Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh

November 2012

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Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh

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November 2012

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.

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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.

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Nwokike, J., H. L. Choi. 2012. *Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh.* 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.

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ACKNOWLEDGMENTS

Data collection was conducted by a local consultant, Md. Mostafiz Rahman, with support from Dr. Zubayer Hussain (SIAPS/Bangladesh) and Mohammad Kibria (SIAPS/Bangladesh).

We are grateful to the following individuals of the Directorate General of Drug Administration for their leadership, direction, and contributions to the assessment—

- Major General Md. Jahangir Hossain Mollik, Director General
- A. Salim Barami, Director
- Md. Ruhul Amin, Deputy Director
- Mrs. Nayer Sultana, Deputy Director

ACRONYMS AND ABBREVIATIONS

ADR	adverse drug reaction
AEFI	adverse events following immunization
API	active pharmaceutical ingredient
BDT	Bangladeshi taka (currency)
BMI	Business Monitor International
BMRC	Bangladesh Medical Research Council
BRAC	Bangladesh Rural Advancement Committee
BSTI	Bangladesh Standards and Testing Institutions
CTDL	Central Drug Testing Laboratory
CDT	common technical document
DCC	Drug Control Committee
DDA	Directorate of Drug Administration
DGDA	Directorate General of Drug Administration
DPA	direct project aid
DQI	drug quality and information
DTL	drug testing laboratory
EDCL	Essential Drugs Company Limited
EPB	Export Promotion Bureau
FDA	US Food and Drug Authority
GMP	Good Manufacturing Practice
GNI	growth national income
GOB	Government of Bangladesh
GRP	Good Regulatory Practice
HPNSDP	Health, Population, and Nutrition Sector Development Program
HR	human resources
ICDDR (ICDDR-B)	International Centre for Diarrhea Diseases and Research Bangladesh
MHRA	Medicines and Healthcare products Regulatory Agency
MOHFW	Ministry of Health and Family Welfare
MoU	memorandum of understanding
MRP	maximum retail price
NCD	noncommunicable disease
NCL	National Control Laboratory
NRA	national regulatory authority
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PMS	Post-marketing surveillance
PV	Pharmacovigilance
QMS	quality management system
RPA	reimbursable project aid
RRA	reference regulatory authority
RSAT	Regulatory Systems Assessment Tool
SAARC	South Asian Association for Regional Cooperation
SARSO	South Asian Regional Standards Organization
SEARO	South-East Asian Regional Office

SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SOPs	standard operating procedures
SRA	stringent regulatory authority
TB	tuberculosis
TGA	Therapeutic Goods Administration
TRIPS	trade-related aspects of intellectual property rights
USAID	United States Agency for International Development
USD	US dollars
USP	United States Pharmacopeia
WHO	World Health Organization

EXECUTIVE SUMMARY

Background

Bangladesh is confronted by high burden of infectious disease and cases of chronic non-communicable diseases are also on the increase. Efforts at confronting these challenges have been remarkable. The world renowned international health research institute, the International Centre for Diarrhea Diseases and Research Bangladesh is credited with the discovery of oral rehydration therapy, oral cholera vaccine, and zinc treatment for diarrhea. In addition, the pharmaceutical market in Bangladesh, which was worth BDT 111.10 billion (USD 1.5 billion) in 2011, is continuously expanding and is Bangladesh's third largest industry. These achievements in health and economic development of the pharmaceutical industry are at times stymied by poor quality products. In 2009, about 25 children died from toxic paracetamol manufactured locally. It is estimated that spurious medicines cost the Bangladesh pharmaceutical industry up to USD 150 million per year. These challenges and the opportunities for tremendous growth in the pharmaceutical industry highlight the need for Bangladesh to develop a world-class drug regulatory authority.

The Directorate General of Drug Administration (DGDA), Bangladesh's national regulatory authority (NRA) was established in 1976 and is charged with the responsibility of regulating Bangladesh's 838 manufacturers of allopathic, unani, ayurvedic, herbal, and homeopathic, and biochemic manufacturers' products. The DGDA has a list of 23,242 products registered in the country. The pharmaceutical industry in Bangladesh provides almost all of the local needs while through its export activities, contributes to foreign exchange earnings.

Methodology

The DGDA invited the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program to provide support for a comprehensive assessment of the Bangladeshi pharmaceutical regulatory system. The objectives of the assessment were to—

1. Review the pharmaceutical products regulatory system from a systems perspective
2. Identify strengths, weaknesses, and opportunities for strengthening pharmaceutical products regulation
3. Review regulatory functions and processes to identify opportunities for improvement
4. Provide data for the conduct of options analysis for strengthening regulatory systems

The SIAPS program used the Regulatory Systems Assessment Tool (RSAT) to conduct a structured assessment of the DGDA, reviewed more than 50 documents, and conducted interviews with key informants. The assessment also reviewed the DGDA's Operational Plan for Strengthening of Drug Administration and Management as contained in the Ministry of Health

and Family Welfare (MOHFW) Health, Population, and Nutrition Sector Development Program (HPNSDP) strategic plan for 2011-2016.

Key Findings

Regulatory Framework and Governance

- *Laws and regulations.* Some laws and regulations are now outdated or are not in convergence with pharmaceutical legislation from other countries, in particular, definitions, classification of medical devices, technical and regulatory requirements for medical devices, mandates on clinical trials, control of prescribing, outdated schedules, lack of regulatory instruments for biosimilars, and requirements for bioequivalence, bioavailability, and pharmacovigilance (PV). It is critical that Bangladesh modernize and consolidate its legislation to provide a comprehensive regulatory framework to guide the development of the pharmaceutical sector.

- *Manpower and funding.* The DGDA is severely understaffed to fulfill its mandate and support the local industry, given the rapidly growing pharmaceutical market, large number of registered products, and large population size. Funding to cover the critical activities of the DGDA and implement the operational plan is inadequate. Fees charged for regulatory services adjusted by growth national income (GNI) per capita are significantly lower than in other countries. A comprehensive costing analysis can inform the DGDA on the adequate level of resources including staffing required to effectively implement its responsibilities.

- *Governance and transparency measures*. There is potential for conflicts of interest in the memberships of committees as some members have multiple roles. The civil society, particularly the consumer group, is under represented in DGDA committees. The committee members are not remunerated to conduct their duties. Other missing key elements of governance measures include lack of formal communication channel with customers including industry, inadequate tracking of key performance indicators, and lack of information sharing.

- *Quality management system (QMS).* A quality manual and quality policy have been developed, but implementation of a QMS is weak. Regulatory registers and an inventory of standard operating procedures (SOPs) and guidelines that would enable the DGDA to track, update, and identify critical gaps are lacking.

- *Regulatory compliance and enforcement*. The legal basis to enforce compliance and implement sanctions for violations is in place, including drug courts. The DGDA can strengthen administrative measures such as publicly posting information on violators.

Regulatory Functions

- *Product evaluation and market authorization*. Delay in registration for new products is often due to infrequent and irregular scheduling of Drug Control Committee (DCC) meetings, lack of manpower, and lack of an electronic information management system. Other challenges

include application forms not in compliance with the common technical document (CDT) format, inadequate registration fees (registration fee index less than 0.3), indications for use not included in the registration certificate, and delays attributed to reviewing application packages sequentially instead of using a parallel process.

- *Licensing.* No electronic system to keep and update the register. For example, the list of retail pharmacies and wholesalers is not publicly available.

- *Inspection.* Significant shortage of inspectors and inadequate time spent during inspections could have compromised the quality of the inspections. The lack of use of risk-based inspection strategies further strains the limited resources. It is estimated that 440-660 inspectors are needed to conduct the type of inspections that would comply with GMP guidelines. The current number of inspectors is less than 30.

- *Import and export control*. The DGDA has a critical role to support the growth of the pharmaceuticals industry by ensuring that local manufacturers comply with global quality standards. Formal cooperation with key stakeholders including the Ministry of Commerce, the National Board of Revenue, and the Export Promotion Bureau (EPB) is not in place. Strengthening such collaboration can help the DGDA and other government agencies to further support the local industry and boost export growth.

- *Quality control*. The DGDA is currently collaborating with the World Health Organization (WHO) to strengthen the capacity of the National Control Laboratory (NCL) to become a WHO pre-qualified facility. Achieving WHO prequalification or global Good Manufacturing Practice (GMP) standards is critical also for local manufacturers, which will ensure the quality of products in the local market and also help them export good quality products.

- *Clinical trials*. Absence of law and regulation that provide explicit guidelines for the conduct of clinical trials can lead to inadequate control of clinical trials thereby exposing vulnerable trial participants and generating unreliable data. There is lack of collaboration between the DGDA and the Bangladesh Medical Research Council (BMRC). Currently limited information is shared on clinical trials and there are no guidance documents or regulation on approval of new investigational drugs.

- *Post-marketing surveillance and PV*. The recent assessment of the Bangladesh PV system highlights the absence of legal and regulatory requirements for PV, an information system, and adequate, active drug-safety surveillance activities.

- *Pricing.* The DGDA's pricing policy and regulation contributes to keeping the prices of pharmaceuticals low in Bangladesh, particularly for the primary healthcare listed medicines. Also, the price marked in the packing materials is another good mechanism to control prices of medicines. However, there is no systematic price-monitoring system in Bangladesh. Absence of a price-monitoring system and inadequate inspections can incentivize retail pharmacies and medicines shops to make illegal profits. Introducing a robust price-monitoring system, such as barcodes in product packages, can ensure the affordability of medicine and prevent counterfeiting.

Recommendations

Because of the existence of an operational plan to strengthen drug administration and management for 2011–2016, it was decided that the analysis of the assessment findings and options for improvement should build on the operation plan so as to facilitate the development of a strategic plan for the entire pharmaceutical system. Also, the DGDA recommended that an action plan should be developed with major stakeholders during the assessment dissemination workshop so as to decide on key priorities and the way forward to implementation of the recommendations. The dissemination workshop participants reviewed the recommendations to determine their orders of priority. The last chapter of this report provides the feedback from the action planning exercise and the implementation plan for short-term priorities. The recommendations presented below are therefore meant to guide the development of the strategic plan and the immediate-term action plan. However, we suggest that addressing the current human resources (HR) constraints first may facilitate implementation of the other recommendations.

- Modernize the DGDA regulatory framework
- Pursue harmonization and networking with other international regulatory authorities to attain global standards and improve efficiency
- Review the vision and organizational structure of the DGDA
- Address the current critical HR challenges
- Develop a comprehensive QMS
- Develop strategies for improving governance in regulatory activities
- Build local technical capacity for regulatory affairs
- Automate the regulatory processes and management information systems
- Implement risk-based and risk proportionate regulatory strategy
- Streamline the registration process
- Develop Good Regulatory Practice (GRP) guidelines
- Revise fees charged for regulatory services
- Properly maintain regulatory registers for all activities
- Develop an action plan for the advancement of the pharmaceutical industry

- Develop timelines for attainment of WHO GMP standards
- Strengthen control on advertisements and promotion and improve rational use of medicines
- Implement the recommendations of the recent assessment of the PV system

Conclusions

The pharmaceutical sector in Bangladesh provides an example of how health and economics intermix. The justification to strengthen the Bangladesh pharmaceutical regulatory system is compelling because of the dual contribution in improving health outcomes and economic development. The DGDA's capacity should be strengthened to protect public health while advancing industrial development in Bangladesh.

BACKGROUND

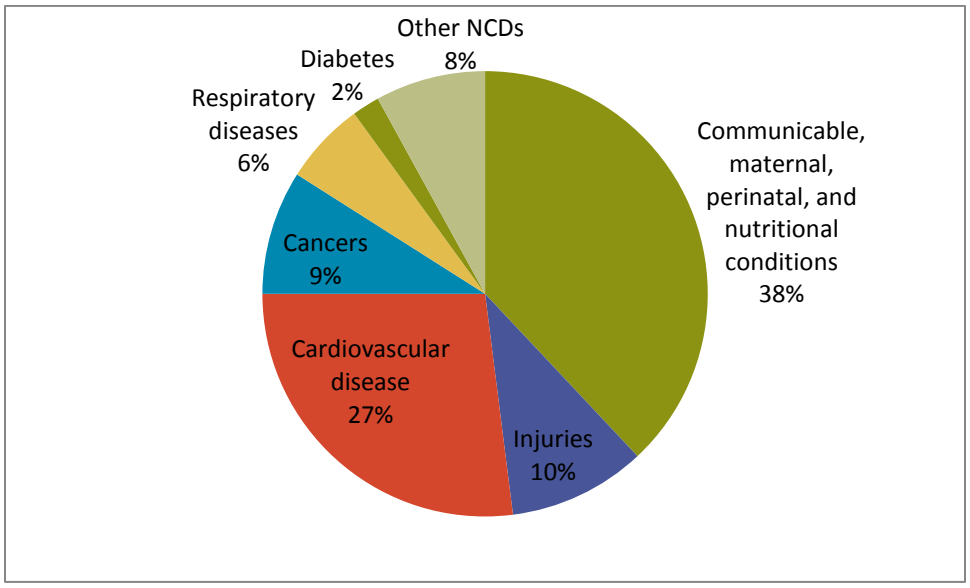
The People's Republic of Bangladesh in South Asia is one of the most densely populated countries with an estimated population of 150 million and a density of 1,033/km^2.[1] More than 70 percent of Bangladesh's population resides in rural areas. Bangladesh is a low-income country with a GNI per capita of $770 and 31.5 percent of the population living below the national poverty line.[1] Bangladesh is ranked 146 out of 187 countries globally in the Human Development Index.[2]

Although health and economic development gains have been consistent for the last three decades, many of the indicators for health in Bangladesh are still within the bottom quartile globally, with a high prevalence of tropical infectious diseases, including pneumonia, diarrheal disease, vector-born disease, and tuberculosis (TB) (figure 1). According to the International Centre for Diarrhea Diseases and Research Bangladesh (ICDDR-B)[3]—a renowned international health research institution credited with the discovery of oral rehydration therapy for the treatment of diarrhea and cholera—pneumonia is a leading cause of childhood mortality in the country. Bangladesh ranks sixth among countries with a high TB burden[4] with the estimated incidence rate of 225 per 100,000 population in 2010.[5] Diarrheal disease and pneumonia in Bangladesh account for 20 percent of under-five child mortality. Bangladesh also has a high prevalence of hepatitis B and C. It is estimated that 7.2-7.5 percent of population in Bangladesh is infected with hepatitis B, which is higher than the prevalence rate of 5.6 percent in South-East Asia.[6,7] Malnutrition and food insecurity are also common; the prevalence of chronic and acute malnutrition is among the highest globally, with 17 percent and 43 percent of children under five suffering from wasting and stunting, respectively.[8] Under-five child mortality and maternal mortality are still high at 45 per 1,000 live births and 240 per 100,000 live births, respectively, in 2010,[5] though Bangladesh has made considerable progress toward the Millennium Development Goals of reducing under-five mortality and improving maternal health.[9]

Although the death rate from infectious disease has been slowly decreasing, the mortality rate from chronic disease has been increasing rapidly. In 2010, noncommunicable diseases (NCDs)

[1]World Bank World Development Indicators 2011. Available at http://data.worldbank.org/country/bangladesh
[2]UNDP. International Human Development Indicators. Available at http://hdrstats.undp.org/en/countries/profiles/BGD.html
[3]The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR-B) http://www.icddrb.org/
[4]WHO. Tuberculosis Country Profile: Bangladesh. Available at https://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=BD&outtype=pdf
[5]WHO. Global Health Observatory Data Repository. Available at http://apps.who.int/ghodata/?vid=4200&theme=country
[6]Mahmood, G., C. R. Debnath, B. Biswas. Seroprevalence of HBsAg Among Blood Donors at Sher-E-Bangla Medical College, Barisal. *Bangladesh Liver Journal*, Vol. 1, No. 1 (2009) doi: 10.3329/blj.v1i1.2624
[7]WHO. Viral Hepatitis in the WHO South-East Asia Region. 2011. http://203.90.70.117/PDS_DOCS/B4752.pdf
[8]UNICEF Country Statistics: Bangladesh: http://www.unicef.org/infobycountry/bangladesh_bangladesh_statistics.html
[9]The Millennium Development Goals Bangladesh Progress Report. 2011. Available at http://www.undp.org.bd/info/pub/MDG%20Progress%20Report%2011.pdf

were estimated to account for 52 percent of all deaths.[10] *Business Monitor International* (BMI) estimates that communicable diseases and NCDs will account for 21.6 percent and 78.4 percent, respectively, of the total disease burden by 2030.[11]



Note: Proportional mortality, % of total deaths, all ages. Source: WHO. NCD Country Profile: Bangladesh 2011

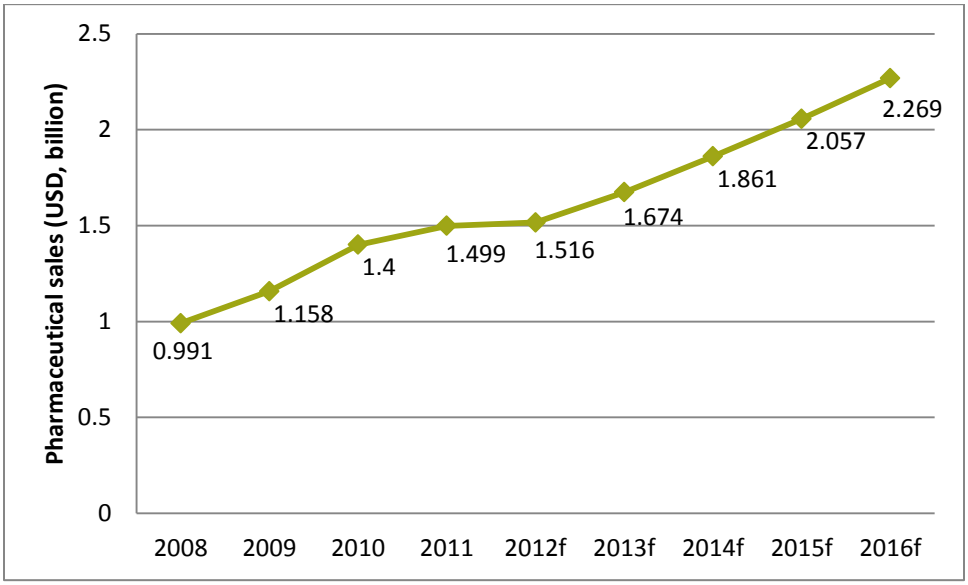
Figure 1. Disease burden in Bangladesh

Bangladesh has a public health infrastructure at the national and regional levels, but the private sector is also an important and influential source of healthcare services. According to a demographic and health survey conducted in 2007, nearly 83 percent of caregivers first sought care for a child with diarrhea in a private facility.[12] Private pharmacies and drug sellers are important and frequent sources of care. The government works closely with a number of large and influential nongovernmental organizations to provide services and conduct surveillance activities, including Bangladesh Rural Advancement Committee (BRAC) and ICDDR-B, both of which have been integral to health systems and program scale-up in urban and rural areas for decades. ICDDR-B has also implemented several clinical trials for *Shigella* vaccine and meningococcal vaccine and recently launched a five-year study to introduce cholera vaccine in Bangladesh.[13]

[10]WHO. NCD Country Profiles. 2011. Available at http://www.who.int/nmh/countries/bgd_en.pdf
[11]*Business Monitor International*. Bangladesh Pharmaceuticals and Healthcare Report Q4. 2012
[12]Bangladesh 2007 Demographic and Health Survey, 2009: http://www.measuredhs.com/pubs/pdf/FR207/FR207[April-10-2009].pdf
[13]ICDDR-B. Introduction of Cholera Vaccine Project in Bangladesh (press release). 2010. Available at http://www.icddrb.org/media-centre/media-releases/cat_view/60-media-releases?start=10

Pharmaceutical Market

The pharmaceutical market in Bangladesh, worth BDT 111.10 billion (USD 1.5 billion) in 2011, is continuously expanding. It is estimated to be the third largest industry in the country and is 1.3 percent of the country's GDP and 40.9 percent of total healthcare expenditures.[11, 14] According to BMI, the pharmaceutical market size will reach BDT 188.71 billion (USD 2.27 billion) by 2016 (figure 2).

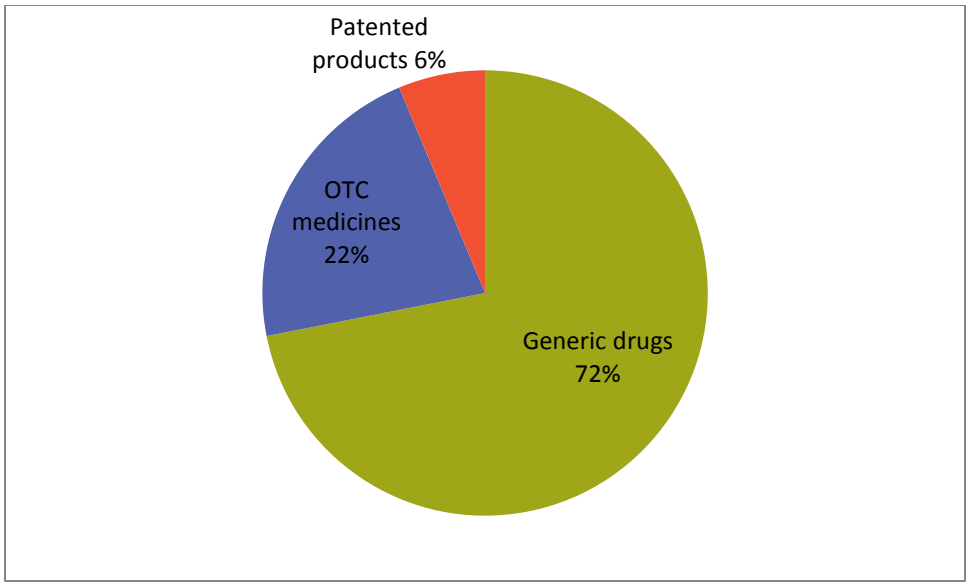


Source: BMI; f, forecast

Figure 2. Pharmaceutical market growth 2008-2016

There are a total of 838 pharmaceutical manufacturers in Bangladesh—265 allopathic, 267 unani, 202 ayurvedic, 25 herbal, and 79 homeopathic and biochemic manufacturers.[15] Of the registered allopathic manufacturers, 260 have their own manufacturing facilities and 5 are multinationals, catering to approximately 95-97 percent of domestic demand. The rest is a share of high-technology products, such as vaccines, biopharmaceuticals, and innovative cancer drugs. Local industry has made significant progress in producing active pharmaceutical ingredients (APIs), although 70-80 percent of raw materials are still imported mainly from China, India, and Europe.[11,14] The pharmaceutical market is made up of mostly generic drugs (figure 3).[11] The number of registered allopathic products is 23,242 for 1,190 molecules, according to the database in the DGDA (as of November 2012).

[14]BRAC EPL. An Overview of the Pharmaceutical Sector in Bangladesh. 2012.
[15]The DGDA website. Available at http://www.dgda.gov.bd/



Source: BMI

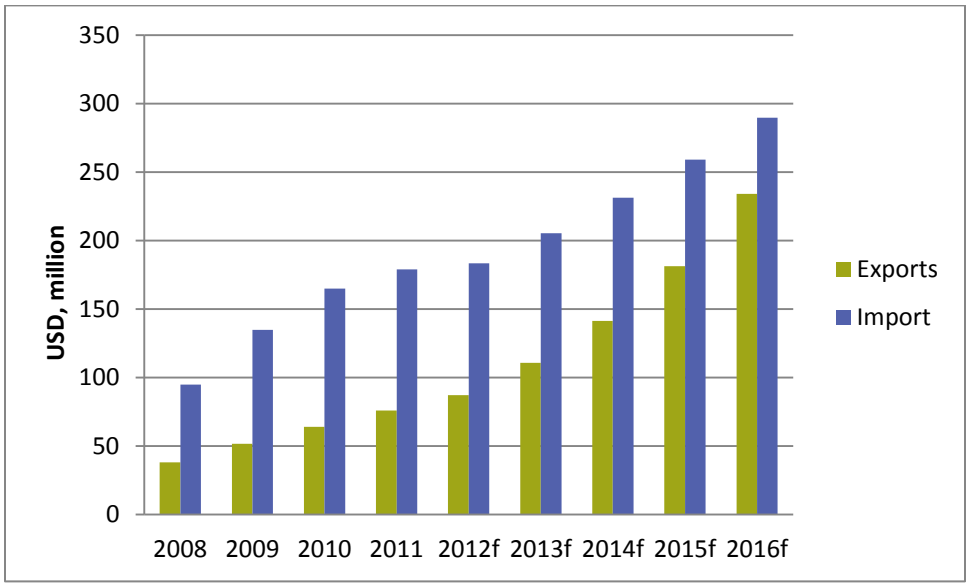
Figure 3. Pharmaceutical market per sector

Several factors are believed to contribute to the rapid growth of the pharmaceutical industry in Bangladesh—increased awareness of healthcare, increase in per capita income, rising population number, emergence of private healthcare services, and the government's increased expenditures in health and pharmaceuticals. In fact, the Government of Bangladesh (GOB) gives the highest priority in supporting continuous expansion of the pharmaceutical industry.[16]

Manufacturers produce more than 500 molecules, which are available in around 5,300 brands and over 8,000 formulations. The local market is highly concentrated with the top 10 pharmaceutical companies making up 70 percent of the total market share.[11] The top 10 pharmaceutical companies are Square Pharmaceuticals, Beximco, Eskayef, Incepta, Acme Laboratories, Advanced Chemical Industries, Opsonin, Renata, Aristopharma, and Drug International.[11] Some of the top local manufacturers meet international GMP standards and are certified by the Medicines and Healthcare Products Regulatory Agency (MHRA), Therapeutic Goods Administration (TGA), and US Food and Drug Authority (FDA).[11,17] However, the rest of the local manufacturers, particularly smaller companies, have yet to meet GMP standards.

Bangladesh still imports 70-80 percent of pharmaceutical raw materials, worth USD 179 million in 2011. Exports have been growing, reaching a value of USD 76 million in 2011, although the local subsidiary of the multinational Swiss company Novartis accounts for half of exports from Bangladesh (figure 4). Bangladesh exports a wide range of products to 87 countries including high-tech specialized products such as hydrofluoroalkanes (HFAs), inhalers, suppositories, hormones, steroids, oncology, immunosuppressant products, nasal sprays, injectables, and intravenous infusions.

[16] Ministry of Health and Family Welfare. National Drug Policy. 2005
[17] International Trade Centre. *Bangladesh Supply and Demand Survey on Pharmaceuticals and Natural Products*. 2007; http://legacy.intracen.org/docman/oeve11926.pdf



Source: United Nations Comtrade Database, Department of Economic and Social Affairs/United National Statistics Division, BMI; f, forecast)

Figure 4. Pharmaceutical trade growth

The medical device market in Bangladesh is relatively small, worth USD 174 million in 2011 because of underfunding of healthcare facilities and high out-of-pocket contributions. However, according to the BMI market forecast, the medical device market will grow about 10 percent per year over the next five years and account for 5 percent of total healthcare expenditures in Bangladesh.

However, the pharmaceutical sector in Bangladesh, as many other countries, faces challenges in ensuring product quality in the supply chain. A drug quality and information (DQI) program implemented by United States Pharmacopeia (USP) noted that 69 percent of paracetamol tablets and 80 percent of ampicillin capsules produced by minor companies were of substandard quality.[18] In 2009, a Dhaka court sent the managing director of a major local manufacturer to jail for manufacturing paracetamol with diethylene glycol which caused the deaths of children. Sources estimate the value of fake and contraband drugs entering the market to be USD100-150 million and most of them are produced in numerous drug factories situated along the Bangladeshi, Indian, Pakistani, Chinese, and Thai borders. These challenges, together with the presence of a huge pharmaceutical industry, highlight the need for a strong regulatory authority with the mandate to ensure quality, safety, and efficacy of health products in Bangladesh. Table 1 provides an overview of the pharmaceutical sector profile in Bangladesh.

[18]Primo-Carpenter, J. 2004. *A Review of Drug Quality in Asia with Focus on Anti-Infectives*. United States Pharmacopeia-Drug Quality and Information Program. Rockville, MD: Global Initiative for Quality Medicines and Their Appropriate Use

Table 1. Bangladesh Pharmaceutical Profile

Pharmaceuticals index	
Population (2011)[a]	148.7 million
GNI per capita (USD, 2011)[a]	770
Number of medicines registered (2012)[b]	23,242
Total pharmaceutical expenditure per capita (USD, 2006)[c]	5.7
Total expenditure on healthcare per capita (USD, 2010)[d]	23
Total pharmaceutical expenditure as % of total expenditure on healthcare per capita	31%
Health workforce per 10,000 population (2011)[e]	0.20
Public expenditure on pharmaceuticals per capita (USD, 2006)[c]	0.6
Financing mechanisms for pharmaceuticals[c]	11% public, 89% private
Medicines policy	
Existence of a national medicines policy	National Drug Policy, 2005. http://www.dgda.gov.bd/images/drug_policy_2005_eng.pdf Draft National Drug Policy, 2012.
Legal provision for medicines legislation	(1) Drug Act 1940 and its amendments (Drug Rules 1945, Drug Rules 1946) and (2) Drug (Control) Ordinance 1982 and its amendments [Drug (Control) (Amendment) Ordinance 1984 and Drugs (Control) (Amendment) Act 2006]
Pharmaceutical industry	
Pharmaceutical manufacturing plants	Total 838 manufacturers (265 allopathic, 267 unani, 202 ayurvedic, 25 herbal, and 79 homeopathic and biochemic manufacturers) http://www.dgda.gov.bd/index.php?menuName=Allopathic&mmn=Manufacturers
Pharmaceutical market size (2011)	BDT 111.10 billion (USD 1.5 billion)
Local manufacturing capacity	20-30% of API manufactured locally

[a]World Bank. http://data.worldbank.org/country/bangladesh
[b]DGDA informant
[c]WHO World Medicines Situation 2011;
http://www.who.int/medicines/areas/policy/world_medicines_situation/en/index.html
[d]Global Health Observatory Data Repository; http://apps.who.int/gho/data/
[e]WHO World Health Statistics 2012, pp.122-123

Policy and Legislative Framework for Medicines Regulation

Key legislation includes (1) The Drug Act 1940 and its amendments (The Drug Rules 1945 and The Drug Rules 1946) and (2) The Drug (Control) Ordinance 1982 and its amendments [Drug (Control) (Amendment) Ordinance 1984 and Drugs (Control) (Amendment) Act 2006]. The National Drug Policy 2005 sought to remove medicines considered harmful, useless, and unnecessary from the market to product the public and provide pharmaceuticals at an affordable price. Provided that the pharmaceutical industry is given high priority by the GOB and expands

its manufacturing capacity and exports rapidly, the National Drug Policy provides a clear vision to support the local industry to manufacture and export good quality medicines and strengthen the capacity of the DGDA. The draft Drug Policy 2012 has been developed and submitted to the cabinet for approval. Figure 5 presents the milestones of the medicines regulatory framework in Bangladesh.

1940 Drug Act (XXIII of 1940)

1945 Drug Rule 1945 (under the Drug Act 1940)

1946 Bengal Drugs Rules 1946

1966 Gazette of Pakistan: Office of the Chief Controller of Imports and Exports. Public Notice, 1966

1970 Dacca Gazette, Part I Government of East Pakistan, Health Department Notification, 1970

1976 Directorate of Drug Administration (DDA), the NRA for drugs, is created

1982 Drugs (Control) Ordinance1982, Drugs (Control) (Amendment) Ordinance 1982, and National Drug Policy 1982

1984 Drugs (Control) (Amendment) Ordinance 1984

1992 Institute of Public Health produces tetanus vaccines

2001 First edition of the national formulary published
WHO approves oral cholera vaccine tested at ICDDR-B

2002 ICDDR-B studies establish that zinc treatment of diarrhea reduces under-5 mortality by 50%

2003 Second edition of the national formulary published

2005 National Drug Policy 2005

2006 Drug (Control) Ordinance Amendment Act 2006
Third edition of the national formulary published

2009 South-East Asia Regional Office (SEARO)/ Department of Family and Community Health (FCH)/Immunization and Vaccine Development (IVD) mission to discuss institutional development plan to build DGDA capacity

2010 DDA upgraded to the DGDA
WHO mission to assess pharmaceuticals in health care delivery in Bangladesh

2012 Drug Policy 2012 drafted and submitted for approval

Figure 5. Regulatory milestones

Current DGDA Mandate and Structure

The Directorate of Drug Administration was established in 1976 under MOHFW. The organization was upgraded in January 2010 to the DGDA which is responsible for medicines regulation. Its mission is to ensure the quality, safety, efficacy, and usefulness of all drugs and medicines that are produced, imported, and marketed in the country and also those exported overseas, and to make essential drugs available and affordable for the common people of Bangladesh. There are 370 positions approved, 135 filled, and 235 vacant. These individuals are tasked with regulatory functions, such as licensing, registration, inspection, quality control, post-marketing surveillance and PV, import and export control, pricing, control of medicine promotion, and advertising.

Major functions of the DGDA include—

- Evaluation of proposals of new projects for all systems of medicines
- Issue and renewal of drug manufacturing licenses
- Issue and renewal of retail and wholesale drug licenses
- Registration and renewal of drug products
- Fixation of price and certification of price for drug products
- Inspection of pharmaceutical establishments
- Approval of block list for the import of raw and packaging materials
- Approval of indent for import of finished drugs
- Surveillance and PV activity
- Prosecution of cases in the drug courts and other courts
- Issue of export licenses, free sales certificates, GMP certificates, and certificates for pharmaceutical products

ASSESSMENT OF DGDA REGULATORY SYSTEMS AND CAPACITY

A comprehensive assessment of the current regulatory capacity of the DGDA was conducted from June 2012 to November 2012 by a team of local and international consultants. The method included document review, structured data collection, and interviews with key informants by using the Regulatory Systems Assessment Tool (RSAT). The RSAT is a baseline assessment tool for the determination of the current status of the national medicines regulatory systems and capacity of the NRA. The RSAT provides verified responses that are compared to the relevant legislation. Findings from the use of RSAT can facilitate the identification of weaknesses, gaps, strengths, and opportunities for improving national regulatory systems. RSAT was developed by adapting existing assessment tools including WHO's Guide for Data Collection to Assess Drug Regulatory Performance, Data Collection Tool for the Review of Drug Regulatory Systems, and Guidance for the Assessment of Drug Regulatory Systems; USP/DQI's Rapid Assessment of Medicines Quality Assurance and Medicines Quality Control; and SPS's Indicator-Based Pharmacovigilance Assessment Tool (IPAT). Assessment questions from these tools were adapted for the RSAT; additional questions were included to address issues of good governance and accountability in the regulatory system.

The assessment included all components of a regulatory system, such as medicine legislation, organizational structure and systems (including governance, guidelines, SOPs, HR, infrastructure, and skills); and the regulatory processes of product registration, licensing and inspection, quality surveillance, and therapeutic information and PV.

The objectives of the assessment were to—

1. Review the pharmaceutical products regulatory system from a systems perspective

2. Identify strengths, weaknesses, and opportunities for strengthening pharmaceutical products regulation

3. Review regulatory functions and processes to identify opportunities for improvement

4. Provide data for the conduct of options analysis for strengthening regulatory systems

RESULTS AND FINDINGS

Regulatory Framework and Management Structure of the DGDA

Analysis of Pharmaceutical Legislation

Although the regulations and policy address key areas of medicines regulations, this legislation, written more than 30 years ago, does not reflect the current state of the pharmaceutical industry in Bangladesh. Recent pharmaceutical developments with regard to standards and agreements, definitions, classification of medical devices, technical and regulatory requirements for medical devices, a mandate on clinical trials, regulatory instruments for biosimilars,[19] and requirements for bioequivalence and bioavailability are not covered as well as outdated schedules. In addition, some parts of the laws are not in convergence with pharmaceutical legislation from other countries. For these reasons, a comprehensive review is needed to compile, update, and further enhance the legal mandate. It is critical that Bangladesh modernize and consolidate its legislation to provide a comprehensive regulatory framework to guide the development of the pharmaceutical sector. However, in recognition of the need to update legislation, Bangladesh has drafted a new Drug Policy 2012 and submitted it to the Cabinet for approval.

The Drug Act 1940 provides requirements in regards to—

- Quality, prohibition of import of certain drugs, customs, offences, penalties, confiscation, and jurisdiction for import and export of drugs
- Quality standards, inspection, quality control, and enforcement for manufacturing, sale, and distribution of drugs

The amendments to the Drug Act of 1940 and the Drug Rules of 1945 and 1946 provide further regulations related to labeling and packing, biologics, and other special products.

The Drug (Control) Ordinance 1982 was developed to further provide requirements in regards to

- Formation of the DCC for approval or the withdrawal of medicines
- Pricing of drugs
- Prohibition of manufacture and sale of medicines without the supervision of pharmacists
- Restriction on import of certain pharmaceuticals
- Restriction on manufacture of certain drugs under license
- Control of advertisement and claims by prior approval of such materials

[19] New versions of existing biologicals whose patents have expired.

- Implementation WHO GMP standards in the manufacturing and quality control of drugs
- Formation of a National Drug Advisory Council for advising the Government on matters related to essential drugs
- Recognition of traditional and homeopathic medicines

The Drug (Control) Ordinance 1982 also defines a rigorous enforcement framework for manufacturing, importing, distributing, or selling unregistered products or counterfeit medicines with imprisonment up to ten years and fines.

- Dealing in substandard medicines is punished with imprisonment up to five years and fines
- Importing raw materials without prior approval is punished with imprisonment up to three years and fines
- Selling or importing medicines at prices higher than the maximum price fixed by the government is punished with imprisonment up to two years with fines
- Illegal advertisement and claims are punished with fines
- Establishing drug courts and enforcing penalties are also provided for in the ordinance

The Drug (Control) (Amendment) Ordinance 1984 defines the process to appeal an order or decision made by the regulatory authority.

The National Drug Policy 2005 recognizes the importance of strengthening the capacity and governance of the drug regulatory authority. It also highlights the need to train DGDA staff and define functions, powers, and responsibilities related to all aspects of regulatory affairs. The policy further defines criteria for registration, ensures sustainable growth of local manufacturing capacity, outlines procurement for private sector, enforces sound drug pricing systems, and ensures updating/maintaining an essential drug list.

DGDA Regulatory Framework

The DGDA is under MOHFW, which implies no autonomy to manage its own funds and HR. The DGDA cannot recruit its own staff, nor can they offer adequate or competitive salaries to attract and retain qualified experts. Countries with mature regulatory systems are often transitioning into autonomous or centralized parastatal agencies with their own management structures, [20] although there is no concrete evidence or study to show that a certain model is the most efficient system to manage regulatory functions.

[20] WHO. *Assessment of Medicines Regulatory Systems in Sub-Saharan Africa*. 2010. http://apps.who.int/medicinedocs/fr/m/abstract/Js17577en/

The responsibilities of the DGDA cover all medicines regulatory functions, such as registration, licensing, inspection, quality control, post-marketing surveillance and PV, pricing, import and export control, control of promotion and advertisement, and control of clinical trials. However, some regulatory functions are not fully operational, such as control of clinical trials or PV, because of significant understaffing and limited resources.

Products regulated by the DGDA include allopathic medicines; homeopathic, biochemic, unani, ayurvedic, and herbal products; vaccines and biologics; medical devices; and veterinary medicines (table 2). The scope of the DGDA does not include food or cosmetics, which are currently regulated by the Bangladesh Standards and Testing Institutions (BSTI). However, the list of products regulated by BSTI is very limited, which allows products in the "grey area" to freely enter the market.[21]

Table 2. Scope of Regulated Products

		Medicines	Vaccines and biologics	Medical devices	Food	Veterinary	Cosmetics	Complementary or herbal drugs
Stringent regulatory authority (SRA)	USA	√	√	√	√	√	√	√
	EU	√	√	√		√		
Neighbors	China	√	√	√	√		√	
	India	√	√	√			√	√
	Singapore	√	√	√		√	√	√
Benchmark	Saudi Arabia	√	√	√	√	√	√	√
	Thailand	√	√	√	√	√	√	√
	Malaysia	√	√				√	√
	Bangladesh	√	√	√		√		√

In 2010, the DGDA has proposed to rearrange its organizational structure into four departments (figure 6)—

- Manufacturing licensing, registration, and import and export control
- Inspection, retail and wholesale licensing, administration, and management information
- Veterinary
- Quality control, post-marketing surveillance, and central drug testing laboratory

[21] *Food Safety in Bangladesh*. Available at http://bdfoodsafety.org/inner.php?SubMenuId=7&DetailsId=37

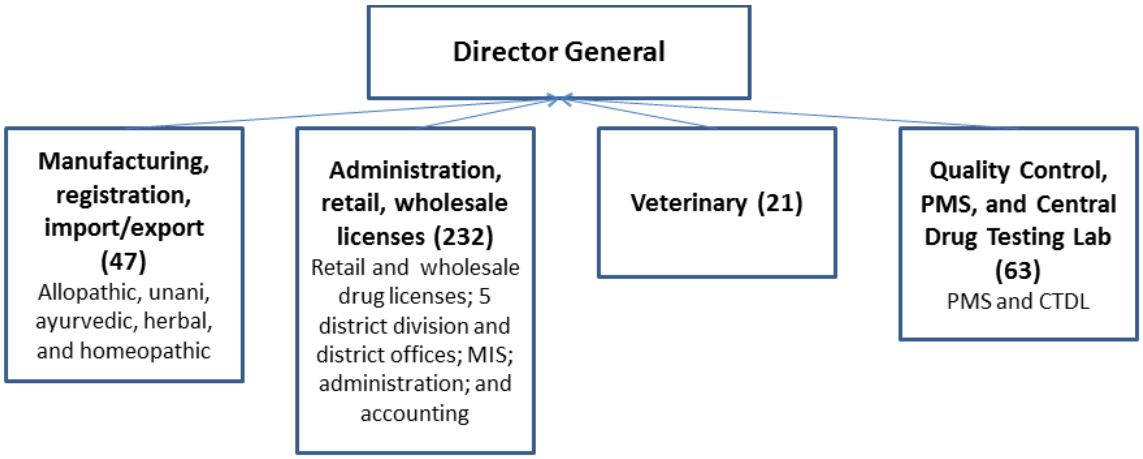


Figure 6. Proposed DGDA organogram

Staffing, Drug Fees, and Funding for Regulatory Activities

Significant deficiency in manpower has been identified as the most urgent issue to be addressed by many other previous assessments.[22,23] A large pharmaceutical market, a large number of registered products, an increasing number of health care professionals, and a large population size require a large and competent national medicines regulatory authority. A competent regulatory authority not only protects the public by ensuring quality, safety, and efficacy of medicines, but also supports the growth of the pharmaceutical industry. According to the DGDA, the estimated number of staff to adequately carry out regulatory functions without compromising the quality of work and performance is 700 to 1000. However, there are only 370 approved posts with more than 60 percent of the positions vacant. Key informants in the DGDA state that it could take one to two years to recruit staff, because the Ministry does not advertise the positions until a number of them has accumulated and they are put out all at once. Inefficiency in the government recruitment system, lack of autonomy due to the statutory arrangement of the DGDA, and unattractive salaries are the factors related to understaffing. Table 3 and figure 7 indicate that Bangladesh has significant understaffing, compared to other countries.

[22]Holloway, Kathleen A. 2010. *Bangladesh: Pharmaceuticals in Health Care Delivery*. Mission Report 24 October - 3 November 2010. Regional Advisor in Essential Drugs and Other Medicines, World Health Organization, Regional Office for South East Asia, New Delhi

[23] Teeranart Jivapaisarnpong, Stephane Guichard. 2009. *Report on the SEARO/FCH/IVD Mission to Discuss with Ministry of Health in Bangladesh Institutional Development Plan for NRA Capacity Building to Resume Local Production of Selected Vaccines and to Prepare Next NRA Assessment Follow-Up Visit*

Table 3. Comparison of Staffing

Country	Population (million)	GNI per capita(USD)[a]	Number of manufacturers	Pharmaceutical market size (USD, billion)	Number of registered products	Number of staff in national regulatory authority
Thailand	70	4,440	714[b]	4.3[c]	N/A	304[d]
Malaysia	29	8,770	250[e]	1.5[f]	6,542[g]	180[h]
Bangladesh	150	780	265	1.5	23,242	22[h]
Korea	48	20,870	830[i]	16.9[i]	~50,000[j]	360[k]

[a]World Bank. 2011. http://data.worldbank.org/indicator/NY.GNP.ATLS.CD/countries
[b]Thailand Investment Review. Aug 2011. http://ns.boi.go.th/english/download/publication_investment/148/TIR-2011-08-11.pdf
[c]Pacific Bridge Medical. Thailand Pharmaceutical Market Updates. 2012; http://www.pacificbridgemedical.com/publications/thailand-pharmaceutical-market-updates/
[d]Food and Drug Administration Thailand; http://www.fda.moph.go.th/eng/index.stm; the figure includes number of pharmacists, nutritionists, food technologists, and other professionals.
[e]From the Malaysian Organisation of Pharmaceutical Industries; http://www.mopi.org.my/
[f]Market size in 2009. Malaysian Organisation of Pharmaceutical Industries
[g]As of 2005
[h]Number of staff only in the central offices of the DGDA http://www.dgda.gov.bd/ and National Pharmaceutical Control Bureau, Malaysia
[i]Korea Food and Drug Administration. *24/7 More Safely, More Healthily*. Number of manufacturers and market size as of 2010.
[j]Interview with KFDA staff
[k]Number of technical staff in Bureau of Pharmaceuticals only. The total number of employees, as of August 2011, was 1,460; http://www.kfda.go.kr/index.jsp

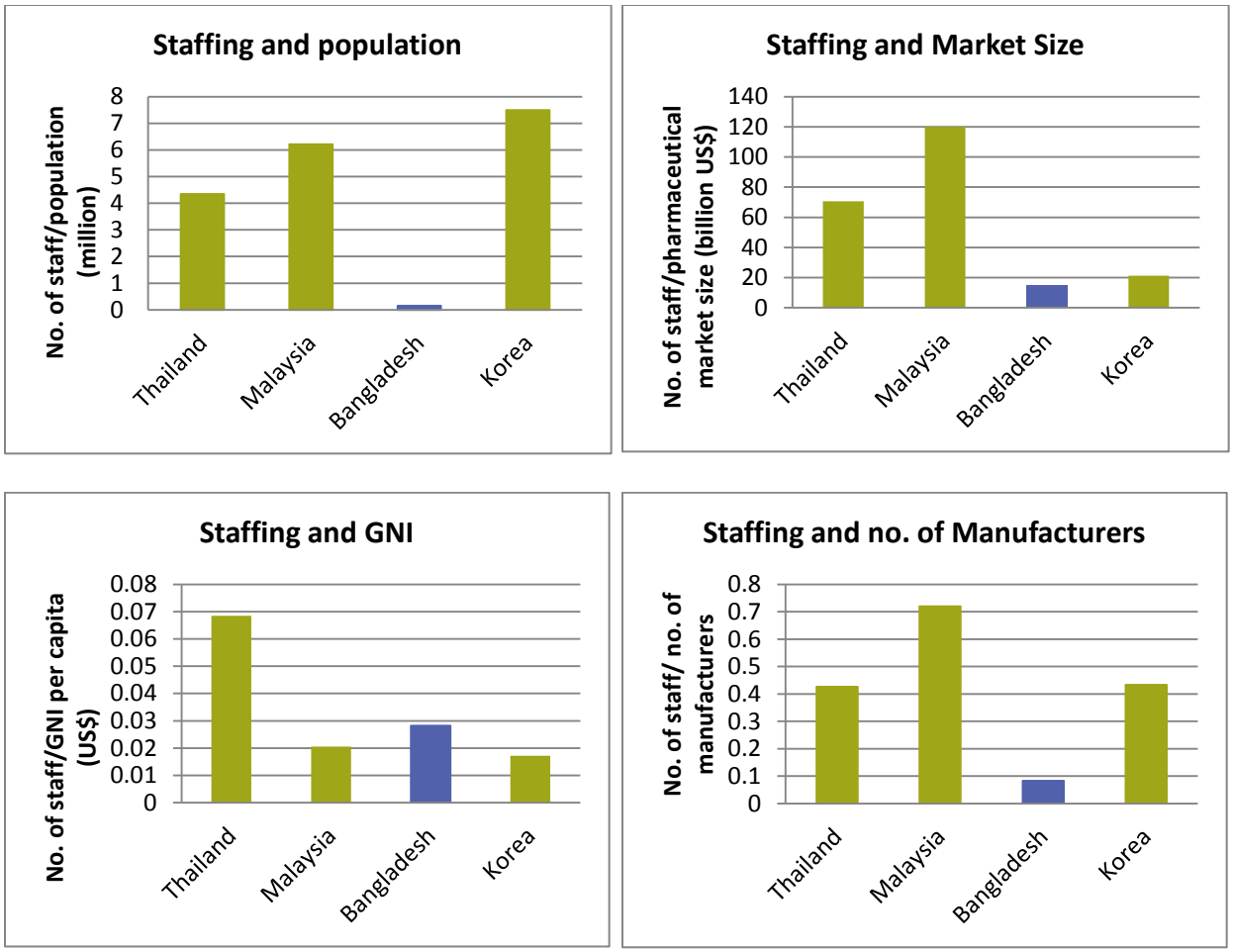


Figure 7. Analysis of staffing

The DGDA published new fees for regulatory services in October 2012 (the fees had remained the same since 1993). The fee is determined by the Ministry of Finance and payments are received by the central treasury. The fees were increased by 100-1600 percent, depending on the type of service. The fees collected until 2011 were less than 10 percent of the annual budget. However, table 4 indicates that the fee charged for regulatory services in Bangladesh is still significantly lower than other countries, such as China, India, Singapore, and Saudi Arabia. Comparison of the fee index (registration fee for new drug approval divided by GNI/capita) indicates that other countries' fee index is within 1 to 1.6, whereas the fee index in Bangladesh is only 0.2 (table 5). This may imply that the DGDA is currently subsidizing the industry. The DGDA may consider different scales of fees charged to importers, leading manufacturers, and smaller manufacturers to strike a balance between raising the bar in regards to the price of pharmaceuticals for the public and increasing revenue. Further costing analysis can help decide the fees that are required for the level of services, allocated staff time for regulatory processes, and other operational costs.

Table 4. Service Fees Collected

	2011-12	2010-11	2009-10	2008-09	2007-08
Fees collected (BDT)	1,277,813	1,281,275	1,225,213	893,775	911,613

Table 5. Registration Fees

Country category	Country	GNI/ capita (USD)	Total health expenditure/ capita (USD)	Initial registration fee (USD)		Fee index	
		(A)		New drug (B)	Generic (C)	B/A	B/C
Neighbors	China	4,940	220.88	7,260	4,696	1.469636	1.54
	India	1,410	54.25	1,500	1,500	1.06383	1
	Singapore	42,930	237.84	69,711	8,627	1.623829	8
Benchmark	Saudi Arabia	17,820	1733.02	25,331	N/A	1.421493	N/A
	Thailand	4,420	237.84	N/A	N/A	N/A	N/A
	Malaysia	8,420	237.84	N/A	N/A	N/A	N/A
	Bangladesh	770	23.29	184	184	0.238961	1

The sources of funding for the DGDA are the GOB, reimbursable project aid (RPA), and direct project aid (DPA). Project aid comes from donors and development partners such as WHO, World Bank Pooled Fund, and USAID. Total budget for the DGDA has been increased by an average of 20 percent every year, except for 2010/2011 (figure 8). However, key informants in the DGDA reiterated that the allocation of funding from the Government is very limited and thus not sufficient to cover its activities. An option for the self-sustainable DGDA is to use the drug fees collected as direct revenue for the DGDA and charge adequate service fees to cover the cost. A comprehensive costing analysis can be conducted to further inform the DGDA on the options for advocating and securing adequate funding.

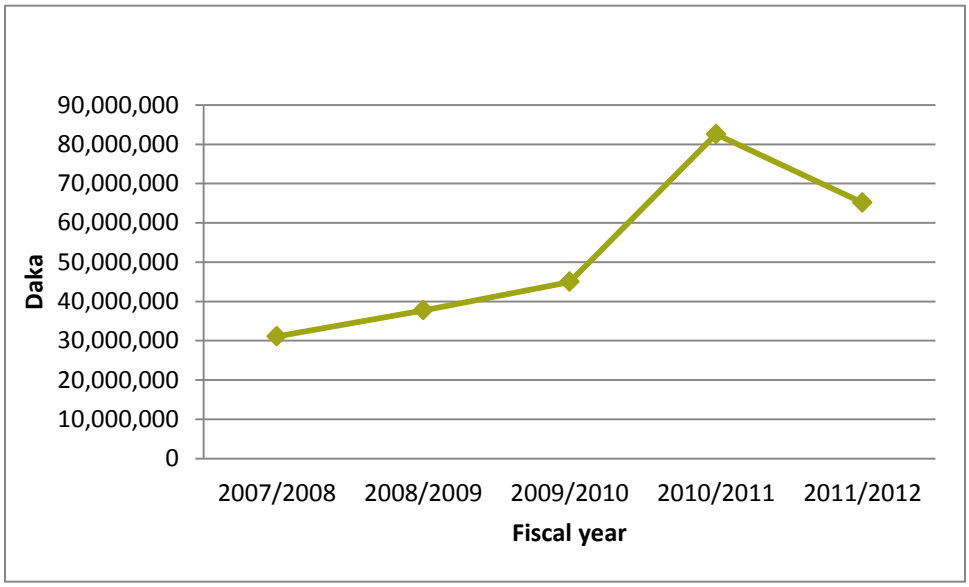


Figure 8. Total budget for the DGDA for the last 5 years

Relationships with Other Regulatory Bodies

Bangladesh is a member of the South Asian Association for Regional Cooperation (SAARC) with seven other countries—Afghanistan, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka.[24] The areas of cooperation among SAARC members include agriculture, biotechnology, economic and trade, science and technology, and social development, among others. The South Asian Regional Standards Organization (SARSO) has been established among the SAARC members to develop harmonized standards to facilitate intra-regional trade and to have access in the global market. Its Sectoral Technical Committee initiated the work and close collaboration on harmonization in areas, such as food and agricultural products, textiles, and quality management.[25] Pharmaceutical-related issues have never been addressed and could be a potential area to bring the members together to set standards on medicines regulatory harmonization.

Currently, the DGDA has no formal relationship with any other medicines regulatory authorities in the region or with SRAs, other than collaborating with the Thailand National Laboratory to send product samples for quality test. Establishing a formal collaboration with other agencies through a memorandum of understanding (MoU) or developmental agreements or by joining regulatory harmonization initiatives, such as the Association of Southeast Asian Nations' (ASEAN) pharmaceutical harmonization and the Asia-Pacific Economic Cooperation's (APEC) regulatory harmonization, can help with building capacity, knowledge exchange, and information sharing.

Governance - Transparency and Accountability

Good governance systems and ethical practices in the pharmaceutical sector have become important priorities globally for improving access to essential medicines. The pharmaceutical sector, globally, has been identified as highly vulnerable to corruption, government inefficiencies, and unethical practices.[26]

Table 6 highlights key indicators in the areas of transparency and accountability. The indicators to measure the DGDA's operational plan are available (table 8). However, the DGDA can further develop the list of indicators to measure the performance of the DGDA and enable it to communicate its achievements to the public and stakeholders. Examples of indicators that are used by other competent regulatory authorities are provided in annex A. The DGDA can also consider its QMS to be ISO certified.

[24]South Asian Association for Regional Cooperation. Available at http://www.saarc-sec.org/
[25]Agreement on the Establishment of South Asian Regional Standards Organisation (SARSO). 2011. Available at http://saarc-sec.org/Agreements/69/
[26]WHO. 2009. *A Framework for Good Governance in the Public Pharmaceutical Sector* http://apps.who.int/medicinedocs/fr/m/abstract/Js17799en/

Table 6. Selected Indicators for Governance and Transparency

Indicators	Yes/no	Notes
Job description for all positions of the NRA	Yes	
Committees with terms of reference	Yes	
Meeting minutes of committees publicly available	Yes	DCC minutes posted on the website
Conflict of interest	Yes	
Declaration of assets	No	
Confidential financial disclosure	No	
Policies, procedures, and guidelines guiding meetings and contacts between the NRA and the regulated industries	Yes	
Dissemination of NRA deliberations/freedom of information/ website	Yes	www.dgda.gov.bd
Ombudsman	No	
Existence of transparency measures and indicators	Yes	Government service rules, citizen charter
Involvement of civil societies in regulatory decisions	Yes	
Inputs solicited before regulations are formalized	Yes	Government executive order
Comprehensive list of guidelines, SOPs, and protocols used by the NRA	No	Partially
Audit or evaluation conducted in the past 5 years to assess the performance of regulatory system	Yes	Only financial audit was conducted in the last year/WHO assessment

Over-representation of the pharmaceutical industry in the committees, such as the Bangladesh Association of Pharmaceutical Industry (BAPI) and Bangladesh Importers Association, is a conflict of interest. The committees' meetings are not taking place as scheduled nor regularly, and some members are often absent. The members of all committees are not remunerated and do not get an honorarium, which does not provide an incentive to come to the meetings. A consumer representative is a member of only one committee. Civil societies who are members of committees are the Bangladesh Pharmaceutical Society (BPS), the Bangladesh Medical Association (BMA), the Bangladesh Chemist and Druggist Association, and the Bangladesh Consumer Association. Consumer groups in particular should be a part of committees, such as DCC, Manufacturing Project Evaluation Committee, Herbal Drug Advisory Committee, and the Adverse Drug Reaction (ADR) Advisory Committee. Table 7 lists all committees of the DGDA.

Table 7. DGDA Committees

Name of committee	Function/role	Consumer group represented?	Frequency of meetings (if known)
Drug Advisory Committee	Advise DGDA on policy and management	No	Ad hoc
Drug Appellate Authority	Appeal	No	Ad hoc
DCC	To approve registration	No	Once or twice a year
Drug Technical Sub-Committee	Technical in-house to provide recommendations to DCC	No	Once or twice a year
Drug Pricing Committee	Price fixation	Yes	Every month
Drug Pricing Technical Sub-Committee	Price fixation	No	Every month
Manufacturing Project Evaluation Committee	Review of proposal for establishing new manufacturing sites	No	Every 3-4 months
Standing Committee for Import	Import	No	Every 5-6 months
Herbal Drug Advisory Committee	Technical	No	N/A
ADR Advisory Committee	Drug safety	No	No meeting in the last 5 years

Some measures to ensure good governance, particularly transparency and accountability, in regulatory functions and DGDA structures are implemented, including involvement of various civil societies in decision-making process, sharing information (such as DCC decisions) on the website, and defined terms of reference for all committees (except for the Drug Advisory Committee). However, key elements are missing, such as specifically preventing conflicts of interest, in which some committee members sit on various committees. Also needed are financial disclosure; a process for two-way communications (no formal meetings or contacts between the DGDA and industry); an ombudsman; and an inventory of all SOPs and guidelines for document control. Implementing these measures can further improve transparency, efficiency, and communication with other stakeholders.

Having a robust monitoring and evaluation system in the NRA is critical to ensure that the objectives are achieved. An external audit done on a regular basis can also provide an independent and critical opinion on the performance of the regulatory system. The DGDA does not have a system for self-assessment of its performance and has not been audited or assessed to evaluate its systems performance for the last five years. Implementing a sound monitoring and evaluation system in the DGDA is one of the most urgent needs.

Quality Management Systems

A QMS helps to ensure that a medicines regulatory authority fulfills its mandate and conducts activities according to defined uniform standards and that each step of the regulatory processes is identified and documented.

According to ISO 9001:2008, the adoption of a QMS should be a strategic decision made by an organization. The design and implementation of an organization's QMS is influenced by its organizational environment, changes in that environment, and the risks associated with that environment. The QMS also depends on the varying needs, particular objectives, products, processes, and the organization's size and structure.

Some guidance documents on QMS (listed below) are published by the Global Harmonization Task Force for medical devices and as part of ISO standards.

- ISO 9000:2005 Quality Management Systems—Fundamentals and Vocabulary
- ISO 9001:2008 Quality Management Systems—Requirements
- ISO 9004:2009 Managing for the Sustained Success of an Organization—A Quality Management Approach
- ISO 19011:2011 Guidelines for Auditing Management Systems
- SG3-N17:2008 Quality Management System—Medical Devices—Guidance on the Control of Products and Services Obtained from Suppliers
- SG3-N15R8:2005 Implementation of Risk Management Principles and Activities Within a Quality Management System
- SG3-N99-10:2004 Quality Management Systems—Process Validation Guidance

The DGDA developed *Quality Manual* (document number QA-002/2010[27]) which defines the vision, mission, and objectives of the authority as well as the responsibilities, procedures, performance monitoring, standards, and resources required to deliver quality regulatory services. The manual also outlines other principles such as comprehensive management and being customer focused. However, greater efforts to implement the *Quality Manual* should be made. For example, the manual requires an internal audit, evaluation of effectiveness, or management review to be conducted using performance indicators (table 8) to ensure the mechanism for reporting results and maintaining records, but no such analysis or assessment was implemented in the last year. The DGDA should consider reviewing and strengthening its QMS and plan to have an organization-wide QMS that is ISO certified.

The SOPs, manuals, and guidelines that are currently used are compiled in table 9. The respondents in the DGDA mentioned that they are currently developing comprehensive SOPs and guidelines for vaccines and plan to adapt them for pharmaceuticals. First, the DGDA needs to inventory all guidance documents in use and then address the areas that require guidance documents, such as guidance for GLP and GCP, guideline on manufacturing biosimilars, etc.

[27]DGDA. *Quality Manual*. 2011. Available at http://www.dgda.gov.bd/download/Quality%20Manual.pdf

Table 8. List of DGDA Performance Indicators

Indicators	Unit of measurement	Baseline (2010)	Projected target	
			Mid-2014	Mid-2016
Drug vaccine testing lab modernized and functional	Functional lab	N/A	1	2
National drug policy revised and approved	Approved policy	N/A	done	done
ADR cell established	Functional cell	N/A	done	done
Number of drugs sampled tested	Number of tests	3500/yr	10000	20000
Number of drug manufacturing units inspected	Number of inspections	700/yr	2200	4000
Number of drug shops inspected		26000/yr	70000	100000
Number of batches of staff that received training on GMP, QMS, accreditation, quality control, and vaccines	Number of batches	N/A	6	10

Source: Ministry of Health and Family Welfare. Health population and nutrition sector strategic plan. Operational Plan: Strengthening of Drug Administration and Management 2011-2016. 2010

Table 9. List of SOPs and Guidelines in DGDA

Titles of documents
Code of Pharmaceutical Marketing Practices
Citizen Charter
Service Fees
Guidance for Industry • Submission of Clinical Trial Application for Evaluating Safety and Efficacy • Requirements for Permission of New Drugs Approval • Post-Approval Changes in Biological Products: Quality, Safety, and Efficacy Documents • Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
Guidance on Clinical Trial Inspection, Jan 2011
List of Application System
Quality Manual (Document #:QA-002/2010)
Registration Procedure of Allopathic Medicines Quality Manual for Inspectorate
Required Documents for Different Activities
Quality Manual for Inspectorate
Inspection Checklist (Manufacturing Sites, Distribution Points, and Pharmacies)
Good Distribution Practice
cGMP Guideline
Draft SOPs for vaccines (AEFI, registration, etc.)

Regulatory Compliance and Enforcement

Enforcement in the pharmaceutical sector is defined as any action taken by NRA to protect the public from medicines-related harm. To ensure compliance with regulations and standards for manufacturing, sales, advertisement, and quality assurance, NRA must have the legal mandate to control products in the market within its jurisdiction. Compliance can be confirmed by conducting GxP inspections of manufacturers, points of distribution, and retail pharmacies. If violation is detected, administrative or judicial enforcement actions can be taken. Examples of administrative measures, which usually do not require judiciary action, include inspections, voluntary correction programs, recalls and license suspension, or revocation. If compliance does

not improve, even after taking administrative measures, the NRA may use judicial tools, such as seizure, injunction, penalties, or prosecution.[28]

The current pharmaceutical laws of Bangladesh provide an enforcement basis for non-compliance, for example—

- Manufacture and sale of adulterated, spurious, and restricted drugs
- Manufacture and sale of substandard drugs
- Unauthorized import of drugs and raw materials
- Sale of medicines at prices higher than the maximum retail price (MRP) by the Licensing Authority
- Theft of drugs from government hospitals and stores
- Illegal advertisement of drugs and claims about their qualities and uses

The DGDA implements both administrative and legal sanctions to address violations (table 10). The actions taken are mostly related to violations of advertisement and promotions and product quality. Administrative measures, such as a warning letter or posting the list of violators on the website can be implemented to educate industry and the public. If non-compliance arises even after several administrative measures have been imposed, legal sanctions should be considered.

Table 10. Number of Enforcement Measures Implemented

Enforcement measures	2011~2012
Written warnings	4
Fines	9
Imprisonment	1
Licenses suspended	15
Licenses revoked	N/A
Production suspensions	56

The DGDA also has an appeal system with its Drug Appellate Authority, which ensures the rule of law and fairness in the regulatory decision-making process, according to the Drug (Control) (Amendment) Ordinance 1984. The presence of appeals and complaints procedures ensures that there is transparency and accountability in the system.

[28] Regulatory Affairs Professionals Society. *Fundamentals of International Regulatory Affairs*. 2010. ISBN: 978-0-9787006-8-3

Regulatory Functions

Product Evaluation and Market Authorization

The Drug (Control) Ordinance 1982 and the National Drug Policy 2005 provide a legal basis and outline the criteria for registration—safety, quality, efficacy, and usefulness. The registration process guideline for allopathic medicines[29] briefly describes the required content of submissions, instructions, timeline, and evaluation procedure. The application forms[30,31] for registering new molecules and products that have already been introduced in Bangladesh are used, but a specific format such as CTD for submissions is not required. However, the DGDA recently developed a guidance document for industry[32] which requires an application for new drug approval for biologics only in CTD format. Products required to be registered include medicines, vaccines, biologics, medical devices, combination products, complementary and alternative medicines (homeopathic and biochemic, unani, ayurvedic, herbal), and veterinary products that are locally manufactured, imported, or donated.

When an application for registration of a new molecule is submitted, the dossier is screened and a summary report is prepared by the DGDA. A technical sub-committee then reviews the summary report and makes recommendations to the DCC, whose members then make a decision on registration (figure 9). The DCC meets two or three times every year on an ad-hoc basis. The new molecules registered in reference countries—UK, USA, Australia, France, Germany, Switzerland, or Japan—are considered for registration and certificates of pharmaceutical products issued by these countries are recognized. This process is followed for imported human products only.

Registration of a new product or molecule that has already been introduced in Bangladesh is reviewed by an internal committee that meets every month and approves the application without further approval from the DCC, given that the product meets quality standards, has been inspected and tested for product quality, and has undergone document review. The registration is valid for five years. According to DGDA and the citizen charter, the registration process can take an average of six months to a year for new molecules and three months for products already introduced in Bangladesh (table 11). The DGDA publishes the list of imported drugs (total 1,377) on their website and maintains a searchable database for locally manufactured products (total 21,865 as of November 7, 2012); 95-97 percent of registered products are generics.

[29]DGDA. Registration procedure of allopathic medicine (in Bengali). Available at http://www.dgda.gov.bd/download/Registration%20Procedure%20of%20Allopathic%20Medicines.pdf
[30]DGDA. Application form of the registration of drugs which are not introduced in Bangladesh (Form DA-2/88)
[31]DGDA. Application form of the registration of drugs which are already introduced in Bangladesh (Form DA-1/88)
[32]DGDA. Guidance for Industry: Requirements for Permission of New Drug Approval (MA-08/2010). 2010

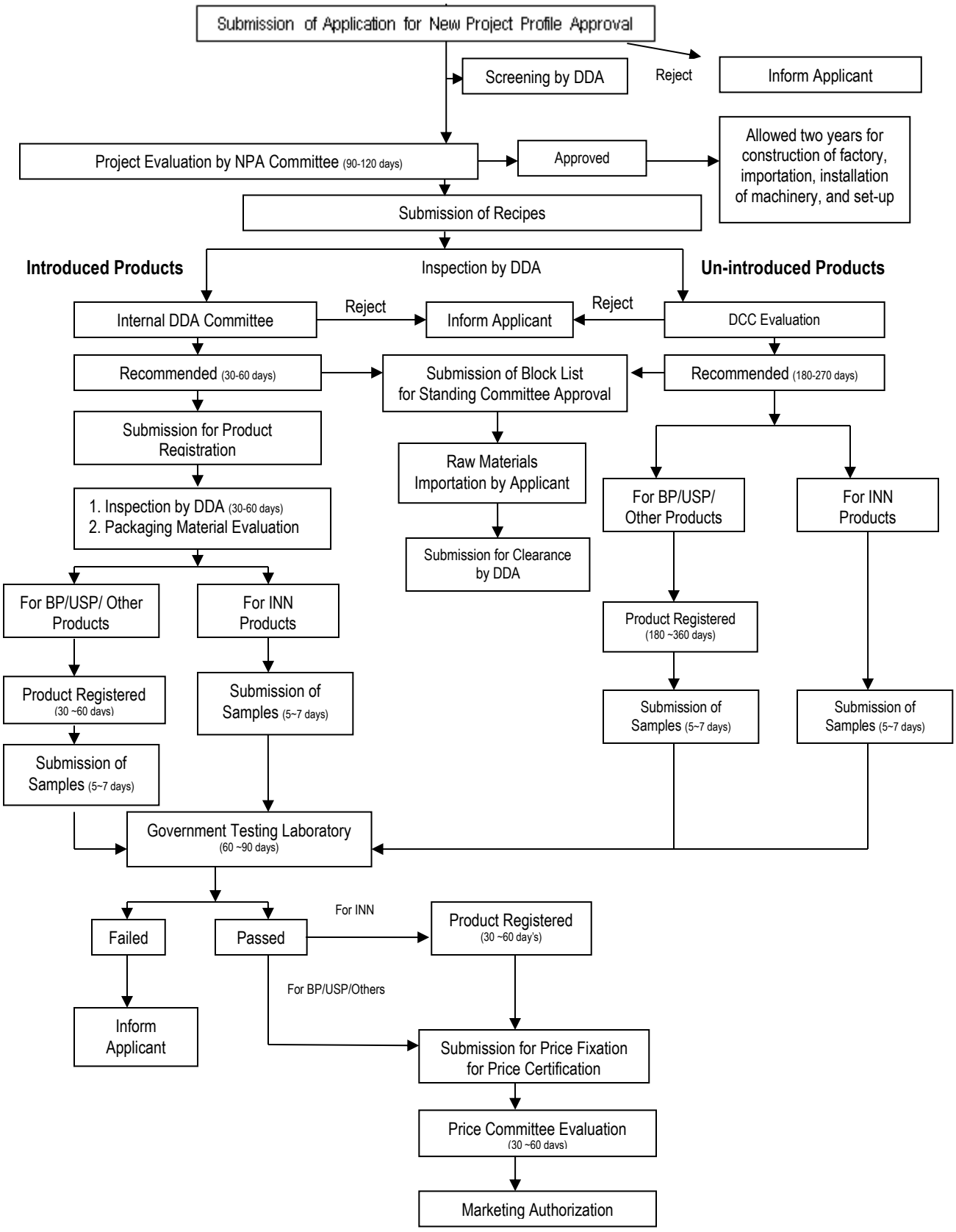


Figure 9. Flowchart for allopathic drug registration

Table 11. Timeline for Dossier Review

Category of country	Country	Expected time for screening application	Expected review time for new drug application	Formal communication opportunities between applicants and authorities during drug review process	Priority/ accelerated review availability (no. of days)
SRA	USA	60	300	Yes	Yes
	EU	10*	210*	Yes	Yes
Neighbors	China	30*	250*	Yes	Yes (210)
	India	N/A	270	N/A	Yes (90)
	Singapore	25*	270*	Yes	Yes (180)
Benchmark	Saudi Arabia	10*	245*	Yes	No
	Thailand	N/A	280 (generic 130)[33]	N/A	N/A
	Malaysia	N/A	N/A	N/A	N/A
	Bangladesh	60	180-360	No formal communication process	No

Note: *working days

The number of registered products is 23,242 for 1,190 molecules, given that Bangladesh has a large amount of generic local manufacturing. It is argued that the NRA should regulate such a large market and reduce the number of registered products.[22] However, such interventions to control registration by introducing restrictions for generics will pose a significant threat to smaller manufacturers who produce quality products at lower prices and will prevent competition. Instead, ensuring quality standards for manufacturers and adequate inspections will self-regulate the market.

Key Findings and Implications

The estimated time taken to register new products is estimated at eight months to a year, whereas the citizen charter provides an expected timeline of six months for registration. The key bottlenecks for timely registration are the irregular schedule of DCC meetings, lack of manpower, a manual process for registration, and delay in lab test analysis, among others.

- Currently, there are only five staffs in DGDA screening the dossier and preparing the summary report for more than 50 application dossiers submitted per month. Severe understaffing in DGDA has a significant impact on the local pharmaceutical industry by delaying the introduction of quality-assured products into the market.

- Irregular meetings of the DCC also have a significant impact on delaying registration. For example, the last DCC meeting in May 2012 was held nine months after the previous meeting; at the May meeting, 359 applications were reviewed. In addition, all committee members are currently providing their services for free. Lack of remuneration causes lack

[33]Siriporn Chawanon. *Drug Control and Registration*. 2010. Presentation available at http://pdpaccess.org/downloads/meetings/2010-geneva/presentations/14.%20Chawanon%20-%20Drug%20Registration%20Thailand.pdf

of motivation as members are fully occupied with the many other professional responsibilities they have.

- All processes and documents are handled manually in the current system. Introducing an online, computerized information management system can significantly improve the efficiency of registration and reduce the backlog by tracking the process, enhancing communications, and improving document management.

- General guidelines exist, but SOPs for the registration process are not in place. For example, there is no guidance document on biosimilars, when a leading local manufacturer, Incepta, is producing biosimilars. There are no GCP and GLP guidelines as well. Currently, the DGDA is developing SOPs for vaccines for registration, marketing authorization, inspection, regulatory action for inspection, inspection and report writing, reporting adverse events following immunization (AEFI), an SOP for making SOPs, etc.

- Registration processes to be strengthened include—

    - Providing an application format that complies with international standards (CTD)

    - Revising registration fees to improve services and fund regulatory activities

    - Revising the registration certificate to include conditions for registration and indications for use

    - Making the registration process sequential (i.e., testing samples only after dossier review) instead of concurrent

Licensing

Medicines regulatory authorities should ensure that all premises, personnel, and practices used for the manufacture, storage, distribution, and dispensing of pharmaceutical products complies with current guidelines on GMP, Good Storage Practice, Good Distribution Practice, and Good Pharmacy Practice.[20] The DGDA is responsible for licensing manufacturers, retail pharmacies, wholesalers, and importing and exporting companies (table 12). The procedure to review and issue a license for manufacturer is summarized in box 1.

Box 1. Licensing Process for Manufacturers

Step 1. Submission of a new project profile for evaluation by the New Project Evaluation Committee after the site is inspected by the DGDA and the committee.

Step 2. Submission of an application for a manufacturing license. The application lists the composition of items to be initially manufactured. Recipes are evaluated by the DCC after inspection of the manufacturing plant. Items similar to ones that are already approved will be evaluated by an internal DGDA committee. For INN products, small quantities of items on the Block List need to be approved and samples submitted for testing and analysis.

Step 3. Submission of the application for packaging and promotional materials. The DGDA officers examine the submitted materials and papers and may inspect the manufacturing unit again.

Step 4. The license may be issued at this stage and the product may be registered with the condition that the manufacturer must use the price approved by the DGDA.

Step 5. Submission of Block List (details of raw and packaging materials to be imported) for prior approval by the Standing Committee for Import.

Step 6. Submission of samples of the first commercial batch for testing and analysis by government laboratories and submission of proposed price for the items. Only the price of 117 primary healthcare listed drugs needs to be fixed by the Price Committee. All other medicines use the indicative price, which needs to be certified by the DGDA.

Table 12. Licenses of Pharmaceutical Establishments

Type of pharmaceutical establishment	License issued?	Licenses valid for (years)	List available?	Number
Manufacturers of pharmaceutical products	Yes	2	Yes	265
Manufacturers of traditional medicines	Yes		Yes	494
Retail pharmacies	Yes		No	97,000
Pharmaceutical product exporting companies	Yes	5	Yes	N/A
Importing companies	Yes		Yes	64
Wholesalers	Yes		No	N/A

Key Findings and Implications

The list of some pharmaceutical establishments is available online, including manufacturers of traditional medicines. However, the register for retail pharmacies or wholesalers is not publicly available, which may give unlicensed dealers an opportunity to operate.

Inspections

Inspections, a part of the overall drug quality assurance system, are to enforce GMP compliance, approve authorization for the manufacture, and monitor the quality of pharmaceutical products in distribution channels and retail pharmacies to protect the public from substandard medicines and counterfeits.[28]

GMP inspections of local manufacturing plants are mandatory for issuing manufacturing licenses and are conducted by a team of inspectors from the DGDA and the Manufacturing Project Evaluation Committee. GMP inspection is required for renewal of the manufacturing license every two years. The Drug Act 1940, the Drug Rules 1945 and 1946, and the Drug (Control) Ordinance 1982 provide the legal basis for enforcement of compliance.

According to the Drug Rules 1946, inspectors are authorized to inspect not less than twice a year all establishments licensed for the sale of drugs and all premises licensed for the manufacture of drugs. Inspectors collect samples for testing, investigate complaints, send inspection reports to the authority, and maintain records of inspections and actions taken. There are inspection checklists for manufacturers, distribution points, and pharmacies. However, there is no comprehensive guideline, SOP, or QMS to ensure that inspections are planned, conducted, documented, and followed up in a consistent way, based on risk assessment.

Table 13 demonstrates a serious shortage of inspectors in DGDA. According to law and given the number of licensed pharmaceutical premises, the number of inspections carried out per year is more than 190,000. This means the DGDA needs 386 to 400 inspectors, but currently there are no more than 40 inspectors. Adequate levels of logistics resources, such as cars, are also required to support the activity, although there are only three cars in DGDA.

Table 8. Number of Expected Inspections

	Number of establishments	Frequency of inspection as mandated by Drug Rule 1946	Expected number of inspections/year
Manufacturer	838	No less than twice per year	1676
Pharmacy retailer	98,000	No less than twice per year	196,000
		Total expected inspection per year	197,676
		Number of inspectors required	386-400

Key Findings and Implications

- Insufficient manpower and logistic resources. Significant shortage of inspectors and resources, especially means of transport and communication, was a major constraint. For example, less than 10 percent of the manpower required for inspections exists. Due to inadequate staffing, inspections are currently conducted for half a day or one day only, which may compromise quality. Also, inspections at distribution channels and retailers are often very limited; 95 percent of retailer owners in rural areas are unqualified and not trained on good dispensing practices.[22] Given that there are more than 70,000 unlicensed shops in the country,[34] the need for adequate funding to conduct inspections has increased.

- No quality management and planning system for inspections. Guidelines or SOPs that cover inspections, follow-up inspections and complaints, registers to maintain records of inspections or actions taken, and risk-based inspections are inadequate or inappropriate. Particularly, using a risk-based approach to define the type of inspection can improve the

[34]Estimated figure based on interview with local expert.

quality and efficiency of inspections in resource-limited settings, such as Bangladesh. (A risk-based approach takes into account the types of products being manufactured and the size of the manufacturing facility.) Given that the top 50 manufacturers are maintaining good quality management and are ISO certified, priority for inspections should be smaller manufacturers who are not certified and do not have the capacity to ensure a QMS.

- No participation in international GMP harmonization initiatives such as Pharmaceutical Inspection Cooperation Scheme (PIC/S). The benefits of joining PIC/S include training opportunities, sharing information on GMP inspection reports among members, participating in harmonization of international GMP guides and guidelines, and receiving information from PIC/S rapid alert and recall system.

Import and Export Control

The National Drug Policy and the Drugs (Control) Ordinance 1982 and its amendments gave protection to local manufacturers by restricting the import of pharmaceutical products that are locally manufactured in Bangladesh. It helped to keep out less-regulated manufacturers from other countries. An import license is required before the products can be imported in Bangladesh, once the manufacturer and product are registered successfully. However, Bangladesh is still relying on pharmaceutical imports, particularly for raw materials and APIs; 70-80 percent of APIs are imported, as there are only a few local companies that have the capacity to manufacture them.[11] Over the last eight years, import of pharmaceutical products grew at 12.9 percent annually while import of organic chemicals grew at 15.8 percent.[14] In 2011, pharmaceutical products worth USD 179 million were imported to Bangladesh.[11] Various interventions from the government, such as planning to establish an API park for manufacturing pharmaceutical raw materials helps to lower reliance on imports.[14,17]

National Drug Policy 2005 was formulated to respond to the rapid expansion and development of the local pharmaceutical industry. Rules and regulations for the export of pharmaceuticals can be found in the country's Export and Import Policy. Bangladesh's export earnings in 2011 reached USD 46.0 million. Pharmaceutical export was growing by 25.5 percent annually over the last seven years, and it is expected to achieve more than 15 percent growth over the next five years, given that most of the top manufacturers have been establishing GMP compliance plants and have received GMP clearance from a number of countries, including Turkey, Yemen, Kenya, Congo, Uganda, Sudan, and Ethiopia.[14] Currently, many local companies have achieved a certain standard level of quality that allows them to export their products to 87 countries, including at least 65 local manufacturers with ISO 9000 and 9001 certificates.[17]

Key Findings and Implications

- The DGDA has a critical role to support the growth of the pharmaceuticals industry by ensuring the quality standards of locally manufactured and imported products.

- The assessment did not identify any formal cooperation with relevant agencies, including the Ministry of Commerce, National Board of Revenue, and the EPB, and such collaboration was also not described elsewhere. Strengthening such collaboration can help the DGDA and other

government agencies to further support the industry recognized by other countries and boost export growth.

Quality Control

Counterfeit medicines pose a significant harm to the public. In 2010, it was estimated that USD 150 million worth of counterfeits were circulating in Bangladesh. Particularly, quality assurance is more challenging in the private sector, as most medicines procured by the public sector are good quality products manufactured by Essential Drugs Company Limited (EDCL).

The DGDA has two quality control drug testing laboratories (DTLs), one in Dhaka and another in Chittagong. Of the 2,687 samples tested in 2011, 4 percent failed (figure 10). Information on any substandard or counterfeit medicines should be publicly available, according to the National Drug Policy. However, such information is not yet published or posted on the website.

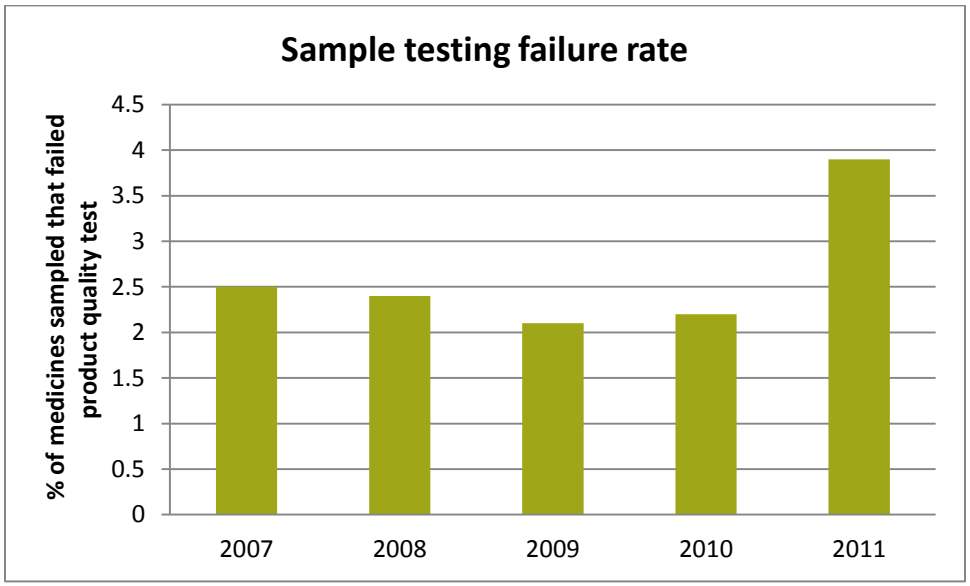


Figure 10. Results of QC laboratory test

In 2009, WHO conducted a regulatory capacity assessment for vaccines and recommended the separation of the National Control Laboratory (NCL) from the Institute of Public Health, which produces vaccines and other products, because of a potential conflict of interest. The NCL is now under the DGDA, focuses on testing vaccines and biologic medicines, and is supported by WHO to strengthen its capacity with staffing, equipment, and expertise. Its aim is to be a WHO prequalified laboratory and ensure QMSs for testing laboratories. Other recommendations by WHO were to develop a training plan, create an institutional development plan for vaccines and drugs, and recruit technical staff for all vacant positions.[23] Upgrading the DTLs is currently ongoing in close collaboration with WHO/SEARO.

Key Findings and Implications

- Strengthen the capacity of DTLs and the NCL to be WHO prequalified facilities by providing more resources for manpower, equipment, and training staff on QMS for the testing laboratories

- Encourage small local manufacturers to get their quality control laboratories also prequalified by the WHO program, which will ensure the quality of products in the local market and help them export good quality products

Clinical Trials

With its large and treatment-naïve population, Bangladesh can be an attractive country in which to conduct clinical trials. Since 2006, 131 clinical trials have been conducted in Bangladesh mostly for therapeutic areas of infectious disease.[35] The DGDA is responsible to control and monitor all clinical trials carried out in the country. Currently, the application for ethical clearance is submitted to BMRC for approval. Once it's approved, the investigator/sponsor submits the application to the DGDA, and then the No Objection Certificate is issued by the DGDA. The DGDA has published the 2010 Guidance for Industry on Submission of Clinical Trial Application for Evaluating Safety and Efficacy and the 2011 Guidance on Clinical Trial Inspection. However, informants indicate that clinical trials are not adequately controlled or inspected because of the lack of manpower. Also, the absence of laws and regulations on clinical trials poses a significant limitation for the DGDA. Currently, the DGDA does not conduct clinical trial inspections, and investigational new drugs that are meant for use in clinical trials are not monitored. To address this challenge, new regulations or guidance on approval of new investigational products and control of clinical trials are urgently needed.

Key Findings and Implications

- Lack of collaboration with BMRC. Currently, the DGDA does not maintain the register of clinical trials and interact with BMRC to ensure that clinical trials are conducted in compliance with the GCP guideline.

- No information sharing on clinical trials. All reports from clinical trials including ADR or AEFI reports should be sent to the DGDA. No reports from sponsors of clinical trials were received by DGDA in 2011.[36]

- No regulation or law to define DGDA's role in controlling clinical trials.

- No guidance documents or regulation on approval of new investigational products that are not registered in the country.

[35] www.clinicaltrials.gov (accessed on 21 Mar 2013)

[36] Stergachis, A., Rahman, Md. M., and Ludeman, E. 2012. *Safety of Medicinal Products in Bangladesh: Assessment of the Pharmacovigilance System and Its Performance.* Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services. Arlington, VA: Management Sciences for Health.

Post-Marketing Surveillance and Pharmacovigilance

Bangladesh has a regulatory framework for PV, and it is one of the priority areas identified by the DGDA in which to build capacity according to the operational plan 2011-2016 (part of the health, population, and nutrition sector strategic plan).[37] As such, individuals within DGDA are responsible for PV and drug information services. However, the PV system is not functional or performing in Bangladesh to detect, assess, and prevent medicines-related adverse events, according to the recent PV assessment conducted in June 2012.[36] No ADR reports were received in 2011, and only 56 product quality-related reports were submitted. Key findings and recommendations from this recent assessment are highlighted below.

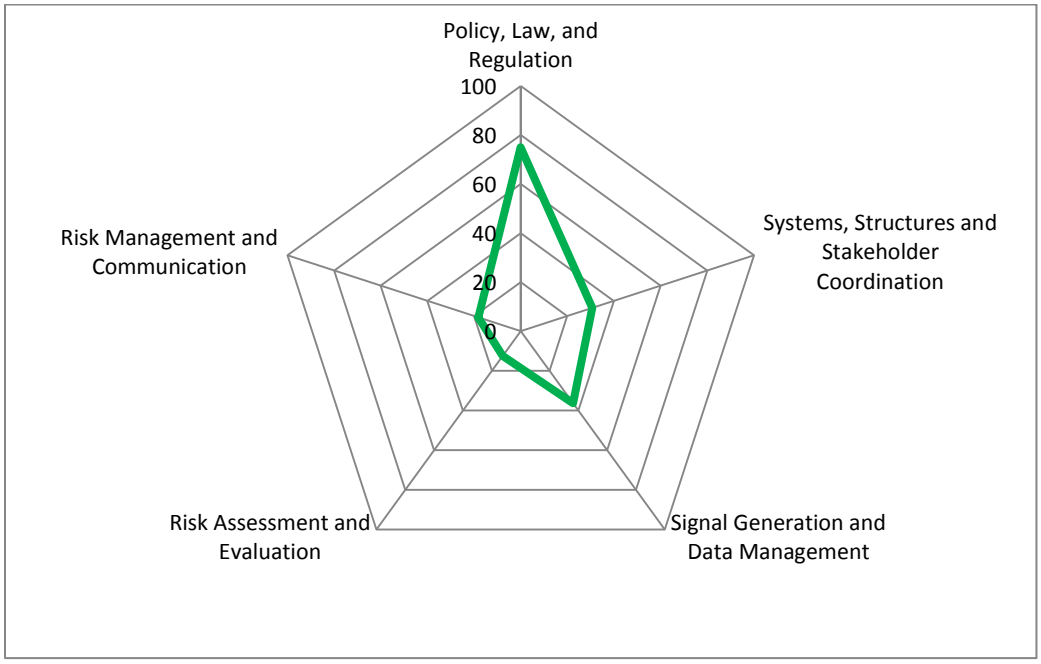


Figure 11. Performance of five PV components in the national system

Key Findings and Implications

- Lack of a legal or regulatory requirement for drug manufacturers to report drug or device-related adverse events and lack of a comprehensive national guideline for PV

- With regard to PV, lack of the following—an official document with a clear mandate, organizational structure, roles, responsibilities, and reporting lines for the PV center; a defined budget; SOPs; up-to-date national guidelines; functional advisory committees supporting both PV and QC; and greater coordination among stakeholders

[37]Ministry of Health and Family Welfare, Bangladesh. Health Population and Nutrition Sector Strategic Plan. 2010; https://extranet.who.int/nutrition/gina/en/node/8159

- Reporting form that does not cover all adverse events, such as product quality or medication errors; no national database exists; not a member of the WHO program for international drug monitoring

- Lack of an active approach to PV; no active surveillance carried out in the last five years; only one survey on product quality was carried out in 2011

- Although some activities related to risk management and communication occur on an ad-hoc basis, there is no formal structure or plan of risk management in DGDA

Pricing

Until 1981, there was no price regulation, and price was determined by manufacturer; price regulation was introduced by the Drug (Control) Ordinance 1982—

- The government may, by notification in the official Gazette, fix the maximum price at which any medicine may be sold

- The government may, by notification in the official Gazette, fix the maximum price at which any pharmaceutical raw material may be imported or sold

- Whoever sells any medicine or imports or sells any pharmaceutical raw material at a price higher than the maximum price fixed by the Government under section 11 shall be punished with rigorous imprisonment for a term which may be extended to two years, or with fine which may extend to 10,000 taka, or with both

Medicines prices in Bangladesh are among the lowest in the world. According to BMI, several factors play a role in lowering the price of medicines. Under the World Trade Organization's trade-related aspects of intellectual property rights (TRIPS) agreement, Bangladesh is not obliged to grant patents until 2016 which allows innovative molecules to be lawfully produced and sold. Competition among local generic manufacturers, low impact of branded products because of low per-capita income, and direct supply from the top 20 manufacturers to retail pharmacies maintains the low prices.

According to the Price Fixation Policy, the DGDA fixes the price of 117 essential medicines listed for primary health care. Once the product is registered, and if the applied price remains within the MRP fixed by the DGDA, an MRP certificate is issued to the manufacturer. If the manufacturer demands a price higher than the MRP, the application should be reviewed and approved by the Drug Pricing Committee. The MRP is fixed on the basis of the mark-up rate set by the committee, which varies from 1.5 to 3.4. This policy ensures that essential drugs are provided to the public at low cost.

For drugs other than essential medicines, the manufacturer gets to set the price of the products. However, the final price should be approved by the DGDA. Manufacturers submit new prices to the DGDA based on the cost of production and the regulatory body checks the proposed price carefully. The DGDA takes into account the purchasing power of the population as well as the

price proposed by other manufacturers (for the same generic drug). The prices of all drugs are printed in the packaging materials.

Key Findings and Implications

- The DGDA's pricing policy and regulation, among other factors, contributes to keeping pharmaceutical prices low in Bangladesh, particularly for essential medicines. Also, including the price in the packing materials is another good mechanism to control price.

- However, there is no systematic price monitoring system in Bangladesh. According to BMI, there was a significant price increase for some products, including life-saving medicines, in July 2011 in major cities with pharmacies' claiming scarcity or short supply of essential medicines. The absence of a price monitoring system and inadequate inspections can incentivize retail pharmacies and medicines shops to make illegal profits. Introducing a robust price monitoring system, such as barcodes in product packaging, can ensure the affordability of medicine as well as prevent counterfeiting.

- Even though generic substitution is mandated, most physicians prescribe branded names in practice. Encouraging and monitoring generic substitutions will help consumers choose the products with lower cost and reduce out-of-pocket expenditures on pharmaceuticals.

OPTIONS AND RECOMMENDATIONS FOR DEVELOPMENT OF A STRATEGIC PLAN

The overarching strategy for the development of the DGDA is contained in the September 2011 DGDA's Operational Plan for Strengthening of Drug Administration and Management 2011-2016 in the MOHFW Health, Population, and Nutrition Sector Development Program (HPNSDP). Its main objective is to ensure the quality, efficacy, and safety of pharmaceutical products by a competent workforce working together in strategic advancement towards improving the health of the people. The operational plan lists specific objectives including—

- Strengthening and building capacity of the DGDA
- Updating and implementing drug regulatory functions
- Supporting the pharmaceutical industries to produce quality drugs
- Improving capacity and standards of the government DTLs for quality control of drugs
- Facilitating the rational use of drugs
- Enhancing post-marketing surveillance activities

These objectives provided high-level direction in terms of the intentions of the DGDA. However, the operational plan did not address the overarching institutional and infrastructural challenges and the lack of regulatory capacity currently faced by the DGDA. These issues must be addressed and a detailed strategic document developed to guide the DGDA in transforming itself into a leading regulatory authority within the South Asia region.

This comprehensive assessment of the DGDA regulatory capacity and processes has therefore provided an opportunity to analyze the current prospects and challenges of the DGDA and identify gaps that may mitigate its ability to achieve the objectives of the operational plan. On the basis of the findings and analysis of this assessment, we have provided recommendations that will help guide the DGDA in achieving the intentions of the operational plan. We think that these recommendations should be transformed into a five-year strategic plan with a clear target of transforming the DGDA into a globally recognized regulatory authority. We have presented the recommendations under the headings of the specific objectives of the operational plan.

Objective 1: Strengthen and Build Capacity of the DGDA

Clearly, the intentions of the DGDA and the realities of its current capacity do not match. The DGDA lacks adequate resources, institutional infrastructure, and the skills to attain its mandate. The scope of the DGDA's regulatory activity is increasing and so is the number and complexity of the health products, pharmaceutical premises, and pharmaceutical personnel that it is supposed to regulate. On the other front the DGDA will need to strengthen its capacity and set out clear objectives so it can become the leading regulatory authority to support the burgeoning pharmaceutical industry. To enable the DGDA to achieve that aim, several activities should be implemented; the following recommendations to strengthen and build its regulatory capacity are proposed in addition to or as an expansion of the ones given in the operational plan.

Modernize the Regulatory Framework

The legislation and regulatory framework, though quite old, are really well written and have provided a good foundation for Bangladesh's pharmaceuticals and medical practice. However, they need to be modernized so that Bangladesh can continue to safeguard public health and remain competitive in the pharmaceutical industry. Some of the challenges with the current legislation include the following.

1. Consolidate existing legislation: To understand and comply with pharmaceutical regulations in Bangladesh requires wading through more than seven pieces of legislation and amendments. The current regulatory framework is complicated and challenging to understand, adding to the regulatory burden of both the DGDA and the industry and making it difficult for the public to understand. These separate pieces of legislation need to be consolidated into one legal instrument. A similar exercise was conducted in the UK in 2012 to consolidate the UK Medicines Act of 1968 and more than 200 statutory instruments into a new piece of legislation.

2. Modernize and harmonize the legislation: Besides not being contemporary and in tune with other countries with stringent regulatory authorities, the current legislation is also limited in scope as it does not adequately address clinical trials and the regulation of advanced therapies. The laws can lead to unintended noncompliance based on the contents, terms, and definitions used. For example, the Drug Rules 1946 contain forms in schedule A that may no longer be in use, and the definitions of diseases—which the regulations say that medicines should not claim to cure—include those that are now curable. The Drug Act (XXIII of 1940), in the definition of drug, does not comprehensively cover modern medical devices and combination products that have been defined by others. For example, the Global Harmonization Task Force defines medical devices as any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related articles which does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means. The US FDA defines combination products as products that are therapeutic and diagnostic products that combine drugs, devices, and/or biological products and other advanced therapies. Bangladesh has an opportunity to modernize and harmonize legislation to meet international standards, reduce the regulatory burden for the industry, and open up more opportunity for international trade and globalization of the Bangladesh pharmaceutical industry.

Pursue Harmonization and Networking with Other International Regulatory Authorities to Attain Global Standards and Improve Efficiency

Harmonization of regulatory requirements is particularly in the best interest of Bangladesh as it will form the basis for advancing export and trade in pharmaceuticals with other countries. Lack of harmonization, convergence, or mutual recognition of regulatory requirements results in inefficiency and duplicative practices and is a major technical barrier to trade. Currently, the DGDA's involvements in regional harmonization activities are very limited, but the opportunities exist. Bangladesh belongs to SAARC, an eight-member group. In its third

Ministerial Conference on Health in Dhaka in April 2005, the Technical Committee on Health and Population Activities considered preparation of a SAARC plan of action in the areas of medical expertise and pharmaceuticals, harmonization of standards and certification procedures, and production of affordable and traditional medicines. Bangladesh also belongs to the Indian Ocean Rim-Association for Regional Cooperation (IOR-ARC) with 19 member states. Tremendous opportunities also exist within the wider Asia Pacific region for collaborative work and support. The following recommendations should be considered for advancing harmonization.

1. Apply for participation in regional harmonization activities of the Association of Southeast Asian Nations (ASEAN) Consultative Committee for Standards and Quality Pharmaceutical Product Working Group, Asian Harmonization Working Party, the Pharmaceutical Inspection Convention/Scheme, and the ICH Global Cooperation Group. The DGDA should adopt regional and international standards for pharmaceuticals and trade including the International Air Transport Association's air transport logistics for time- and temperature-sensitive healthcare products. In addition, because of the prevalence of herbal medicines in Bangladesh and the role of the DGDA in regulating them, membership in the Pacific Regional Forum for the Harmonization of Herbal Medicines may be advisable.

2. Develop MOUs with NRAs from other countries based on criteria that include opportunities for improving research and development capacity in critical areas of interest; opportunities for capacity building, training, mentoring, and sharing of regulatory intelligence; and opportunities for advancing pharmaceutical exports and trade. Several NRAs have MOUs and international cooperation agreements; for example, the USFDA has many such agreements, and the Korea FDA has MOUs with Indonesia and Vietnam.

3. Strengthen collaboration with WHO. Already WHO has provided tremendous support to Bangladesh to improve the pharmaceutical sector and, in particular, bring the DTLs up to WHO standards. WHO also provides training in several areas to support development of country regulators. India's participation in the WHO prequalification program for its manufacturers and products in the areas of HIV/AIDS, TB, and malaria medicines has provided international recognition to Indian manufacturers and advanced its pharmaceutical industry. Bangladesh should accede to the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and pursue WHO prequalification to enable its manufacturers to have their products purchased by UN bodies.

4. Establish a mutual recognition agreement on GMP inspections with neighboring countries that Bangladesh considers to be reference regulatory authorities (RRA). As part of the strategy to protect its industry from substandard/spurious/falsely-labeled/falsified/ counterfeit medical products (SFFC), Bangladesh should sign the MEDICRIME Convention and become a member of the Forum on International Pharmaceutical Crime.

5. Streamline product registration and develop regulatory instruments for medical devices (abbreviated procedures for products already approved by SRA and RRA, statutory timelines for review of applications, etc.).

Review the Vision and Organizational Structure of the DGDA

NRAs, particularly those from countries with strong pharmaceutical industries, should be of adequate size, expertise, and capacity to support their roles and mandates. It is clear from this and previous assessments that the DGDA currently does not have that structure. The first action to address the challenges with the DGDA's institutional capacity is to review its vision and engage in a comprehensive organizational restructuring to meet that vision. The vision statement for a regulatory authority the size of the DGDA should be ambitious, targeted, and competitive. The vision statement should include assertions to the effect that the DGDA intends to balance its dual mission to promote and protect public health and to promote innovation and industrial growth. Improving health outcomes and economic growth should feature very well in the vision statement of the DGDA. Options for a new organizational structure for the DGDA are given in table 12.

One example of a country that recently made changes in structure is Pakistan where the new Ordinance 1 of 2012 provided for the establishment of the Drug Regulatory Agency of Pakistan, an autonomous body under the administrative control of the federal government, to replace the previous Federal Drugs Control Administration.[38]

[38] The Gazette of Pakistan, Extra, Nov. 13, 2012. Available at http://www.na.gov.pk/uploads/documents/1352964021_588.pdf

Table 9. Options for a New Organizational Structure for the DGDA

Option and example country	Description	Pros	Cons
1 Thailand	Directorate General: DGDA retains its current structure	This structure is already familiar and, because most of the DGDA's funding (particularly staff salaries and recurrent costs) is covered by the government, it is not vulnerable to control by the industry.	Salaries are low, infrastructural development is slow, and conflict exists because the government also owns a manufacturing facility (EDCL).
2 Korea	Agency for Drug Administration: DGDA is reorganized into an agency of MOHFW	This structure allows for the establishment of a different salary structure that will allow the agency to hire and retain skilled manpower. The agency will still have MOHFW as the controlling authority.	The source of funding for such a structure will have to be determined and may include additional funding from the government and/or increases in application fees for the regulated industry.
3 Saudi Arabia	DGDA becomes an autonomous entity	This structure will facilitate institutional growth, the hiring and retention of highly skilled staff, and running it as a business enterprise. The organization reports directly to the President.	This will need to be a cost-recovered institution, because the organization is a body-corporate, it will have to rely heavily on services and fees charged to remain solvent.

Address the Current Critical Human Resources Challenges

The findings of this assessment reinforce those of previous ones about the huge challenges that the lack of adequate HR poses to adequate regulatory functions. According to WHO, the severe manpower shortage in the DGDA makes it extremely difficult for all regulatory functions to be adequately undertaken, and it was recommended that the manpower shortage be rectified as a matter of urgency.[22] This assessment considers that addressing critical HR needs should be a major part of the 2011-2016 strategic plans. We provide the following recommendations as part of that strategic plan.

1. Conduct a comprehensive review of the HR requirements for the DGDA. Such a review should be extensive, evidence-based, and require in-depth analysis of the skill mix with consideration of the future roles the DGDA will play in the evaluation and approval of advanced therapies. Several factors should be considered and compared to an RRA to define adequate staffing. Some of the factors may include the size of the pharmaceutical market, the number of pharmaceutical industries, the scope of products regulated by the NRA (food, drugs, and medical devices), scope of regulatory functions (from premarketing approvals to post-market surveillance), number of products registered, number of applications processed in a year, number of inspections, percent of generic versus new chemical entities, number of meetings, number of violations and enforcements, etc.

2. Analyze and propose options for addressing HR needs. Once the requisite number and skills of staffs are determined, then options should be considered for addressing those HR needs. Two options are available: recruit into the DGDA all skills needed in-house or keep a pool of external reviewers, consultants, and competent institutions to conduct some of the work of the DGDA. However, it must be mentioned that recruitment into DGDA may not address the needs without a review of salaries. Total monthly pay and benefits for a director's position at the DGDA is the equivalent of USD 500 whereas a similarly qualified person working in the pharmaceutical industry is paid about USD 3000. Although we are not advocating salary levels that are similar to the private sector, reasonable increases in the salaries of the regulators will help to reduce attrition, hire and retain highly skilled staff, and reduce perverse incentives.

3. Institute service level agreements. It will be challenging for the DGDA to recruit and keep all the skills needed in-house. Most NRAs make use of external reviewers and evaluators and contracts with competent institutions to conduct some regulatory functions. The DGDA should institute service level contracts when engaging such individuals or institutions.

Develop a Comprehensive QMS

The DGDA's quality manual requires that it conduct internal audits to evaluate its services. During the assessment, we were not given access to any audit report from the DGDA. Though the intentions of the quality manual are correct, it is limited in scope and ambition. The following recommendations will help improve the situation.

1. Develop overarching QMS for the DGDA. The current quality manual has expired and needs to be revised. The opportunity to revise it should be used to develop an overarching QMS that will reflect the DGDA's organizational structure, vision and mission, mandate, and objectives and that will guide its determination to meet customer needs.

2. Pursue ISO 9001:2008 certification for the DGDA. The process can be initiated by inviting a standards organization to review and assess the QMS developed and compare it with the requirements of the ISO 9001 standard.

Develop Strategies for Improving Governance in Regulatory Activities

The DGDA appears keen and interested in improving transparency; just recently the citizen charter was launched. The DGDA has a right-to-information form on its website in line with the Right To Information Act, 2009. The DGDA also posts its annual report on the website and sends copies to the media. Recent reports state that Bangladesh made it easier to start a business after reform in 2009.[39] Challenges still exist with respect to dealing with the industry, disclosure of information, and the functioning and membership of committees. A report from a recent WHO

[39] The World Bank and the International Finance Corporation. Doing Business 2013: Smarter Regulations for Small and Medium-size Enterprises. Available at http://www.doingbusiness.org/~/media/GIAWB/Doing%20Business/Documents/Annual-Reports/English/DB13-full-report.pdf

mission stated that many of the same people sat on the different committees which could result in conflicts of interest in decision making.[22] The following recommendations should be considered for inclusion in the strategic plan.

1. Conduct an internal audit of the DGDA as required by the quality manual. Regulatory authorities such as the Central Drug Standard Control Organization (CDSCO) of India and Bangladesh's other presumed competitors in the pharmaceutical trade routinely provide audits and reports of legislative enquires into the functioning of their regulatory authority. For example, in India in May 2012, the parliamentary standing committee on health and family welfare released its 59th report on the functioning of the CDSCO. The report is publicly available online.

2. Strengthen the functioning of committees. The assessment found that some of the committees do not meet frequently as planned, and securing quality time from the members for regulatory activities can be challenging. There is no remuneration provided to any of the committee members. To secure quality time from such highly skilled individuals and demand them to avow conflict of interest, the government should provide adequate remuneration and be very clear about expectations. One option for achieving this is service-level contracts with committee members and external expert reviewers. Also, the number of committees can be expanded, particularly if the intention is to have a lean DGDA. During the assessment, the current status of the National Drug Advisory Council (NDAC) was not clear. Such a committee with important responsibilities should be functional and meet frequently.

3. Strengthen DGDA's transparency. The DGDA should ensure that the decision-making process is evidence-based and open to public scrutiny. The meeting minutes for the DGDA committees should be available online. Currently, only the DCC meeting minutes are available online. Also, all members of the committees should have their profiles, conflict of interest declarations, and voting records available online.

4. Involve the civil societies and consumers as equal partners in regulatory activities. The regulatory authority, industry, and the civil society constitute the tripartite partnership for regulatory governance. The assessment indicates that participation of the civil society in drug regulatory activities is very limited. The DGDA should revise membership of the committees to ensure representation from civil society. The DGDA should also ensure that the public has access to the citizen charter and understand their rights under the Right To Information Act, 2009.

5. Develop detailed performance metrics and make the DGDA accountable for reporting on key indicators. The HPNSDP operational plan contains some indicators; however, detailed performance metrics need to be developed and reported annually to monitor the activities of the DGDA. Such metrics should cover all regulatory function and processes.

Build Local Technical Capacity for Regulatory Affairs

With the recent advancement in pharmaceuticals and other health technologies, many regulators, even in developing countries, have realized the need to update their knowledge. In Bangladesh, like most other developing countries, the lack of HR for regulatory affairs is profound. Several options exist for addressing this; we have provided some recommendations below. On the whole, the type and level of skills required for regulatory activities should depend on the priorities of its medicines and the need for globalization.

1. Introduce a curriculum in regulatory topics to medicine and pharmacy schools. The DGDA should collaborate with local academic institutions and other stakeholders to revise the curriculum to include topics in regulatory science. Certification in regulatory affairs should also be considered.

2. Partner with SRAs to avail DGDA staffs of available trainings. Opportunities should also be explored to develop and implement strategies to stimulate technology transfer ahead of the TRIPS 2016 with a focus on obtaining relevant skills to evaluate advanced therapies for locally common diseases including gene therapies, large molecular-weight biologics, combination products, personalized medicines, and medical devices.

Objective 2: Update and Implement Drug Regulatory Functions

The DGDA has the responsibility to perform several regulatory functions. The assessment found that the technical resources and infrastructure for achieving this expectation is limited. For example, the DGDA's transactions are recorded manually in hard-copy files spread all over the organization. Many important regulatory registers are not available or are not frequently updated; registration is badly impacted by the manual process. The HPNSDP operational plan mentions this as a challenge, but did not develop an activity to address it. The following recommendations will address the need for a modern management information system.

Automate Regulatory Processes and Management Information Systems

One of the key challenges faced by the DGDA is the lack of automation of its processes. The assessment identified this as a major setback that requires immediate attention. The DGDA cannot realistically attain its objectives without the help of modern information and electronic systems. WHO recommends that, for the frequent, rapid retrieval of information, computerization is the most viable means of recording and keeping track of applications and marketing authorizations. The USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is currently working with DGDA to explore opportunities for the use of PharmaDex (a web-based tool) for drug registration. The DGDA should continue with the current efforts but also address other electronics infrastructure needs.

1. Review the features of PharmaDex and provide timelines to achieve electronic submission of registration applications and processing. The new tools will be able to

facilitate registration, drive the use of the CTD application format, and facilitate the availability of regulatory registers and timely sharing of regulatory information.

2. Enhance the website. The DGDA website should provide sufficient information to clients and consumers on how products are regulated in Bangladesh. The website should also be used for educating consumers and the public about the activities of the DGDA. The development of PharmaDex and enhancement of the website can be implemented at the same time.

3. Define all aspects of DGDA functions and processes targeted for automation. Such an exercise can guide the achievement of the overall objectives for an organization-wide information systems infrastructure. Some of the components of such a system will include the electronic registration tool, regulatory registers, archiving tool, structured product labeling, traceability, electronic reporting, video conferencing facilities, and built-in performance indicators.

4. Develop a comprehensive electronic document management system including an integrated enterprise regulatory information management system.

5. Consider the use of modern technologies for fighting the pervasiveness of counterfeits; legislation should include requirements for traceability to facilitate recalls and implement other interventions to secure the Bangladesh supply chain (example the use of mobile authentication).

Implement Risk-Based and Risk-Proportionate Regulatory Strategies

The current strategy where the DGDA spreads its resources to regulate all products, premises, and personnel equally to meet its regulatory mandate is not efficient and nor results oriented. Many developed-country regulatory authorities have embraced risk-based approaches to contain escalating costs and resources required for regulation while still protecting public health. The following recommendations should be considered for adoption.

1. Develop a risk-based inspection strategy. The assessment found that the DGDA does not meet its inspection target—to inspect 255 local allopathic medicine manufacturers and 98,000 registered medicine shops in the country—every two years. However, not all manufacturing sites present the same level of potential danger to the public. The UK's MHRA has developed risk-based inspection tools to rate producers or the industry on basis of the estimated risk they could pose to consumers. This PIC/S also recommends simple and flexible quality risk-management tools that may be used by inspectorates when planning the frequency and scope of GMP inspections.

2. Develop a risk-proportionate registration system. Registration applications can be subjected to three types of assessment—verification, abridged, or full. WHO advises developing-country NRAs to use abridged assessment whenever possible by identifying reference countries or authorities whose regulatory decisions are considered acceptable or recognizable and conducting assessments of applications on the basis of established

criteria. These assessments would have to be made within the limits of on one side, a reasonable certainty of filtering out substandard, unsafe products and, on the other side, by the available human and material resources.

Streamline Administration and Improve Capacity for Registration of Medicines

The assessment found that several guidelines and SOPs are not in place, which is consistent with the findings of the WHO mission report. Availability of harmonized standards, SOPs, and guidelines will streamline the medicine registration process. This assessment found factors that negatively affect timely registration, including availability of DCC meetings, lack of manpower, and a manual process. The assessment found that the DGDA has accumulated a backlog of registration and other regulatory applications. Streamlining the registration process helps to avoid duplicative reviews, reduce backlogs, and ensures timely access to essential medicines. The following recommendations will address some of the gaps found during the assessment and should be part of the operational plan.

Develop Good Regulatory Practices Guidelines

WHO states that GRPs aim to improve the efficiency and effectiveness of regulatory agencies and of regulators themselves. One of the instruments for achieving the aims of GRPs is the good practice guidelines (GxPs) which includes the GCP, GLP, GMP, GDP, GRP, and GPP. Following good practice guidelines and QMS ensures that NRAs have guidelines and SOPs in place and that they also develop guidance documents to facilitate industry compliance with the regulations. The critical guidelines and guidance documents should converge with international ones to reduce the regulatory burden. They should address quality, safety, and efficacy and reflect the other issues that impact the regulation of medicines, including the national drug policy, pricing, cost-effectiveness analysis, clinical need or therapeutic novelty, and benefit/risk assessment. The DGDA should consider the following recommendations to develop its menu of GxPs.

1. The DGDA should make an inventory of the required guidelines, SOPs, and checklists and ensure that all necessary guidelines and standards are in place.

2. The DGDA should develop guidance documents to inform industry of the interpretation of the regulations or its current thinking. Examples of critically needed guidance documents include ones for GDP to address standards for securing the integrity of products in the supply chain, guidance for biosimilars, and internal guidelines for GRP.

3. DGDA should explore opportunities for the adoption of common international technical requirements and their transposition into national regulations.

4. DGDA should improve the registration process to ensure timely access to essential medicines. Implementing a fast track for new, essential medicines is one option. Another option is to use a parallel review process rather than a sequential process. In a parallel process, the dossier review, testing of the samples, and the GMP inspection of the factory

happen in parallel, whereas in the sequential process, the samples are tested only after the dossier review is completed and found satisfactory.

5. The DGDA should develop the regulation of medical devices by exploring opportunities for technical assistance from regional harmonization groups such as the Asian Harmonization Working Party and participating in the International Medical Device Regulators Forum.

Revise Fees Charged for Regulatory Services

The assessment found that the fees charged by the DGDA for its services are lower compared to those of other countries. In general, it is necessary to increase the fees. However, this argument can only be built on evidence that the current charges are not commensurate with the cost of services provided and therefore costs are not sufficiently recovered. Application fees also have impact on the local industry in particular. Although fees were revised during the assessment, we have provided these options to subsequently inform decision making.

1. Conduct a cost and revenue analysis to assist the DGDA in understanding the cost of its services vis-a-vis the revenue that it generates.

2. Develop a transparent system to set-up fees for the regulatory activities. Design the fees to encourage local industries, based on products manufactured and local therapeutic needs. Figure 12 provides an example of an algorithm for segmenting application registration fees.

3. Determine how much user fees can be used for funding the industry. Several developed-country NRAs depend on user fees and government funding for their services. Complete reliance on user fees may lead to regulatory capture where the industry dictates to the regulatory authority. Funding should focus on ensuring sustainability and improving revenue through appropriate fees for services.

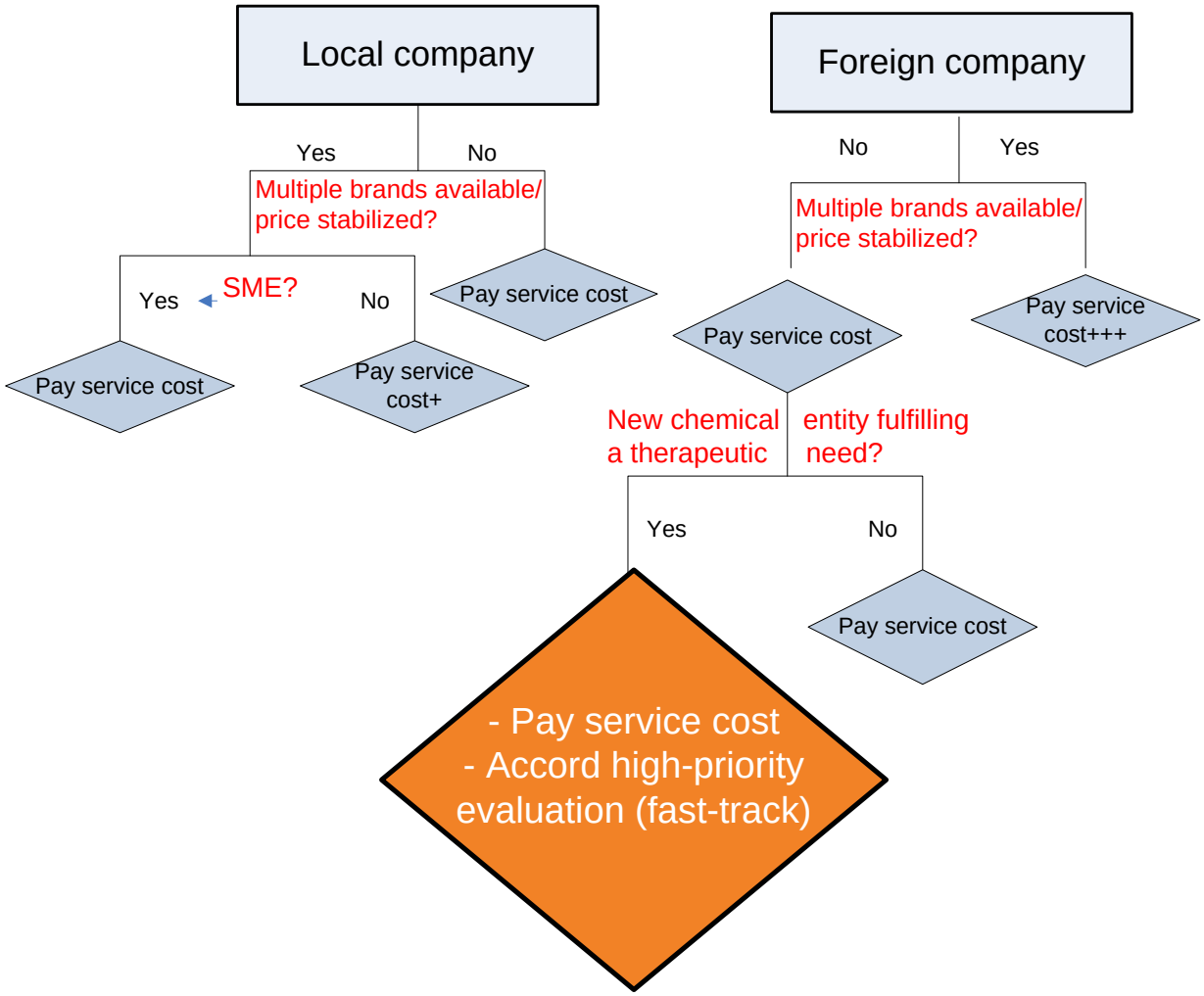


Figure 12. Algorithm to set up service fees

Develop and Maintain Regulatory Registers

The assessment found that some critical regulatory registers are not available or not routinely updated; for example, the registers for retail pharmacies or wholesalers are not publicly available. Regulatory registers are the first step in regulation because they provide a list of approved products, premises, and personnel. Access to updated regulatory registers alone can contribute to informing consumers and patients about their healthcare decisions. The development and maintenance of regulatory registers is critical to other areas of the regulatory process. In the immediate, the DGDA should implement the following recommendations.

1. Develop an inventory of regulatory registers in accordance with legislation and the needs of the authority.

2. Ensure that up-to-date regulatory registers are publicly available and provide a minimum level of information to the public.

Objective 3: Support the Pharmaceutical Industry to Produce Quality Drugs

The assessment found that the pharmaceutical industry in Bangladesh provides almost all the local needs while being a major source of foreign exchange earnings. The local industry basically consists of the EDCL, wholly owned by the government. The EDCL provides 100 percent of the essential medicines needed by the public sector. The private sector industries are very active, both locally and abroad. The DGDA reported that the Bangladesh pharmaceutical industry supply drugs to about 87 countries.

Develop an Action Plan for the Advancement of the Pharmaceutical Industry

The proposed NDP 2012 objectives include supporting the industry to keep pace with the changing global market and to modernize and expand operations of the pharmaceutical sector to international pharmaceutical markets. The GOB is also very keen about attracting foreign investment in the pharmaceutical sector and plans to exploit the limited window till 2016 when Bangladesh will have to adhere to the TRIPS agreement. The following recommendations will contribute to what is already planned in the operational plan to grow the local pharmaceutical industry.

1. The DGDA should target specific areas on the basis of the needs of the local population and comparative advantage for the development of innovation in pharmaceuticals. This will guide efforts at clinical trials, pharmaceutical research and development, and inform the selection of foreign NRAs with whom to partner. Special attention should be accorded to research and development in the areas of vaccine development for infectious diseases including TB, diarrheal illnesses, pneumonia, shigella, hepatitis, etc., and chronic non-communicable diseases, such as diabetes, cancer, and kidney diseases.

2. The DGDA should collaborate with the pharmaceutical industry, the Ministries of Trade and Industry, and other stakeholders to organize a high-level stakeholders meeting to discuss options for advancing the pharmaceutical industry in Bangladesh.

3. The DGDA should collaborate with the EDCL to achieve WHO GMP standards, become ISO certified, and ensure that it sets the best practice standards for the rest of the other local manufacturers. If the EDCL attains WHO GMP standards, then the DGDA will have the moral high ground to enforce that standard with private sector manufacturers. During the last inspection of the EDCL, the DGDA recommended an upgrade of EDCL facilities to achieve GMP standards; management of EDCL committed to pursuing that objective.

4. The DGDA should develop guidelines for communication channels and meetings with the industry. It appears that the current practice is that pharmaceutical industry representatives visit the DGDA virtually every day to follow up on their applications.

Frequent and ad-hoc meetings with the industry are disruptive and expose the regulators to corrupt practices. On the other hand, the DGDA should provide opportunities for meeting with the industry in a transparent and helpful manner and be ready to guide the industry through compliance with the regulations.

Objective 4: Improve Capacity and Standards of Government DTL for Quality Control of Drugs

From the assessment findings, Bangladesh has benefited from support from WHO in upgrading the capacity of the DGDA in QA/QC. The current upgrade of the NCL is funded by the GOB and the World Bank. The equipment for the NCL is provided through a MOU between the GOB and WHO. The NCL focuses on vaccines and biologicals. Several WHO missions, including the SEARO/FCH/IVD mission to discuss institutional development, plan for local production of selected vaccines provide directions for strengthening DGDA's capacity in QA/QC.

Develop Timelines for Attainment of WHO GMP Standards

Current efforts to upgrade the testing laboratories to WHO standards are consistent with Bangladesh legislation. Sections 15 of Ordinance No. VIII of 1982 stipulates that every manufacturer of drugs shall follow WHO GMP standards and that any manufacturer that does not follow such good practices will have their manufacturer's license cancelled or suspended. Therefore, there is a regulatory tool for enforcing GMP standards in Bangladesh. The DGDA should consider the following recommendations.

1. Continue to work closely with WHO to upgrade the DTL and NCL and implement other WHO recommended interventions.

2. Work with their local industry to achieve WHO GMP standards. The achievement of these standards will ensure that the products they manufacture will obtain international recognition and legitimacy and also provide an entry into the international market. This is particularly important for the non-ARVs, reproductive health, pediatric diseases, and neglected tropical disease (NTD) medicines, the areas where Bangladesh seemingly has a comparative advantage over its neighboring manufacturing giant, India. The DGDA should develop a timeline for the achievement of this objective.

Objective 5: Facilitate Rational Use of Drugs

The assessment identified huge challenges facing rational use of medicines in Bangladesh. However, opportunities for addressing those challenges may arise from the implementation of the next NDP and should be exploited. The operational plan also has developed interventions for improving rational use of medicines.

Strengthen Control on Advertising and Promotion and Improve Rational Use of Medicines

With multiple branded generics and competition in the pharmaceutical market in Bangladesh, control of advertising and promotion is very important. There are other challenges facing rational use of medicines as well and some of these were mentioned in the WHO mission in October 2010. The DGDA should consider the following recommendations.

1. Implement recommendations of the WHO 2010 mission. Also explore opportunities for improving the regulation and rational use of unani, ayurvedic, biochemic and other complementary and alternative medicines by making information on them readily available.

2. Strengthen the control of advertising and promotion. Current laws and the Code of Pharmaceutical Marketing Practices provide the regulatory framework for the control of advertising and promotion of medicines in Bangladesh. These regulatory instruments are adequate as they were developed according to global standards including the WHO ethical criteria for medicinal drug promotion, the International Federation of Pharmaceutical Manufacturers & Associations Code of Pharmaceutical Marketing Practices, and the Association of the British Pharmaceutical Industry Code of Practice for the Pharmaceutical Industry. However, the challenge is in implementation and enforcement because DGDA is unable to contain the promotional activities. Recent reports indicate that there is no adequate monitoring of drug promotional activities or vetting of advertising aimed at prescribers or the public and recommends that a system and committee to monitor drug promotion be established.[22] The DGDA currently has only one staff who has the responsibility for the review, approval, and monitoring of industry promotional activities. This level of staffing is definitely inadequate. Also, the activities of the unit are conducted manually and there are no electronic standards for labeling. Potential interventions to address this area may include the adoption of global labeling standards, such as structured product labeling (SPL), a standardized electronic file format that enables anyone to create, send, and receive product labeling content. Second, the DGDA can develop service-level contracts with external consultants. These consultants can review packaging, labeling, and promotional materials that are submitted electronically and submit their recommendations to the officer at the DGDA for regulatory action.

3. Provide information on the indication for which a medicine has been registered including other conditions for use.

4. Develop risk proportionate guidelines for regulating advertising and promotion of medicines. Efforts at regulating the promotion of products should be risk proportionate with high-risk prescription-only medicines being more closely monitored than over-the-counter and complementary medicines.

Objective 6: Enhance Post-Marketing Surveillance Activities

The operational plan provides for the establishment of the drug information and adverse reaction monitoring cell of the DGDA. Recently, the DGDA, in collaboration with the USFDA and USAID through an interagency agreement implemented by SIAPS conducted a comprehensive assessment of the PV system and its performance in Bangladesh.

Implement Recommendations of the Recent Assessment of the PV System

The DGDA has been without a unit for the monitoring ADRs and promotion of rational use of medicines. The need to set up a PV unit for this purpose is long overdue. The DGDA should work with partners to address this, consistent with the proposed activities of the HPNSDP operational plan.

1. The DGDA should implement the recommendations of the SIAPS report.

2. Establish drug information and an ADR monitoring cluster.

3. Improve surveillance of safety and quality of marketed products through membership in the WHO international monitoring program, strengthening of the national PV program, and the establishment of a post-marketing quality surveillance program to monitor the quality of approved products.

4. Develop strategies for preventing entry of spurious medicines from neighboring countries, particularly India and Myanmar. A lot of spurious products in the Bangladesh market are from abroad.

5. Join other international groups, for example, by signing the MEDICRIME Convention to facilitate the fight against poor-quality products. The MEDICRIME Convention is an international treaty against counterfeit medical products and similar crimes involving threats to public health.

CONCLUSION

The pharmaceutical sector in Bangladesh provides an example of how health and economic development intermix. The justification to strengthen the Bangladesh pharmaceutical regulatory system is compelling because of the dual contribution in improving health outcomes and economic development from a strong, local pharmaceutical industry. The DGDA's capacity should be strengthened to protect public health while advancing industrial development in Bangladesh. The sound regulatory system can ensure quality, safety, and efficacy of medicines and support the achievement of quality standards in pharmaceutical manufacturing in Bangladesh. The way forward should be toward effective implementation of priority actions identified through this assessment and the subsequent action plans developed by stakeholders. To achieve those objectives, political leadership, commitment, and substantial investment in human and infrastructural resources will be needed.

ANNEX A. MATRIX FOR DEVELOPING THE ACTION PLAN

Area to be addressed	Short term, 6 months	Medium term, 1-2 years	Long term, 3-5 years
Regulatory framework and management structure			
Regulatory framework (including legislation and regulations)	Fill vacant post in DGDA	Train newly recruited personnel	Consolidate modern legal framework
Harmonization	Harmonize format for different activities		Develop and harmonize all DGDA guidance and manuals
Organizational structure	Analyze and assess HR requirements	Upgrade organizational structure on basis of work load	Recruit additional manpower per upgraded organizational structure
HR	Capacity building of HR		
QMS	Develop quality manual	Develop performance indicators	Implement TQM
Governance (transparency and accountability)	Train DGDA staff to provide good governance	Effective implementation of good governance	
Technical capacity	Assess technical capacity of DGDA staff		
Automation and information technology	• Do requirements analysis • Re-engineer business process	• Develop software • Procure hardware • Start operation	Maximize online system
Regulatory functions			
Risk-based regulatory strategy	• Write guideline for inspections • Recruit manpower for lab and hire experts • Prepare training module, documents format, and SOP to develop HR for drug testing lab	• Perform bioequivalence study • Develop clinical trial protocol and write law • Train	• Perform clinical trial (pass law, develop hospital facilities and HR skills) • Perform phase II study
Administration and capacity for registration	• Hire expert manpower • Create guidelines, SOPs, CTDs for all medicine systems • Allocate funds (reinvest 25-50% of user fees to NRA for in-house development) • Allocate funds for logistic support	• Recruit manpower • Train • Develop logistics (transport, equipment)	Implement automation (MIS) and logistics (infrastructure at HQ, divisional and district offices and to setup regional testing lab)
GRP guidelines	Review registration procedure and gap analysis	Adopt GRP guidelines including GCP, GLP, GMP, GDP, GPP, related SOPs	

Area to be addressed	Short term, 6 months	Medium term, 1-2 years	Long term, 3-5 years
Regulatory registers	Develop format development and collect data on retail pharmacies (DGDA can start immediately with district officers)	Make information available for all registered products by automating registration system	• Prepare register for all outlets (retailers and wholesalers) including appointed pharmacists • Make prescription/patient information (data) publicly available • Develop tracking systems (barcode) • Develop online ADR reporting system • Develop register of product recalls
Fees charged for regulatory services		• Revise fees, such as inspection, source validation (inspection), amendment fees • Increase imported product registration fee • Exempt fees (new project approval, recipe evaluation, product registration) to encourage the local raw material manufacturers	
Pricing	Implement price monitoring guideline/SOP	• Revise pricing policy for essential products • Upgrade pricing guideline • Prepare SOP per above guideline	Create laws
Inspections	• Train existing HR • Provide sufficient logistic support • Provide security support during inspection • Budget for sample collection • Budget for inspection (do you have a cost analysis?) • Develop quality manual and QMS in DGDA (needs technical support) • Increase the number of inspections	• Recruit manpower • Obtain transport	Establish offices at district level

Area to be addressed	Short term, 6 months	Medium term, 1-2 years	Long term, 3-5 years
Licensing of manufacturers, importers, wholesalers, and retailers	• Limit the number of retailers (as per pop. ratio) • Conduct frequent inspection of manufacturers, retailers, and importers • Increase the number of inspections	• Import license should be valid for two years instead of five years (currently, it is five years) • Make manufacturing licenses valid for two years	Introduce community-based retail license
Import and export control	Create dedicated cell for export		• Assign inspector from DGDA to customs, National Board of Revenue (NBR), Export Promotion Bureau (EPB), in respective areas • Establish API park
Quality control/ WHO GMP standards	• Adequate HR • In-house/ oversees training of HR on QMS and vaccines • Company should follow the latest WHO GMP guidelines	• Adequate budget for machine and equipment maintenance as well as to buy reagents for chemical • Accreditation of private drug testing laboratory	• Establish DTL at divisional level • Establish competency approval certification system for the company's key personnel; DGDA would be the certification body for personnel (developing the system requires some time)
Rational use	**Objective** Choice of proper medicine for specific disease **Current practice** About 27% of patients are diagnosed by registered doctors but the rest are treated by self-medication, chemist, or quack doctors **Action plan** • Prepare SOP • Increase awareness through seminars, symposiums, workshops • Sensitize health professionals • Prepare a treatment guideline • Advertise in print and electronic	**Action plan** • Enhance public awareness • Ensure continuous market monitoring • Publication of drug bulletin • Educate community about rational use of drugs • Request that health professionals avoid multidrug therapy • Prepare a national guideline • Investigate feasibility of generic substitutions • Conduct drug utilization review	**Action plan** • Suggest that authorities introduce laws to prevent irrational use of drugs • Introduce rational use of drugs in medical school curriculum • Institute training program in hospitals • Review current drug list and drop unnecessary molecules • Publish Bangladesh National Formulary (BDNF)

Area to be addressed	Short term, 6 months	Medium term, 1-2 years	Long term, 3-5 years
	media		
Control of promotion and advertisements	**Current situation** Advertisements and promotional materials are circulated without the prior approval of Licensing Authority **Action plan** • SOP for control of promotional materials and advertisements • Request that print and electronic media not promote without authorization • DGDA will publish advertisements to make people aware • Ensure punishment for unauthorized advertisement	**Action plan** • Organize seminar, symposium, workshop for medical professionals • Train HR • Institute responsible fund allocation • Monitoring system to be improved • Monitor and take action against unauthorized advertisements in newspapers and TV as per • Section 21 of drug control ordinance 82. • Prepare a national guideline	**Action plan** • Collaborate with other NRAs • Track Internet for illegal promotion and sales; develop IT support • Amend law
PV and post-marketing surveillance	**Action plan** • Immediately activate adverse drug reaction monitoring cell of DGDA and advisory committee • Conduct workshops with medical professionals and collaborate with other NRAs • Develop awareness of code of good ethical marketing • Request Bangladesh Medical and Dental Council (BMDC) and BMA to implement code of good ethical medical practice • Make ADR monitoring in government hospitals mandatory • Preparation of SOP	**Action plan** • Conduct workshops with medical professionals • Publish ADR manual • Perform intensive hospital monitoring • Prepare national guideline	**Action plan** • Collaborate with WHO and other NRAs on drug safety information exchange • Make ADR monitoring in all hospitals and clinics throughout country mandatory • Promulgate law
Clinical trials	**Action plan** • Prepare SOPs • Form committees • Develop MOUs with other NRAs • Request that BMRC and Bangladesh	**Action plan** • Train respective personnel • Budget for HR • Develop guideline to conduct clinical trial	**Action plan** • Do continuous training • Collect clinical trial reports and publish • Accredit laboratory

Area to be addressed	Short term, 6 months	Medium term, 1-2 years	Long term, 3-5 years
	Institute of Medical Science (BIMS) start clinical trial centers immediately	• Develop MOUs with other countries • Intensively monitor clinical trial process • Ensure health and safety of volunteers and compensate in case of health hazard	• Monitor lab facilities and clinical trial centers • Implement GCP and GLP • Promulgate law

ANNEX B. STRATEGIC PLANNING FOR THE DGDA

Vision	**Proposed option** To ensure the safety, quality, and efficacy of drugs, we want to upgrade the regulatory authority to become a robust, effective, efficient, and autonomous leading medicine regulatory authority to keep pace with international standards.
Mission	**Considering the mandate of the legislation, the following option is proposed** To ensure production and availability of safe, efficacious, and quality medicines for human and animal use at affordable price. **In executing its mission, the DGDA commits itself** To control manufacturing, importation, distribution, sales, and post-marketing surveillance per the existing legislation and policy.
Values	**Following values are proposed** Transparency, accountability, integrity, efficiency, and professionalism
Stakeholders (clients)	Ministry of Health and Family Welfare Ministry of Finance Ministry of Fisheries and Livestock Ministry of Home Affairs Drug Manufacturing Association Bangladesh Pharmaceutical Society BMA Faculty of Pharmacy Bangladesh Chemist and Druggist Association Ministry of Law
Stakeholders (partners)	Ministry of Commerce Ministry of Industries WHO USAID World Bank Bangladesh Pharmacy Council Korea International Cooperation Agency (KOICA)
Scope	DGDA's jurisdiction includes regulation of human medicines including medical devices, veterinary medicine, and traditional (unani, ayurvedic, homoeopathic, biochemic, and herbal) medicines
Core regulatory functions and services	1. Licensing and registration of drugs and drug products 2. Cancellation and suspension of registration of license 3. Combating production, distribution, and sales of illegal medicines 4. Manufacturing facility inspection – manufacturing facilities and drug outlets, routine inspections, concise inspections, follow-up inspections, inspections against complaints, inspections for GMP certifications, etc. 5. Collection of samples on random basis for testing and analysis 6. Control of advertisement and promotional materials 7. Enforcement of drug laws 8. HR development of pharmaceutical industries through training

ANNEX C. PERFORMANCE INDICATORS (EXAMPLES)

Category	Indicators
Management	Number of audits/management reviews/self-assessments carried out in the last year (per quality manual)
	Number of filled positions out of total approved positions
	Number of staff that participated in regulatory affairs training in the last year
Enforcement	Number of violations against which administrative measures were taken in the last year, out of the total number of violations registered
	Number of violations against which legal sanctions have been applied by the judiciary in the last year, out of the total number of violations submitted to the court
Inspection	Number of planned pharmaceutical establishment inspections conducted, out of the total number of planned inspections for • Manufacturers • Retail pharmacies • Wholesalers Number of clinical trial inspections carried out in the last year, out of the total number of clinical trials registered in the country
Licensing	Number of pharmaceutical establishments (manufacturers, wholesalers, importers/exporters, retail pharmacies, etc.) licensed, out of the total number of pharmaceutical businesses in the last year
	Number of renewal certificates issued for pharmaceutical establishments (manufacturers, wholesalers, importers/exporters, retail pharmacies, etc.)
Quality surveillance	Number of samples collected, out of the total number of samples planned for collection
	Number of products tested, out of the total number of products submitted/collected
	Number of products that failed quality testing, out of the total number of products tested
Registration	Number of registered pharmaceutical products • New applications for registration of products containing new APIs • New applications for registration of generic/well-established multi-source products • New applications for medical devices • New applications for biologics/vaccines • New applications for registration by fast-track procedure • Applications for variation of data • Applications for renewals • Applications for export certificates • Other (specify):
	Average time to evaluate and register • Generic products • Products containing a new API • Fast-track products
	Percent of all medicines in the essential medicines list that are registered
	Percent of all medicines in the standard treatment guidelines that are registered
	Percent of all products procured from the CMSD that are registered
	Average number of products registered for top 100 conditions in the country
	Average percent price reduction of products for the top 100 conditions in the country
PV	Number of risk-mitigation recommendations that were informed by PV data and activities

Category	Indicators
	Number of medicine-safety actions (other than mere ADR reporting) taken to inform clinical management, revise guidelines, make regulatory decisions, or educate health workers and patients
Medicines information	Number of essential therapeutics information services provided to support training healthcare providers, revise treatment guidelines, and make regulatory decisions
	Number of advertisements/promotions found to be in violation of the law, out of the total number of promotions/advertisements approved (indicate year)
	Number of labels/inserts found to be inconsistent with what was approved during registration, out of the total number of labels and inserts assessed (indicate year)