.

Key features include[7]—

- Designed as a web-based system—allows for online application and information sharing with the regulated industry and consumers

- Provides modular structure—helps NRA departments integrate and coordinate their work, from product registration, licensing, and pre- and post-marketing inspections, to quality control, PV, and administration.

- Built-in document tracking and management system—facilitates archiving, documentation, management, and retrieval of dossiers and provides a platform to develop electronic document management systems
- Uses international standard dictionaries—provides standard terminologies and dictionaries with built-in international nonproprietary names, the Anatomical Therapeutic Chemical classification system, and the Medical Dictionary for Regulatory Activities

- Provides one-stop access to a regulatory approval package—enables access to product approval history, approval letter, and approved product information

- Enhances performance monitoring—monitors built-in key performance metrics and generates activity reports for the NRA

[7] Srivastava, U. Draft Pharmadex Bangladesh User Manual. Arlington, VA: SIAPS; 2015.

The generic version of Pharmadex was designed by MSH to be freely available to NRAs in developing countries; however, it was essential to customize it to a country-specific version that would define regulatory processes, workflow, scope of regulatory functions, structures and systems, roles and responsibilities, SOPs, guidelines, human resources, and infrastructure within the country. The legislation, rules, and laws within the country were taken into consideration during the design of the program.

Design of a Bangladesh-Specific Pharmadex

As such, a Bangladesh-specific Pharmadex was developed that determined data elements for each function of regulatory authority and the decision-making process within DGDA. The new system is expected to strengthen the DGDA's capacity to regulate licensing, registration, and inspection of medicines. A Bangladesh-specific medicine registration application template and flow of work (annex 1) within Pharmadex were defined based on feedback from the DGDA taskforce. The final versions of the DGDA CTD templates were incorporated into Pharmadex. The existing database of DGDA's list of registered drugs, manufacturers, and pharmacies for both local producers and importers were also validated for effective drug registration process flow within the online system.

Compilation of the Bangladesh-Specific Pharmadex User Manual

Following the development of the Bangladesh-specific Pharmadex, a user manual was developed to serve as a resource guide to pharmaceutical companies and DGDA officers on how to enter information and operate Pharmadex. It comprises the applicants' registration profiles and all relevant applicant administrative processes pertaining to DGDA.

User Acceptance Testing of Pharmadex–DGDA Officers and Pharmaceutical Company Representatives

As part of the implementation process, hands-on testing sessions and demonstration of Pharmadex has been conducted for DGDA staff. In addition, a consultative workshop was facilitated by SIAPS for 14 representatives of the top 7 pharmaceutical companies in November 2014. The user acceptance testing for both groups provided:

- A demonstration of the system so that stakeholders can provide feedback for the improvement of Pharmadex
- An overview of the implementation plans and future directions
- Hands-on practical exercise on data entry and processing
- Understanding of the application process, review flow, and functionalities of Pharmadex

Procurement of Computers to Operate Pharmadex

To support the smooth and efficient operation of Pharmadex, SIAPS procured 35 computers, printers, and an uninterrupted power supply for DGDA. A letter of agreement was also signed by the DGDA in partnership with SIAPS with the understanding that SIAPS will facilitate the maintenance of the computers for a period of one year and that the DGDA will be responsible for

all maintenance of the equipment after the expiration date, thereby, facilitating ownership by the Government and sustainability of the intervention.

Official Launch of Pharmadex and CTD Guidelines

The registration module of the Bangladesh-specific Pharmadex has been completed and is ready to be launched in September 2016 on a pilot basis at a few selected pharmaceutical companies. To further prepare for the pilot launch, four sets of on-the-job training were also organized for DGDA officers to enable them to practice reviewing actual CTD-based dossiers that were submitted by four pharmaceutical companies, who were participating to show their support for the directorate and the new review process. The practice session was planned such that the staff performed dossier reviews based on their functional roles as outlined in the Pharmadex workflow. Furthermore, as a part of the positioning of Pharmadex, a user/applicant request form was developed for DGDA, which has been sent to selected pharmaceutical companies to collect legacy data and information to build a Pharmadex database comprising all the necessary data required to launch the system. Once this step is completed, DGDA will send out an official letter to selected manufacturers requesting them to submit a CTD-based dossier to register a product and also to submit their application through Pharmadex.

Additionally, two SOPs for the applicant (pharmaceutical companies) and for DGDA staff have been developed that will be used as a work aid in conjunction with the Pharmadex User Manual. Two workshops have also been conducted for the established MTs on how to design capacity development plans for all stakeholders in order to achieve sustainable capacity-building results. The CTD guidelines and training resource packages have been provided to them.

Major Expected Outcomes of the Adoption of the CTD Format through Pharmadex

Obtaining marketing authorization for the sale of medicines in Bangladesh is quite cheap and easily achieved because of inadequacies in the technical documents submitted to DGDA to support registration. This contributes to unknown quality, unsafe, and ineffective products to being available on the market. Consequently, SIAPS is providing technical assistance to DGDA to improve the performance of their regulatory systems through a series of strategic steps. One of the more important first steps is to improve medicines registration and granting of marketing authorization in Bangladesh to be in accordance with international standards through the adoption of CTD formats and guidelines. Pharmadex was also developed as an online medicine registration system tailored to the Bangladesh context that will aid in streamlining medicine registration and overall management of regulatory functions, such as registration, licensing, surveillance, quality testing, and inspection. Pharmadex also provides the platform for the introduction of CTD-based dossiers. Furthermore, to ensure GRP, question-based templates on screening, administrative, and labeling and quality were developed for DGDA officers for the evaluation of the dossiers. The adoption of the CTD format using Pharmadex as a platform ensures that the necessary and required data and information supporting product-labeling claims by pharmaceutical companies are justified.

RECOMMENDATIONS

Immediate Goals

Immediate next steps should include the following in order to complete the adoption and implementation of CTD and the Pharmadex IT solution.

- Establish the post-registration processing menu that is available in Pharmadex and communicate how to use it to stakeholders
    - Post-amendment applications
    - Expiring and expired registration
- Develop the Bangladesh Amendment guidelines
- Roll out Pharmadex to all pharmaceutical companies in Bangladesh
- Expand the modules of Pharmadex to include (investigate what is already available in the DGDA website)
    - Inspection
    - Surveillance
    - National Control Laboratory
- Develop the dissolution and labeling CTD guidelines for stakeholders
- Develop and introduce the Bangladesh CTD guideline (module 5 on bioequivalence)
- Compile all frequently asked questions from stakeholders and establish a guide to be posted in Pharmadex
- Continue to build the capacity of all stakeholders, as needed

Long-Term Goals

- Examine the potential for collaboration with local academic institutions and other stakeholders to revise the curriculum to include detailed topics on CTD guidelines, which are currently inadequate.
- The DGDA should collaborate with pharmaceutical manufacturers, the Ministries of Trade and Industry, and other stakeholders to organize a high-level stakeholders meeting to discuss options to further advance more of the indigenous pharmaceutical manufacturers to the level of international standards.
- Revise the Drug Act 1940 and Drug Control (Ordinance) 1982 to adequately address contemporary issues and challenges and to include recommendations for adopting the international standards of medicine registration.

- Address the over-representation of the pharmaceutical manufacturers association in the DGDA regulatory committees, such as the DCC, to avoid conflict of interest.

- The DGDA should adopt some measures to ensure good governance, particularly transparency and accountability, in regulatory functions and DGDA structures implemented, including involvement of various civil societies in the decision-making process.

- Analyze and propose options for addressing human resource needs and also for DGDA to be financially self-sustaining.

LESSONS LEARNED AND CHALLENGES

- It is important for full, early-on strategic engagement and buy-in of stakeholders including the DGDA, MOHFW, and the pharmaceutical companies after the initial assessment before any intervention areas are identified. The DGDA should be orientated to have a clear understanding of their technical needs and complexities that might arise, such as the extensive shift from their current minimal standard and all paper-based structure.

- Country context, need, and readiness of the key stakeholders are some of the determinants for success of an intervention as the adoption and adaptation of new tools and technology may require more time than initially anticipated, especially for such high-level activity.

- Automation of the product registration process should take place after introducing some form of electronic database that contains legacy data and improving the administrative approval process. Technical capacity of the organizations, including changes in their regulatory framework and developing guidelines and SOPs, takes a significant amount of time to develop.

- Upgrading the registration of medicines function of the DGDA to international standards was quite a slow process because of the challenges in the technical capacity of DGDA to review scientific information in medicine dossiers to assess quality and efficacy of medicines.

- Quite a number of DGDA officers still have limited computer knowledge which could potentially limit implementation and navigation of Pharmadex as more efforts are needed to automate the process effectively.

- Creating and building strong ownership of CTD and Pharmadex by the DGDA should be done as soon as possible.

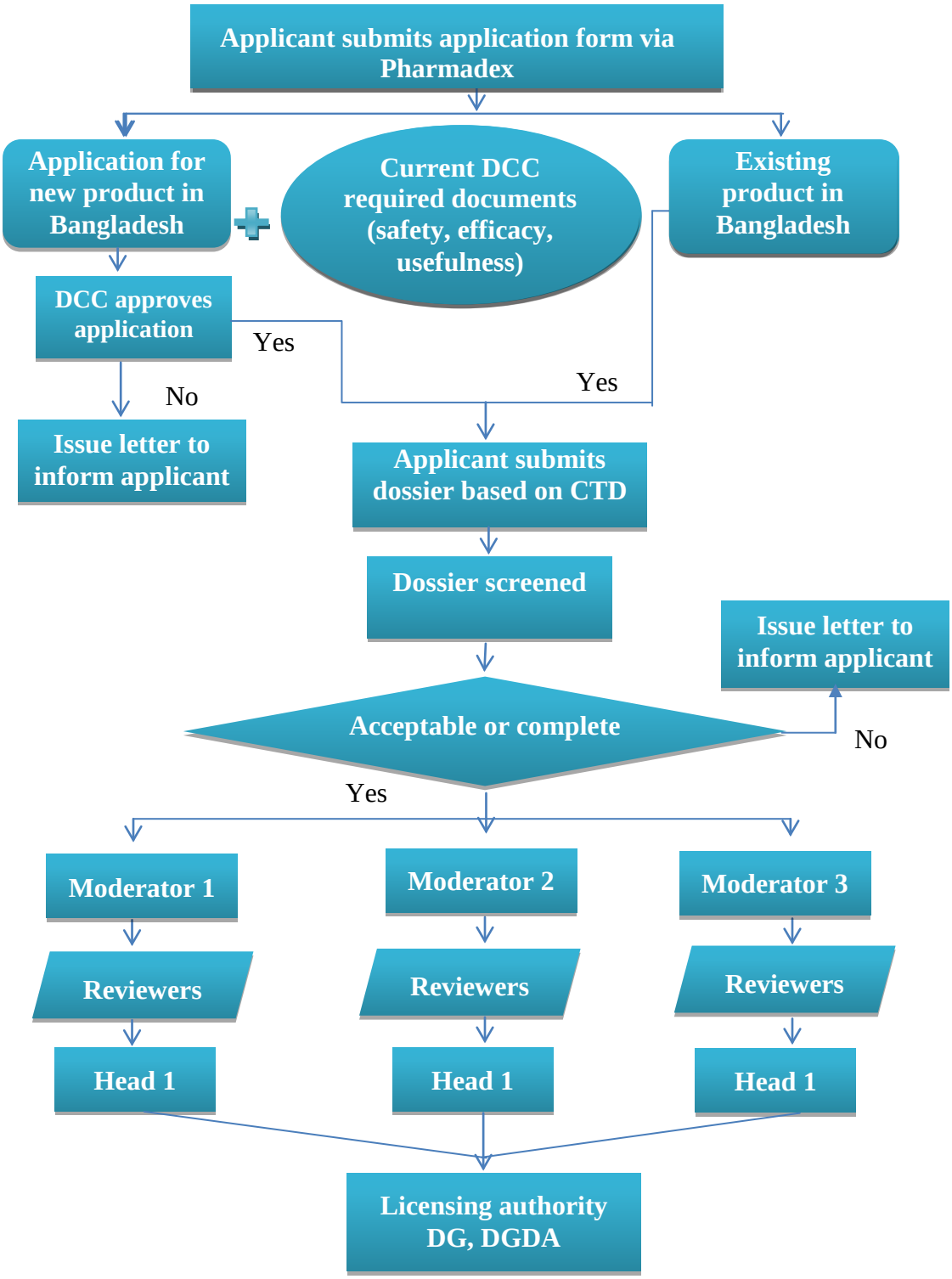
- Introduction of the CTD format and CTD-based dossiers may involve additional cost that may result in a slight increase in the prices of drugs.

- Full adoption of CTD and implementation of Pharmadex for the registration and licensing of medical products should include time for manufacturers to build their capacity, which will allow for a smooth transition from the old system to the new international standards.

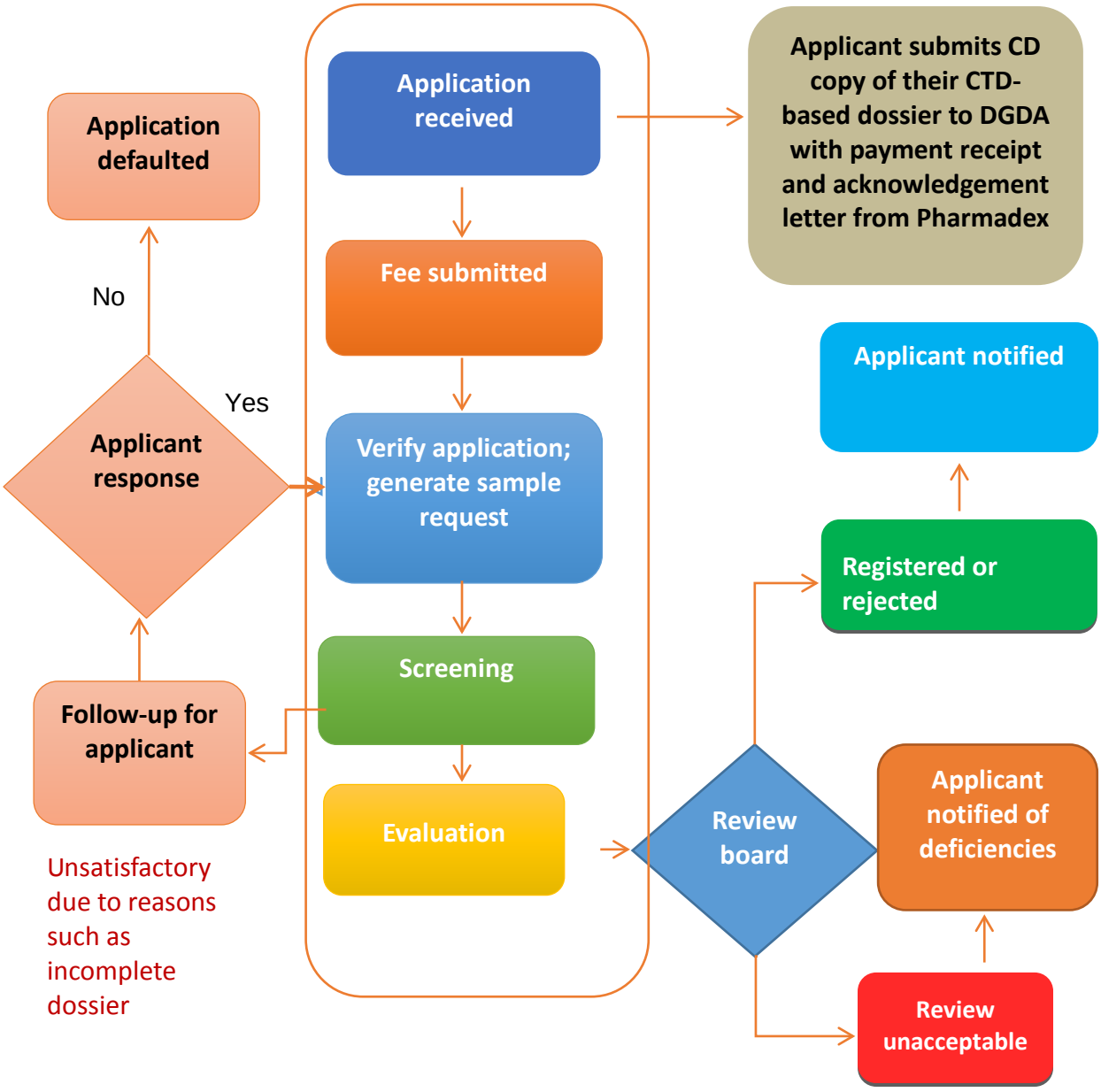
- Increase the collaboration with other technical implementing partners to double efforts to combat corruption, improve leadership, and enact policy change.

ANNEX 1. BANGLADESH-SPECIFIC PHARMADEX APPLICATION FLOW

DGDA Proposed Application Process Flow



Application Processing in Pharmadex



ANNEX 2. PHOTOS

Group photo of DGDA officers that received CTD training

CTD training of DGDA officers

Consultative meeting with pharmaceutical companies' representatives

User acceptance training for DGDA staff and pharmaceutical company representatives

Handing over of computer to DGDA