

**The Centre for
International
Public Health Policy**



GOOD MANUFACTURING PRACTICE IN THE PHARMACEUTICAL INDUSTRY

Working paper 3, prepared for Workshop on 'Tracing Pharmaceuticals in South Asia',

2-3 July 2007, University of Edinburgh

Funder: ESRC / DfID

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1. Objectives

The aim of our study is to map regulation, production, distribution and consumption of pharmaceuticals in two South Asian countries, namely India and Nepal and to understand the contexts of pharmaceutical use in South Asia. This paper is concerned with the role of regulation and its enforcement in India and Nepal with respect to one specific regulatory requirement - Good Manufacturing Practice (GMP)¹ - the guidelines which govern the production, distribution and supply of a drug.

Compliance with GMP is a necessary condition for marketing authorization, in other words domestic and foreign producers of pharmaceutical companies cannot sell or market their drugs without it in the West and North. While GMP compliance has not been universally adopted in the developing world, governments in less developed countries are under pressure to comply with GMP requirements when granting marketing authorizations to domestic companies and the West has developed a variety of strategies to ensure that developing countries adopt the rules. GMP requirements require major investment in upgrading manufacturing facilities and this has implications for local producers. An interesting empirical question is the impact of these changes on local markets and on access to and affordability of medicines in developing countries.

The pharmaceutical industry operates in a multi billion pound/euro/dollar global market place. Its operations are highly complex and so too is its governance or regulation. There is a plethora of cross cutting supranational and national regulatory structures and legal systems to navigate, but the key to understanding these regimes is the way in which they link to trade regimes and sanctions. From the perspective of developing countries, the West has established the rules of trade and set the barriers for market entry. These rules originate in the EU and US but if successfully overcome, are the gateway to new markets. The large multinational Indian pharmaceutical companies have now adapted their manufacturing processes to comply with international rules and standards. So too have their governments as signatories to trade regimes

¹ With respect to pharmaceutical supply chain, it is important to look also at Good Distribution Practice (GDP) and Good Storage Practice (GSP). The GMP standards typically include recommendations on both, the GDP and GSP, we will need to pay attention to the extent to which GMPs cover GDP and GSP and the differences in coverage between developed and developing countries. The present version of the paper deals mainly with GMP standards.

through the WTO and other trade treaties: India, for instance, is currently setting up a Central Drugs Authority of India similar to the US Food and Drug Administration.² In the next section we explore the rationale for and the nature and evolution of these rules from the economic and the public health perspective.

2. The role and types of pharmaceutical regulation - information asymmetry and consumer protection

The need for regulation derives from information asymmetry between the pharmaceutical producers on one side and consumers and medical practitioners on the other side. That means that consumers are not able to assess safety or observe quality and efficacy of medicines on their own and neither can the medical practitioners who decide on their behalf. The pharmaceutical industry is the main knowledge generator in the field. The response to information asymmetry is the requirement by the state for consumer and public to put in place regulatory safeguards at every stage of the pharmaceutical production cycle to ensure that all drugs are properly tested and produced and that tests results available to regulatory authorities are complete and unbiased. There is no stage of drug life cycle which is not regulated and documented whether it is the laboratory phase of a new molecular entity discovery, testing in clinical trials, or the licensing, manufacturing, and distribution.

Detailed accounts of the history of pharmaceutical regulation can be found in Lee and Herzstein (1986), Permanand (2006), Braithwaite & Drahos (2000), Danzon & Keuffel (2005), and Immel (2000). In brief, the regulation of pharmaceuticals evolved at the national level in response to public health concerns (typically, urged by drug disasters that required immediate changes and strengthening of safeguards). With globalization of pharmaceutical markets, some aspects of regulation, especially those concerning quality, safety and efficacy, were taken to the supranational level. The complexity of the area means that it is not within this paper's remit to provide an overview or comprehensive account of pharmaceutical regulation except to draw attention to a number of areas of interest. First, as we note at the outset, regulation is strongly linked to trade and market entry. Second, the regulatory regimes, enforcement mechanisms and sanctions vary considerably across the drug development and production cycle, depending on

² See Indian Embassy (2007) or Bureau Report (2007).

the interests and power of the various parties. Third, the regulatory codes themselves vary both in strength and legal jurisdiction reflecting the power and interests of the various stakeholders.

At one end of the regulatory spectrum is the WTO trade regime which governs intellectual property and patents. This sits in the regulatory structure of the WTO trade regime known as TRIPS. The Treaty was developed by and for the pharmaceutical industry but is actively promoted by governments through the WTO negotiating apparatus. This regime unlike all the others has its own law enforcement and dispute settlement regime linked to trade sanctions and is aggressively pursued. At the other end and by far the weakest end of regulation is self-regulation which is used by pharmaceutical and medical professional bodies with respect to pharmaceutical marketing and relationships between medical practitioners and pharmaceutical and other industries (e.g., *Code of Practice of the Association of the British Pharmaceutical Industry*, *Code on Interactions with Healthcare Professionals* by the Pharmaceutical Research and Manufacturers of America, or *Australian Pharmaceutical Manufacturers Code of Conduct*).³

At the national level, there are the pricing restrictions (including price ceilings for essential drugs and profit margins) and marketing agreements (e.g., bans on DTCA in most countries). Finally, there are the quality and safety standards which govern the lifecycle of drug production and distribution which are developed at national level but which are converging through international agreements.⁴ Table 1 illustrates five of the key bodies in the west concerned with developing international guidelines in respect of the drug life cycle (we examine these together with monitoring and enforcement in later sections).

Table 1: Pharmaceutical production standards

Drug life cycle	Guidelines	WHO	ICH	EU	UK	US
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³ The incentives for self-regulation might be intriguing. Braithwaite (1993) discusses initiatives of Ciba-Geigy, pharmaceutical company with bad reputation, to introduce more stringent self-regulatory standards. Certainly, such standards or certification serves as a shortcut to a better name. Instead of continuous reputation building that takes decades of trustworthy practices, companies upgrade their standards at once, rely on the reputation of regulatory body or association approving the standards or certification and suddenly jump to the high quality producers' club.

⁴ The process of developing these standards has been more complicated in that they had been developed to a certain extent at national level, then taken to the international level through the WHO, further adjusted and strengthened at national level and again harmonized at international level through the International Conference on Harmonization. The finalized and harmonized standards are then adopted at national level and possibly adjusted further to local conditions. See more details in Section 3 on GMP standards.

Drug discovery	Good Laboratory Practice	x	x	x	x	x
Clinical trials (phase 1,2,3)	Good Clinical Practice		x	x	x	x
Manufacturing	Good Manufacturing Practice	x	x	x	x	x
Distribution	Good Distribution Practice	x	x	x	x	x
Post-marketing surveillance	Pharmacovigilance	x	x	x	x	x

Standards are not legal rules they are guidelines but nevertheless when linked to enforcement regimes and sanctions can be very powerful. For example, the WHO GMP standards and inspections procedures that are primarily used in developing countries are linked to marketing authorisation and to procurement. Thus the WHO will not procure drugs through the GDF unless the company has GMP. Similarly, the WHO advocates for the implementation of public drug procurement systems with built-in quality control mechanisms, typically represented by the requirement of GMP certificates, in developing countries.⁵ The WHO also suggests sanctions that should be imposed on manufacturers failing to comply with the GMP. The responsibility of the implementation, monitoring and enforcement of the GMP is however shifted to individual governments which raises issues about their capacity to do so.

2.1 The trend towards harmonisation of pharmaceutical regulation

The first steps to regulate the pharmaceutical industry were taken in England and Switzerland at the break of the 19th and 20th century. In the US, the Biologics Control Act of 1902 introduced requirements on inspection and testing of facilities and products of biologics manufacturers and the Pure Food and Drug Act of 1906 established the first government regulatory agency (now FDA). Quality and safety control mechanisms were introduced by national regulatory authorities in response to health disasters such as the elixir sulfanilamide⁶ in 1938 or the thalidomide⁷ one in the early 1960s (Braithwaite and Drahos 2000: 382). The US introduced first safety standards for pharmaceuticals in 1938. After the thalidomide tragedy, the US introduced even more

⁵ 'Delhi Model' for public drug procurement is such a system and has been presented by the WHO as an example to follow in other Indian states as well as other developing countries (see e.g. Chaudhury et al. 2005).

⁶ Elixir sulfanilamide was a toxic cough syrup that killed 107 people in the US (Braithwaite and Drahos 2000).

⁷ Thalidomide was marketed in Europe as a sleeping pill and also prescribed to pregnant women to treat morning sickness. Although safe in adults, it was toxic to fetuses. More than 10000 babies were born with deformities in the 1960s (Braithwaite and Drahos 2000).

stringent approval procedures requiring a proof of efficacy in addition to safety before marketing pharmaceutical products. European Community and many other countries followed the US example and introduced drug regulation (Braithwaite and Drahos 2000: 382; Shadle 2004).

From then, pharmaceutical regulation was shaped at national level by various incidents and the interests of various stakeholders in pharmaceutical industry and health care. Countries have been working toward more complex and coherent regulatory requirements, strengthening and adding control mechanisms, making the documentation of various processes and test results mandatory. Although the market authorization of new products became more costly to drug producers, a high level of quality and safety standards has two main benefits for industry. First, the fulfilment of regulatory requirements makes the industry 'trustworthy'. Secondly, costs of high standards create barriers to market entry and competition and thus result in concentrated markets. The high costs of regulation and drug development are used to argue for stronger IP protection. Strictly enforced IP regulation together with GMP creates additional barriers to entry for generics producers who might follow the GMP standards, thus sustaining monopolistic markets.

The global pharmaceutical industry is a powerful player in the evolving pharmaceutical regulatory landscape. There is no doubt that the pharmaceutical industry is a major driver behind the policy of harmonisation. This is not to say that pharmaceutical companies do not take advantage of the different standards and regulations across different countries to game the system. For example, faced with foreign markets with different and possibly stricter regulation, the burden of complying with country specific requirements might be considerable. Braithwaite (1993) argues that law evasion rather than breaking the law is typical for the pharmaceutical industry. The strategy involving

“an impure or understrength product that is forbidden from sale in one country being dumped in another nation with looser laws...is often an element of a much more sophisticated international law evasion strategy whereby the firm develops an integrated plan of where it will do the early testing and where it will do its final testing;

where it will seek marketing approval first, second, third, penultimately, and ultimately; and where it will locate manufacturing of the new product” (Braithwaite 1993).

Although game playing by pharmaceutical companies should be reduced by harmonization of pharmaceutical regulation it also plays to the interests of the pharmaceutical industry because the compliance with harmonized rules opens doors to several markets at once, e.g. FDA approval gives access to the worldwide market.

The first attempt to globalize pharmaceutical regulation was made by the WHO through the “Action Program on Essential Drugs” and the “Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce” in 1975. In the Certification Scheme, exporting countries certify domestic pharmaceutical companies as manufacturers of drugs that are authorized for the domestic market and with production facilities regularly checked for compliance with the WHO GMPs Act (Braithwaite and Drahos 2000).

In parallel, the European Free Trade Association (EFTA) introduced a Pharmaceutical Inspection Convention (PIC) in 1970. Members of PIC (EFTA but also non-EFTA countries) “reciprocally recognize inspections of pharmaceutical manufacturing plants based on exchange of inspection reports to ensure credibility, which includes compliance with the WHO GMPs Regulations” (Braithwaite and Drahos 2000: 377). This move made the EU the lead in the harmonization process of pharmaceutical regulation. A further extension of European pharmaceutical market was then done through bilateral agreements with the US, and Japan and from 1999, through the international harmonization of pharmaceutical regulation (International Conference on Harmonization, ICH).

The process of harmonization was not straightforward and easy as it is always the question of who has the power to persuade others and whose rules will be followed. In the 1980s, the US FDA was reluctant to join the EU and Japan in the harmonization process but

“[g]iven European dominance in the industry and Japanese agreement to cooperate, the US had little choice but to agree. Even then it hesitated. But after the US Pharmaceutical Manufacturers Association (PMA) commenced active collaboration, emphasizing the

dangers of exporting the US drug lag to the rest of the world, the FDA had to join the process to defend its position” (Braithwaite and Drahos 2000: 372).

To date a number of guidelines and standards have been harmonized via the ICH.⁸ The ICH stresses the advantages of uniform guidelines and mutual recognition agreements adopted by signatories that eliminate duplicative testing and documentation before marketing authorization in different countries, thus bringing public health benefits, decrease in regulation costs and speeding up the approval process.⁹

3. Good Manufacturing Practice (GMP) guidelines

GMP “is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization” (WHO 2004).

GMP guidelines represent minimal standards that are a necessary condition for marketing authorization. Drugs are considered to be adulterated, if GMPs are not met. GMP standards are, however, only guidelines and alternative processes and control mechanisms can be used under the condition that equivalent assurance is attained.

GMP guidelines typically comprise strong recommendations on quality management, personnel, production facilities and equipment, documentation and records, production and in-process controls, packaging and identification labelling, storage and distribution, laboratory controls, validation, complaints and recalls, and contract manufacturers.

The first version of GMP guidelines for manufacturing, processing, packing, or holding finished pharmaceuticals was introduced by US FDA in 1963 (Immel 2000). Four years later, the WHO version of GMPs was prepared by a group of consultants at the request of the Twentieth World Health Assembly (WHO 2004). From then, there were several amendments and extensions of

⁸ Braithwaite and Drahos (2000) mention that 19 trilateral guidelines were finalized by the ICH conference of 1995 and another 19 were to be finalized by the ICH conference of 1997.

⁹ Abraham and Reed (2001), however, argue that the harmonization process led to lower regulatory standards and traded drug safety, risk assessment and public health for the market expansion of the pharmaceutical industry.

the guidelines and many countries developed their own GMP guidelines which are based on the WHO guidelines:

- WHO GMP guidelines are primarily used by pharmaceutical regulators in developing countries; these are less strict than European or US GMP standards;
- International Conference on Harmonization, ICH-GMPs;
- EU-GMPs;
- FDA-GMPs;
- GMP standards in other countries such as Australia, Canada, Japan, Singapore, Russia¹⁰;
- International Organization for Standards (ISO);
- Pharmaceutical Inspection Cooperation Scheme (PICS) and
- common practices within the industry, license reviews, and crisis management control are also sources of GMPs (Grazal and Earl 1997).

In 1991, GMP standards were harmonized at the EU level (MHRA 2007). In 1999, the International Conference on Harmonization, a common project of the EU, Japan and the US, brought *GMPs for Active Pharmaceutical Ingredients*, which apply in signatory countries, the EU, Japan and the US, and also in other countries (e.g., Australia, Canada, Singapore).

The enforcement of GMPs rests on individual states: in the US, the responsibility is with the FDA; in the EU, with National Regulatory Agencies (e.g., MHRA in the UK); in Australia, with the Therapeutic Goods Administration; in India, with the Ministry of Health.

¹⁰ According to Mrazek and Fidler (2004) Russian GMP standards are even less stringent than the WHO GMP standards.

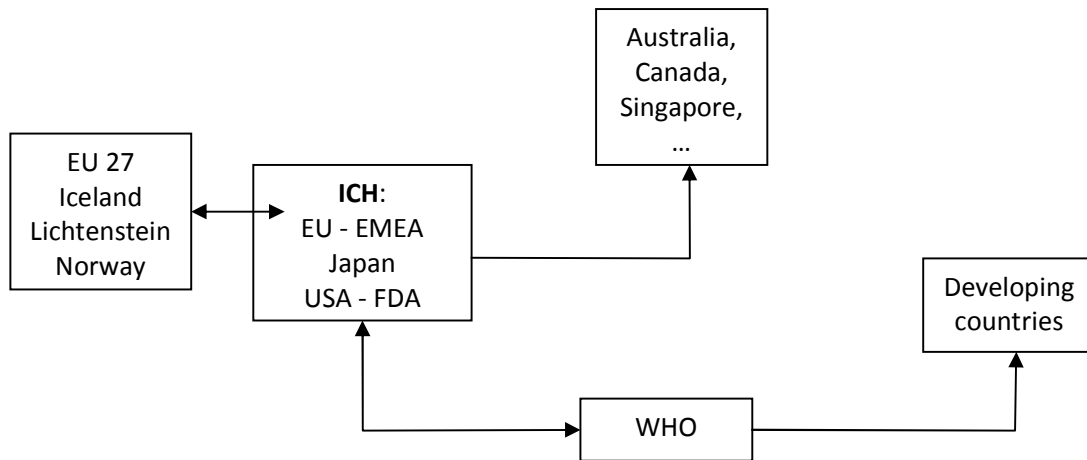


Figure 1: GMP development groups

The next subsections focus on individual national and supranational agencies, their procedures and relationships among them to see how GMP standards are inspected, recognized and enforced. GMP is not a low cost exercise, neither for pharmaceutical companies, nor for governments. Although the standards are guidelines rather than legally binding rules in practice they can be enforced in a number of ways including procurement of drugs in bulk by government bodies, NGOs or INGOs. For governments this means developing capacity to implement and enforce the regulation.

3.1 WHO

The WHO GMP guidelines, complemented with guidelines on the inspection of pharmaceutical producers, are primarily used in developing countries. These guidelines are, however, also embedded in GMP standards of developed countries, where they typically represent a subset in more detailed quality and safety assurance systems. Even in developing countries, these guidelines are often adjusted to local conditions and their implementation, inspections of manufacturing facilities, licensing, and enforcement is with government bodies of individual states. In India, for instance, the responsibility is with the Central Drugs Standard Control

Organization, Ministry of Health and Family Welfare. In Nepal, the national GMP guidelines are prepared and enforced by the Department of Drug Administration.

The WHO recommends several types of inspections of manufacturing facilities to check compliance with the GMP. These inspections are adjusted to specific situations (short description of these inspections can be found in Appendix: 33).

For all companies, controls should be regular and according to the WHO instructions, ideally on annual basis. For large companies, controls might be split into several smaller checks during a longer period such as validity of manufacturer's license or the GMP certificate. Although these frequencies are mentioned as ideal, and maybe exactly because of that, it is important to find out/estimate how far are these ideals from the reality and what the consequences of the gap between ideal standards and practice are for the quality of drug production in developing countries.

The WHO makes also suggestions on regulatory actions in the case of non-compliance. These include the requirement of correction of unsatisfactory situations, product recall and in extreme cases withholding the authorization and closure of a factory. The final decisions about corrective actions, however, depend on national regulation of individual states.

3.2 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

The ICH is a common project of regulatory authorities and representatives of pharmaceutical industries in EU, Japan and the US to discuss issues related to approval and marketing authorization of new medicinal products in these three regions. Namely, the six parties involved are the European Commission and the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare and the Japanese Pharmaceutical Manufacturers Association, the US FDA and the US Pharmaceutical Manufacturers Association. In addition to these principals, there are three observers representing non-ICH countries – WHO, the European Free Trade Association and Health Canada - and the international Federation of Pharmaceutical Manufacturers Associations provides a secretariat for the ICH.

The primary objective is to harmonize regulatory requirements related to quality, safety and efficacy of medicinal products and to support mutual recognitions by the three regulatory authorities. Mutual recognitions based on the exchange of data and assessment reports eliminate duplicative testing and inspection procedures and thus decrease costs of and speed up the introduction of new medicinal products to the markets.

Among other guidelines, the ICH harmonized those applying to human medicines, *Good manufacturing Practice Guide for Active Pharmaceutical Ingredients* (ICH Q7A) which were developed and recommended for adoption in the EU, Japan and the US in 2000. National regulatory authorities implement, monitor and enforce compliance with these standards, which are required for marketing authorization.

3.2.1 European Medicines Agency (EMA)

In Europe, there are three different legal frameworks for the registration of pharmaceutical products as established by the EU: Centralized Procedure, Decentralized Procedure, and Mutual Recognition Procedure. The Centralized Procedure for the approval of drugs, coordinated by the EMA, is mandatory for biotechnology and other high technology products, orphan drugs, and new active substances not previously authorized in the EU and which are for the treatment of HIV/AIDS, cancer, and diabetes or neurodegenerative disorders. The Decentralized Procedure is carried out by the authorization agency of the state in which the pharmaceutical manufacturer seeks the marketing approval for its product. Through Mutual Recognition Procedure then, this manufacturer can apply for the marketing authorization in other EU member states. In such a case, the first country authorizing the concerned product has to produce a detailed assessment report which is circulated to the other member states.

In this section we overview the centralized procedure and other activities of the EMA and then focus on one national authorization agency in the EU, the UK Medicines and Healthcare products Regulatory Agency.

The EMEA was established by a Directive EC 2309/93¹¹ and in operation since 1995 as a decentralized agency of the EU. Its main responsibilities concern the scientific evaluation of applications for marketing authorization of medicinal products and monitoring the safety of medicines in the EU. In contrast to the US FDA, the EMEA works as a scientific body that draws on resources of national regulatory authorities. It does not have any executive power. Its evaluations are submitted to the EC which issues the marketing approval or decides about the withdrawal of specific products from the market. The EMEA complements activities of national authorization agencies and also serves as an umbrella organization of these national bodies. The agency facilitates the exchange of information on GMP certificates via EudraGMP database and on safety of authorized products via EudraVigilance reporting system (more details are available in Appendix: 34).

For marketing authorizations granted under the centralized procedure in the EU, initial inspection is carried out under contract to the EMEA. The first inspection is typically carried out by the Supervisory Authority concerned, i.e. the Member State in which the product is to be made or imported. Subsequent inspections are normally carried out routinely by the same authority although there is provision for one Member State to inspect in non-Member States on behalf of another (MHRA 2007).

The EC negotiates Mutual Recognition Arrangements (MRAs) between the Community and third countries, which include mutual recognition of standards of GMP and arrangements to ensure compliance by pharmaceutical manufacturers. “Under an MRA, the Regulatory Authorities accept each other’s Inspection Reports and routine inspections by one authority of manufacturers in the other’s territory is not required. In addition, the re-testing of imported products are normally not required” (MHRA 2007).

Regarding the inspection of facilities in third countries, it is not clear whether the inspection focuses only on a specific drug or drug group that is to be marketed in the EU or whether GMP certifications of plants are also granted. According to MHRA, inspections are drug related but

¹¹ Originally named as the European Agency for the Evaluation of Medicinal products and renamed as European Medicines Agency in 2004.

Indian companies usually assert that they have EU certified facilities. This is an issue that needs to be followed up.

3.2.1.1 UK - Medicines and Healthcare products Regulatory Agency (MHRA)

The MHRA is an executive body of the Ministry of Health. It assesses quality, safety and efficacy of medicines and authorises them for marketing in the UK. It also carries out post-marketing surveillance and regulates clinical trials for medicines and medical devices.

The MHRA has five inspectorates that monitor the compliance of pharmaceutical companies with the UK and EU regulation. These are Good Clinical Practice, Good Distribution Practice, Good Laboratory Practice, Good Manufacturing Practice, and Good Pharmacovigilance Practice Inspectorates.

Compliance with GMP and GDP standards by all holders of and applicants for manufacturer's and wholesaler's licences in the UK is required by MHRA. The inspections follow the EU Directive for medicinal products for human use. 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002' contain details on this directive and guidance on its implementation. (MHRA 2007)

The MHRA carries out inspections of all applicants for manufacturer's or wholesaler's licence and then periodically during the life of that licence with the maximum interval of 2 years for manufacturers and 3 years for wholesalers and for overseas manufacturers. Note, that the UK Medicines Inspectorate does not licence overseas manufacturing sites but inspections, pre-arranged or unannounced, are carried out only for specific marketing authorisations and focus on a product to be imported to the UK. In this case standards applied must be the same as those valid in the UK.

The UK Inspectorate currently carries out regular inspections in a number of countries, including USA, India, China and Japan both in connection with national requirements and on behalf of the European Medicines Agency (EMA).

3.2.2 USA - Food and Drug Administration (FDA)

Activities of the FDA are much broader than activities of the EMEA and the MHRA in that it focuses on protection of health in general and regulates food, drugs, medical devices, biologics, animal feed and drugs, cosmetics and also radiation-emitting products. Within these areas, however, its roles are similar to the EMEA and the MHRA. The FDA assesses new products, approves their marketing and operates post-marketing surveillance. In addition, the FDA has an executive power and can directly sanction non-compliance with GMP standards or violation of other types of pharmaceutical regulation.

FDA uses term 'current GMP' (cGMP) to emphasize that manufacturers have to employ up-to-date technologies and systems in order to comply with the regulation. FDA cGMPs incorporate the ICH Q7A guidance for active pharmaceutical ingredients. In 2002 the FDA adopted systems approach for its inspections (the list of systems that are included is provided in Appendix: 34).

For the inspection of a specific system, several types of APIs that use this process/system should be selected for proper check of the system. Thus, the structure of inspections differs from the one applied by the MHRA in the UK.

In the case of foreign manufacturers, inspections cover only APIs that are to be marketed or already marketed in the US. There are special reporting instructions for foreign producers. Centre for Drug Evaluation and Research's Office of Compliance, Foreign Inspection Team receives and evaluates all inspection reports and maintains a complete file for each foreign drug production facility.

3.3 GMPs in developing countries

While focusing on pharmaceutical industry and market in India and Nepal, we can see two different effects GMP standards have on local industries. The first one is an attempt to acquire GMP certificates on the black markets and it would be interesting to study the effect of such companies on competition in the pharmaceutical market. The other impact is the creation of barriers to entry and/or to growth of domestic drug manufacturers (pushing smaller companies that cannot afford the upgrade to the higher standards out of the market).

Indian pharmaceutical industry is more developed than the Nepali one with significant export not only to less developed countries but also to developed markets. Several Indian companies have already overgrown into MNCs with manufacturing and marketing activities abroad. These companies, in order to reach foreign markets, had to upgrade their production facilities to standards of developed countries long before similar standards were required by Indian regulatory bodies. Thanks to their scale, these companies do not have any difficulties to meet continuously increasing standards. The process of strengthening of requirements in India, and other less developed countries, creates a pressure on smaller companies that focus on domestic markets. Although it is impossible to separate effects of the recent changes including TRIPS, intensified competition and more stringent GMP standards, it is not surprising that these factors accorded in their impact on Indian pharmaceutical industry and resulted in its consolidation.

In Nepal, pharmaceutical companies are much smaller and less advanced technologically. Nepali pharmaceutical market is small, especially when compared to its Indian and Chinese neighbor. Due to its small size, production of many drugs is not profitable for Nepali pharmaceutical industry and with high quality requirements on exports represented by GMPs, it is almost impossible to compete with MNCs and Indian and Chinese pharmaceutical giants. Here, the imposition and strict enforcement of GMPs might lead to significant barriers to growth of domestic companies.

In the present version of the paper we focus only on Nepal. We look at how government representatives and pharmaceutical producers perceive and respond to requirements to implement and enforce GMP standards. A few notes on Indian regulatory authorities and GMP standards are provided in Appendix: 35.

3.3.1 Nepal

These notes from Nepal and issues of GMP certification are tentative and derived from initial interviews and ethnographic research by the Nepal research team. They are reproduced here to provoke discussion and pointers for possible future avenues of inquiry.

Allopathic medicine in Nepal has a relatively recent history in the context of Nepal, introduced around 1860 with the first hospital being the Kathmandu Bir hospital built in 1890. The limited supply of medicines to Nepal was via India (and the British Embassy for the elite; Interview, Kathmandu University, April 2007) until the first “people’s movement” of 1950. From this period was started the more systematic development of the health sector. Nepal started to manufacture its own drugs from the 1950s, focusing initially on medicinal plants and herbal forms and was located under the Ministry of Forests. The Royal Drugs Laboratory was set up as a pilot in 1965, and then converted to Royal Drugs Limited (RDL) in 1972 the first production unit in Nepal (Interview, APPON, Kathmandu, December 2006). The first private company, Chemidrug Industries Pvt. Ltd. was opened in 1971 (Interview, Kathmandu University, April 2007). The drug Act of 1978 resulted in the Department of Drug Administration (DDA) being set up in 1979 (still part of the ministry of forests). Precursors to the Drug Act included the Black Marketing & Other Social Offences Act, 2032 BS (1975), and the Drug Abuse Control Act, 2033 BS (1976).¹² By 1979 there were two Nepalese companies but around 1000 Indian ones; Nepal was an extension of the Indian market. It wasn’t till after the late 1980s, however, that the nascent Nepalese industry started to mushroom. Relocated to a part of the Ministry of Health, the DDA has overseen this growth of the Nepal Pharmaceutical industry to its current size of 45 registered Nepali companies, and been responsible for the regulation of the industry. Currently the DDA is located in Babar Mahal (no where near the ministry of health), behind which is found the National Medicines Laboratory (till recently known as the Royal Drugs Research Laboratory), also established as a part of this act.

The objectives of the DDA are as follows:

“to regulate all functions relating drug like misuse and abuse of drugs and its raw materials, to stop false and misleading advertisement and make available safe, efficacious and quality drug to the general public by controlling the production, marketing, distribution, sale, export-import, storage and use of drugs” (DDA 2007).

The strategies to do this include:

“Selection of essential drug to promote rational use of drugs; Establishment of regional offices at all five regions for effective decentralization: Strengthening of National Medicine Laboratory as an Independent National Drug Control Laboratory; Drug

¹² See Dixit (2000) for a full list of all the Acts pertaining to health, and their development in the context of Nepal.

Registration on scientific facts; Promotion of rational drug use; Development of an efficient drug information system to disseminate the relevant information; Encouragement to promote and establish pharmaceutical industries to achieve self-reliance in the production of essential drugs; Effective inspection to ensure the quality of marketed products; Prevent misuse of antibiotic to combat antimicrobial resistance; Strengthen national industry to comply with WHO-GMP" (DDA 2007).

Since 1984 the DDA has its own code of manufacturing practice, which is written in Nepali and published along with the WHO GMP code of practice (in English). The WHO GMP code was revised and published in 1998, and despite the WHO revising their GMP codes in 2003, this part has not been updated in the DDA's publication. We were told by a senior drug administrator that the DDA is in process of publishing a new code as the 1984 DDA code does not explain certain things clearly; for example, it is written in the code that fresh air is necessary while producing drugs but it does not explain what is meant by "fresh air." When asked about overlap between the DDA code and WHO GMP code, he replied in vague terms, saying that most of the WHO GMP standards are incorporated in the DDA code (Conversation, senior drug administrator, DDA, June 2007).

From the 1990s the DDA made the upgrading of facilities to WHO prescribed GMP standards mandatory. The deadline was set for April 2007, but to date only eight companies have managed this. The current director of the DDA described that the WHO GMP certification for Nepali companies remains "optional" at present, with the DDA's own Code on Manufacturing of Drugs the only legally binding requirement. In our first interview with senior DDA officials, we were told the following regulations have been developed:

1. Drug registration regulations
2. Drug standard regulation
3. Drug Inquiry and Inspection Regulation
4. Drug manufacturing code.

The essential drug list was first produced in 1986; updated in 1992, 1997, and the last update 2002. The Drug Bulletin of Nepal (DBN) was first published in Nepal in 1992, and has a series of

editorials on regulation, GMP, spurious and fake drugs and the other issues affecting the Nepal pharmaceutical industry. Lists of registered companies are published as well as banned drugs and combinations. Currently their print run is 7,000 copies and they distribute to all the pharma companies, associations, ministries and hospitals as well as to retailers and wholesalers via their associations. Also in the DDA are available copies of the Nepalese National Formulary, the June 2000 “Standards for Pharmaceutical Regulation and Care”, the National Drug Policy 1995, The National List of Essential Drugs Nepal (third revision, 2002), and the November 2005 Draft of “National Good Pharmacy Practice Guidelines”.

GMP certification was described to us by the DDA as necessary only for export, although the WHO does inspect for drugs and products linked to their “own purposes” (for example vaccination programmes, TB drugs for DOTS, ARVs etc.). The WHO role is mainly indirect, through the DDA. While the Association of Pharmaceutical Producers of Nepal (APPON) are supposed to be assisting with this process, and doing trainings around GMP they are deemed by many to be of little help (as one company director stated: “they take our money and drink whisky”!). They have a volunteer pharmacist from Japan currently helping them with this process of developing guidelines and trainings. APPON is currently more involved in lobbying for dollar rates for imports from India and regulating that all foreign imports should have their batches labelled in Nepali (that is in protecting the interests of the Nepali manufacturers).

3.3.1.1 GMP issues

The director of the DDA described the GMP certification process as part of the Essential Drugs and Medicines Programme. The DDA conducted the initial training in country, with support from the WHO which is “technical and financial”. However, the difficulties they face in implementing the GMP process were described to us as three fold. Firstly, the staff issues and their lack of expertise; this is not only DDA staffing problems (they have only five staff members who check that rules are being followed), but the lack of expertise in the company staff. While there are increasing numbers of graduates now coming out of the universities, to date they have little experience. Secondly there are difficulties with the concept itself. Some manufacturers say that they already sell well, so why do they need GMP? They have a “market perspective”, and as their drugs pass their own product tests, why do they need it? They complain about the

investments required for upgrading when they see little benefit. Thirdly, the GMP concepts themselves are changing and becoming more stringent. The DDA is responsible for the evaluation of the company GMP certification and for giving the certificate, and no-one from the WHO comes to evaluate this.

One group of senior management workers for one of the GMP certified companies explained that there was flexibility in the timings of the implementation because of the recent difficulties in Nepal – the recent political environment, with strikes and other industry problems. Others described the sheer production of paperwork required for monitoring as overwhelming, besides the prohibitive costs. The director of NPL said that initially their production dropped after implementing GMP standards. They used to have “quality control”, but now this has shifted to “quality assurance” with greater stringency. This shift was described to us by another company’s senior manager as follows:

“Quality control is not in common use now. We call it quality assurance. Before while checking quality, they used to check at the end. But now they say that if we check it right from the beginning then quality is assured right from the beginning. The quality of excipient, whether the raw material is mixed properly or not, whether it is weighed properly or not, coating, punching, if everything is done properly, all this is checked. This is called SOP” (Interview, Kathmandu, 20 April 2007).

We were further told that the concepts themselves have changed a lot since NPL started to implement them, like for example the AHU (air handling units) which are stricter, or the use of “reverse osmosis” having replaced “demineralisers” for the water they use. The costs to run these new units have increased as well, and the size of the backup generators required to keep manufacturing standards up with the regular power cuts have increased.

CTL pharmaceuticals have recently upgraded to GMP certification standards. The director of the company told us that the initial cost outlay had been 4 crore rupees. This had spun them from a profit making business into one with large debts. An ex-employee of Royal Drugs stated that there was no way that this company could afford to upgrade to GMP standards. One particular complaint was that despite this initial outlay, the Nepal market was small and it would be

difficult to recruit costs (the size of the Nepal market is stated to us a particular difficulty for Nepal to develop its own injectables; the market is just too small). Not one person we have spoken to in the business thinks of export as a possibility, all concentrating on the Nepal market. We have heard repeatedly the attempt by NPL (a GMP certified company) to export to India as the cautionary tale; the first batch was held in customs on the border with India as samples were sent to Lucknow for quality control checks. All the drugs expired in the interim and had to be destroyed.

This is how the GMP process was described to us by senior CTL staff:

“What WHO/GMP is that, the WHO has defined, a set of rules, how it is to be done and what all is to be done. All these checklists should be in a recorded form. Like where have raw materials come from, and then these raw materials have to be checked in QC, that is quality control lab. Now even the packaging material is kept under surveillance for 24 hours. If there won't be any growth of bacteria, fungus etc then it is cleared. Then only it is sent from ware house to storeroom. This is also recorded. In WHO/GMP, it should be recorded that this raw material has come, checked, verified, ok, or rejected. Then there are labels: yellow, green and red. First all raw materials have yellow label, which means that it has just arrived. Then it is sent to lab. If it is verified then it is labelled as green and it is sent inside. If the material is rejected then it is labelled as red and is kept outside and returned to the one who had supplied these raw materials. Even the packaging materials like carton, bottles, caps, stripes, files etc are kept in a quarantine area. After 24 hours of surveillance, it is sent to store. This is also recorded. Now after it is sent to store there are two areas: one is grey area and another is black area... (he went on to describe the parameters for batch weight, that the individual's names responsible are recorded, and the percentage variation allowed)... And if it differs then we can find out exactly where the problem was. This we call SOP, standard operation procedure. This is also under WHO guideline. And then finally after this, the thickness, diameter, hardness is checked. After it is ready, it goes to grey area for secondary packaging. For primary packaging like putting it in a bottle or stripes, it is done in black area. Now to pack this in cartons etc it goes to grey area (Interview, Kathmandu, 20 April 2007).

Proud of their capacity to do so, and the new facilities, we were shown around these. Their director and marketing manager talked of commitment to ethical practice, and gaining GMP certification was a part of this. After a tour of the production facilities, we were told by the production management team that GMP certification considers many elements: the premises; personnel; quality control; production; sanitation and hygiene and finally, documentation. As they phrased it all the GMP process “should be done per documentation and documented”¹³. Each and every activity is prescribed in detail through Standard Operating Procedures (SOPs), which are strategically displayed in Nepali and English throughout the site. The DDA was described as responsible for the guidelines that are set up for this end, and then responsible for their implantation.

In a conversation with a senior pharmacology professor, he referred to the problem in Nepal as one of quality versus cost. He referred to amoxicillin, which is now produced by nearly all the Nepali companies. It costs around 4-5 rupees, but if you find it for less than this then in his opinion the quality must be compromised. He reckoned that the current director at the DDA is good at his job, and working hard at trying to keep prices low while maintaining quality; he is working at trying to get GMP certification implemented. It is difficult, he said, as smaller companies used to send “goondas” around to him to ask why GMP is being put into place. They said that it is driving up their costs and the prices of affordable medicines. It is tension between cost and quality. The current DDA director is an advocate of uniformity of price for generics, we were told but currently apart from Paracetamol, which the government has capped the price of, the industry decides on the prices of drugs.

As one wholesaler pointed out to us, the stringent regulations demanded by GMP certification has resulted in some Indian companies being unable to import their products, and their products not being re-registered by the DDA. As it was phrased to us: “It didn’t send some papers so it is not found in Nepal’s market” (Interview, wholesaler, Kathmandu, 12 April 2007). The wholesaler in question wanted the particular product, but the company said that they were now unable to get the product past customs. As another example, the producer of “strepsils”

¹³ Ian Harper and Samita Bhattarai visit to CTL Pharmaceuticals, April 2007.

(BOOTS) entered into a contract with a Nepali company to make this in Nepal, but because the company does not have GMP certification Strepsils are no longer available on the Nepal market.

Does GMP signal high quality?

Despite some companies having GMP certification, some of those we interviewed remained unconvinced that this improves quality of drugs. For example, the pharmacist responsible for the pharmacy at Dhulikhel hospital in Kavre district took down a bottle of paediatric amoxicillin (PERIMOX) made by Deurali-Janata Pharmaceuticals, a Nepali company with GMP certification. He pointed out that the marker to fill to was on the label not on the bottle, that the sticker was put on by non professionals, that there is no child proof top, and that the measuring top, made of plastic are not always correct. Would you give this product GMP certification he asked rhetorically? He then brought down a bottle from Sandip (which had been given as a donation to the hospital). The line was marked in the glass, there was a child proof top, and every ingredient was mentioned on the label (not just the active ingredient). Nepali companies have not yet “matured” he said. He said that he likes to say that “pharmaceutical companies kill more people than Bin Laden!” When asked how the company could have received GMP certification he just shrugged. As a consequence, when a Medical Representative comes to him suggesting they buy that companies product, he does not trust the quality of the product based on whether they are certified or not, but has the products independently checked. This lack of trust extends to the rifampicin supplied by the government in the DOTS programme. He “doesn’t believe” in the government purchased rifampicin. When I mentioned the new global procurement system, requiring GMP certified quality, he still insisted that Lupin would be getting lots of commission and he doesn’t trust their products either. He has clinical evidence from this hospital that the drugs provided by the DOTS programme don’t work he told us. Such is his mistrust of the system, that he based his opinion of the efficacy of drugs from his own empirical relationship with treatment outcomes, stating that the CTL rifampicin is OK in his opinion and advises those patients who can afford it to buy their TB drugs privately.

A pharmacist who works in the privately owned pharmacy in the Maternity Hospital explains the registration process with the DDA for a new drug (Interview, pharmacist, Kathmandu, 9 April 2007):

SD: In Nepal, what happens is that, whenever a pharma company has to produce a certain product, it has to register itself in the DDA to get a manufacturing license. And then to manufacture the products it has to register the product in the DDA. But first they have to get a license for the “industry” (here he means company). Firstly they have to register the “industry”. Then after that the surveillance will be done by the DDA. After the approval of DDA they get the manufacturing license. Then they proceed with it. Then they have to give foil details. They need to print manufacturing license on this foil.

IH: So they can't sell it without this?

SD: They can't. After this, the DDA again check everything and then only the product can be brought into the market. After this they are allowed to make trials (He meant raw materials trials here). First they are allowed to import the raw materials. If it is a controlled drug then they are allowed to import a limited amount. After they receive these controlled/narcotic substances then they are supposed to report to the DDA that they have received this much amount of this drug. Then they do successive trials (trials of raw materials) until they get the good formulation. After having the formulation, they pack the drug and send it to RDRL (NB Royal Drugs Reference Laboratory), which is just behind the DDA. There they check the quality and see if the drug has met the criteria. Since we don't have our own Nepalese Pharmacopoeia, we solely rely on Indian pharmacopoeia or British Pharmacopoeia... A Pharmacopoeia tells you how to manufacture a drug, what are the criteria for manufacturing a drug. For example, if you have to make a tablet then, what are the raw materials necessary, what analysis must raw materials pass through, to be included in the formulation etc.? The Pharmacopoeia gives a series of rules and tests that has to be carried on raw materials. And after that you can carry on to make a drug. Even after making a drug, it has to pass through a series of tests before it can come to the market. If you refer to the Indian pharmacopoeia in the beginning then all these stages must comply to the Indian pharmacopoeia throughout. If they fail to do that then the whole batch would fail. It cannot come to the market. So the RDRL after checking everything qualifies... Then the industry submits the RDRL report and the drug sample to the DDA for the product

license. After getting the production license, they produce it and then they send it to the market.

From an interview with one wholesaler, his experience is that some doctors are now only prescribing GMP certified company products as a way of ensuring quality. He suggested that this was the case even with those commonly prescribed drugs produced in Nepal (e.g., Amoxicillin). The question of doctors and prescribers trusting certain brands over others is a complex one, particularly in the generic market. For example, with Fluoxetine we have been told that residents at the teaching hospital are taught to prescribe the drugs from companies they trust, not write the generic name on prescriptions. Given that the practice of “substitution” by retailers is common place, particularly outside hospitals, and that many medical representatives for drug companies pay substantial incentives for doctors to prescribe their products there are a number of issues at stake here.

Did Drugs Nepal stop producing rifampicin because of the stipulation of GMP certification?

This information comes from an interview with the current director of APPON, KK, who worked for Royal Drugs Nepal, and was responsible for the production of Rifampicin in the 1990s for the National Tuberculosis Programme. This was prior to the development of the WHO global procurement mechanism the Global Drug Facility (GDF), through which Nepal is currently supplied its anti-tuberculous drugs (purchased initially by DfID, then the Global Fund). It addresses how quality control was dealt with in relationship with Japanese support, prior to GMP certification in Nepal (notes were taken during the interview so this is a summary of what he said, not direct quotation):

“Royal Drugs produced 150 and 450 mg tablets for the Nepal Tuberculosis Centre (NTC). This production started, he thinks, in 1990 (NB - Ian: I think it was later than this). There was a campaign in TB management called DOTS, a “WHO slogan”. On this ground the Japanese Government wanted to help the NTC, by providing the medicines. They supplied the capsules for one year, and these were made in Japan. Dr Bam (who was then the Director of the NTC) asked why they could not buy from Nepal? It would be cheaper and they could sustain the supply. A group from the Japanese Pharmaceutical

Manufacturers Association (JPMA) came to Nepal, and with some people from JICA they visited Royal Drugs. At this time KK was chief of the Capsule Section. The machinery they had for capsule production was manually operated and they did not have the capacity to produce the required amount. The group were interested and said OK, but they said that you need to make a plan. The new machine would require a new chamber as it wouldn't fit in the existing one. The manager said that if they assure supply then they would build the new section. KK then designed it. The WHO also came as well to look at GMP standards and he designed it according to these norms. If I visit Royal Drugs today he said I would still find this rifampicin section.

“The JPMA expert came and stayed at this time for one month. KK was delighted and he learnt much at this time. For example, say you have a batch of drugs, Batch 1 he explained. This is then divided into Lot A, Lot B, Lot C, Lot D. If the machine produces one batch then this is 200kg (4 X 50 kg Lots). The JPMA expert said take 5g from each lot, mix them up and test this for quality. If it passes then Batch 1 passes. They did this for each batch that they produced. In this way they produced the first six batches and for each batch they sent a sample like this to Japan for testing, and Royal Drugs also tested them. Six batches made up about 3 months supply for the national programme. They also had to send this quality report to Japan as well; they read these closely and then they said that both the tests they did, and the RD tests were OK. For 4-5 years they supplied the NTC with these drugs.

“The first lot of active ingredients came from Japan directly to the NTC. Then for the first year that RD made the rifampicin the raw materials came from Japan as well – they were then confident with the quality of the product. The capsules came from India or Thailand. For the active ingredient, Japanese labour costs were high and so the raw materials were expensive. They asked RD if they could buy the raw materials themselves. RD then bought this from China and Hong Kong, as they were on the WHO approved list. But if a company was new, they would test the active ingredients themselves. This is “vendor management”, and while they don't visit the company itself, they test the product. One benefit was that they could buy in dollars from China, which meant less excise duty. This was more if it was bought with rupees, be that either Nepali

or Indian. RD got the raw materials from China for an initial two year contract, and procured from there for a total of five years. After this time the management of Royal Drugs changed and that of NTC changed as well, and no one wanted Royal Drugs to produce the rifampicin capsules anymore. He thinks that some other company probably provided “in the pocket” some incentives to the NTC.

In response to direct questioning if this was related to the GDF, and GMP certification, he replied that he did not know about that but thinks it was related to bribery that they lost the contract. The change of management is the cause - then you lose your personal connections. No-one remembers the history after a while. It was only in 2002 when the DDA has given the mandate that every company has to have GMP certification by 2007. At the time when they were producing rifampicin it was not mandatory, so that was not the reason in his opinion. I asked if this had anything to do with DfID buying the drugs, after JICA stopped and if they had different rules about quality, and he replied that JICA were happy with the quality, but he does not know about DfID.

Government regulation currently states that any tender for the government procurement of drugs must be accompanied by the appropriate paperwork, which includes GMP certification. Despite this, and that the old state run Nepal Drugs (ND) doesn't have GMP certification, contracts for public procurement are awarded as a priority to ND (this is described in more detail in the Nepal drug distribution paper).

An example of “the politics of GMP”

In a conversation with a senior advisor to the Ministry of Health, IH was told the following in relation to the politics of GMP. The J-Vaccine (for Japanese Encephalitis) for Nepal was paid for by Japan and procured from a company in China, but this was not GMP certified. This year (2007) they could not buy it, despite Japan saying they were happy with the quality and willing to give the money. But the money was not given directly to the Nepal government, but to UNICEF, and they were unable to buy it to then gift to the government because it was not GMP certified. The manufacturer has not yet applied for GMP certification. The WHO, or other UN agencies, cannot procure any drugs without GMP certification. While this example is suggestive

of some of the issues at stake with GMP certification in a heavily aid dependent state like Nepal, it needs to be followed up in more detail.

Getting around registration: DTCs?

Some (private) hospitals have established Drugs and Therapeutics Committees (DTC). For example the Norvic hospital director explained that their committee – established in February 2006 - allows them to procure from any part of the world, even if that drug is not licensed in Nepal with the DDA. He explained that the DTC formation has been encouraged by the DDA who “don’t have physicians”, although the government says what the makeup of the committee should be. The DTC then can “import” medicines not registered, for example important drugs for their hospital cardiac medicines (the hospital specialised initially in cardiology – and has expanded from that). They have to produce “documents” – studies and outcomes from these drugs. Thus they are able to provide data for later registration.

A recent communication in the Kathmandu University Medical Journal suggested that these committees have a supportive function for the DDA: “In developing countries like Nepal, where the pharmacovigilance programs are in its primitive stage, the DTC has immense responsibility in ensuring drug safety. This committee can also act as an advisory committee to the policy makers and drug regulatory authority of Nepal for drug safety matters based on their experiences” (Palaian and Mishra 2005).

GMP and export

No Nepali company yet exports any pharmaceutical product. However, GMP certification is also required for Ayurvedic products. In an article on the WTO website (Shakya 2005), on the experience of a Nepali Ayurvedic company (Gorkha Ayurved Co.) to export medicinal herbs, the author expresses surprise that they required GMP certification. The company had no idea that this was necessary (or that buyers could also ask for other internationally harmonised standard of Sanitary and Phytosanitary Measures (SPS). When the company set about the process of heading towards GMP certification, they found the RDRL (and the Department for Food Technology and Quality Control – DFTQC) “without any plan of policy regarding SPS standards,

including GMP certification procedures”, particularly for Ayurvedic products (Shakya 2005). Although acceding to the WTO, it seems that there were few attempts to strengthen the institutional capacity to practically develop this. The company had no idea that the DDA had already called for all pharmaceutical companies (including Herbal ones) to abide to WHO GMP certification, as a prerequisite for the SPS mechanism. Shakya is critical that the DDA had not prepared itself for accreditation processes, nor determined the basic mechanisms that companies should take. Businesses were pretty much on their own, suggests the author. The company had huge outlays, including hiring a foreign expert to assist in the process.

It seems apparent that one consequence of attempting to harmonise its regulatory capacity will be a greater dependence on foreign assistance (both technical and financial) for this process.

4. Discussion and further questions

Although TRIPS agreement is presented as the main threat for drug availability and affordability in developing countries, our preliminary research highlights how domestic producers find compliance with ever more stringent GMP standards a major obstacle for domestic production of affordable pharmaceutical products. Most major classes of drugs are now off patent and so while TRIPS affects future production of new products, GMP affects generic compounds.

From what we have learnt so far, compliance with GMP standards is an important barrier to entry, sustainability and possibly, market expansion for small drug producers in both Nepal and India. In Nepal, the main preoccupation of local producers is production for domestic markets. Companies do not aim to export their pharmaceutical products; they merely strive to secure their position on the Nepali pharmaceutical market. National health programmes are dependent on international aid, financial and in kind, and bulk drug procurement usually bypasses national government and is processed by international agencies such as the Global Drug Facility. Given that such agencies rely on large and GMP certified pharmaceutical manufacturers, Nepali companies do not have access to significant part of the domestic market which restricts their possibilities to recoup costs of investments when products are tied to stringent quality assurance systems.

We do not question the importance of quality controls. The issue rather seems to be about how much quality assurance at each production and distribution stage is really required and what are the costs of these marginal controls to pharmaceuticals manufacturers in developing countries. Further areas for future research are outlined below.

We need to examine the capacity of regulatory authorities in developing countries to develop, monitor and enforce manufacturing standards: staff, in terms of numbers and expertise, and financial resources.

It would be useful to look from the producers' perspective, at the cost of compliance with GMP standards and how it is reflected in price. How much does it cost to introduce quality assurance systems? How costly is the training of staff necessary for implementation of these new systems? What are the fees for auditing and GMP certificates? How are GMP certificates issued and paid for?

Another series of questions refers to how actors in domestic markets perceive GMP certification. Do distributors and retailers require GMP certificates from manufacturers to be sure about product quality? Is GMP certificate a sufficient proof of quality? An ethnographic question here relates to the *symbolic* impact of GMP certification, and how ideas around it circulate amongst various actors in the system. How has GMP certification fed into perceptions of quality and trust of particular companies' products, and how does it feed into how doctors, retailers, wholesalers and others perceive quality?

It would be useful to understand the strategies which are being adopted to overcome GMP regulation and how effective these are from the producer perspective? We also need to talk to the standard setters in the West to understand the standard setting process. What are the issues that these setters of standards perceive to be at stake in countries such as India and Nepal?

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Appendix

A.1. WHO – types of inspections

Routine inspections are full inspections of all components of GMP that are carried out when the producer is newly established, has introduced new products, applied for the renewal of license, has not been inspected in the last 3-5 years, or if there is a record of non-compliance. In contrast, concise inspections focus only on selected indicators and identification of significant changes. They are applied if there is a record of compliance with GMP standards. Follow-up inspections are designed to check whether corrective actions recommended at the previous inspections were successfully implemented. Special inspections are carried out if there are any complaints or recalls related to substandard quality of products or in case of adverse drug reactions and can be focused on a specific product, group of products, or operation. The last type of inspections, quality systems reviews, describes a quality assurance system that has been satisfactorily implemented and manufacturer's policy for quality assurance.

Announced inspections are recommended for regular visits to evaluate new plants, products, renewal of license. Unannounced inspections are required for concise, follow-up, and special visits. Such inspections and/or their variations are recommended and employed also by regulatory authorities in developed countries.

A.2 EMEA activities

From May 2007, the EMEA administers a Community GMP Database, EudraGMP, which aims “to facilitate the exchange of information on compliance with good manufacturing practice within the European medicines network” (EMEA, 01 May 2007). The database is open only to EC, EMEA and national medicines agencies (EU member states, Iceland, Lichtenstein and Norway) and it contains information on all manufacturing and importation authorizations and all GMP certificates issued by the national medicines agencies within the network and also reports on deficiencies encountered during inspections conducted within the network or in third countries.

Within the EMEA, the Committee for Medicinal Products for Human Use (CHMP) coordinates the centralized procedures, arbitrates in cases when member states do not agree on marketing authorization of a specific product, and acts in cases when public health is at stake. The centralized review process works through a network of European experts from 27 EU member states and three EEA-EFTA states, Iceland, Lichtenstein and Norway.

The CHMP also monitors safety of authorized products via the reporting system, EudraVigilance, and makes recommendations to the EC if any changes in marketing authorization of specific products or product’s withdrawal from the market are necessary (EMEA, 2007).

GMP guidelines for medicinal products are stated in Directive 2003/94/EC and have two parts: one applicable to the manufacture of medicinal products and one covers GMP for active substances used as starting materials (EMEA web, 2007). It is the second part that is based on ICH Q7A guidelines on active pharmaceutical ingredients. The EU Guidelines also include a number of specific and detailed annexes focusing on particular activities.

A.3 US FDA – system approach

In 2002 the FDA adopted systems approach for its inspections, meaning that the following systems (ICH Q7A references) need to be audited:

- quality (Quality Management, Change Control, Rejection and Reuse of Materials, Complaints and Recalls, Contract Manufacturers),
- facilities and equipment (buildings and Facilities, Process Equipment, Documentation and Records),
- material (Materials Management, Storage and Distribution, Water, Documentation and Records),
- production (Documentation and Records, Production and In-Process controls, Validation, Specific Guidance for APIs Manufactures by Cell Culture/Fermentation),
- packaging and labelling (packaging and Identification Labelling of APIs and Intermediates, Agents, Brokers, Traders, Distributors, Repackers, and Relabellers) and

- laboratory control system (Laboratory Controls, Documentation and Records, Validation).

ICH Q7A sections on personnel, Documentation and Records apply to all systems.

FDA inspections are of two types. Surveillance inspection is a routine inspection of manufacturing facilities. Compliance inspections are for-cause controls or follow a violative surveillance inspection to verify corrective actions taken.

Inspection approaches applied by FDA include

- full inspection option which is a broad and in-depth evaluation of compliance with the Quality System and at least three other systems (could be both surveillance and compliance inspection)
- abbreviated inspection option – provides an update on manufacturer's conformity with cGMPs and it includes an inspection of the Quality system and at least one other system but altogether not more than three systems (could be also both surveillance and compliance inspection)
- compliance inspection.

A.4 India: Pharmaceutical regulation and GMP standards

General information about drug regulatory requirements are provided by the Central Drugs Standard Control Organization, Ministry of Health and Family Welfare. The production, import, distribution and sale of pharmaceuticals is regulated by the Drugs and Cosmetics Act, 1940. This act has several schedules that apply to pharmaceutical industry:

- Schedule M - specifies the general and specific requirements for factory premises and materials, plant and equipment and minimum recommended areas for basic installation for certain categories of drugs;
- Schedule T - GMP specifications for manufacture of Ayurvedic, Siddha and Unani medicines;
- Schedule Y - clinical trials legislative requirements;
- GCP guidelines for research in human subjects, based on Declaration of Helsinki, WHO guidelines and ICH requirements for GCP, drafted by the Ministry of Health, Drug Controller General of India and Indian Council for Medical Research;
- The Pharmacy Act, 1948.

Chaudhuri (2005) mentions difficulties of small pharmaceutical companies to adhere to GMP standards, especially high investments necessary for upgrading their production facilities (pp. 248-252).

"India, Germany signs fast track agreement to fasten pharmaceuticals export" (J. Alexander; Pharmabiz, Jan 02, 2007) – fast track approvals of drugs from Indian manufacturing facilities approved by the US FDA or EU; also there is Indo-EU working group which was supposed to meet in April 2007 to discuss mutual recognition of GMP certification.

"Government of India has approved setting up of Central Drugs Authority of India (CDA) as an autonomous organization to revamp the drug regulatory system, bringing about uniformity of drug licensing, and to improve quality and safety of drugs. CDA is envisaged to have separate divisions for regulatory oversight of clinical trials, new drugs, medical devices, cosmetics, vaccines and biologicals, good manufacturing practice-compliance etc." (Indian Embassy, 2007)

Other sources of information on CDA: "Central Drug Authority will be formed in six months: Dr Ramadoss" in Pharmabiz, January 15, 2007; "Health ministry seeks cabinet nod for CDA, states not keen on centralizing drug administration" by JC Mathew, 2006; "Pharma industry frowns on formation of the Central Drugs Authority of India" by N Vijay, Pharmabiz January 13, 2007; "AIDCOC approaches MP, political parties against move to Central licensing of pharmaceuticals" by S Shastri, Pharmabiz May 14, 2007.

"The much-hyped National Pharmacovigilance Programme, flagged off by the union health minister about nine months ago, is yet to begin in its right earnest. Though the Central Drugs Standard Control Organization (CDSCO) has finalized the list of coordinating centres at the regional level, the centres are not fully functional so far." JC Mathew, 'National Pharmacovigilance Programme yet to take off' in Pharmabiz, August 10, 2005.

On GMP compliance:

'State FDA cancels licenses of 165 pharma units for non-compliance of GMP' G. Babu, Pharmabiz, April 23, 2007;

'Kerala lagging in Schedule M implementation, 70 units non-compliant' V Narayanan, Pharmabiz, April 10, 2007;

'Kerala to ban PCD players without cGMP & manufacturing license' PB Jayakumar, Pharmabiz, August 10, 2005;

'Government moots to scrap loan-licensing system' JC Mathew, Pharmabiz, August 09, 2005.

On retailers:

"The government proposal to implement Good Pharmacy Practices and a system of accreditation of pharmacies in the country should set in motion a revolution in pharmaceutical retailing in the next few years." PA Francis 'Changing pharmacy practices', Pharmabiz, November 29, 2006;

'Many retail pharmacies in Kerala flouting Rule 65 of Drugs & Cosmetics Act' V Narayanan, Pharmabiz, May 25, 2007.