Working Paper 310

Drug Quality and Safety Issues in India

Maulik Chokshi
Rahul Mongia
Vasudha Wattal

September 2015

INDIAN COUNCIL FOR RESEARCH ON INTERNATIONAL ECONOMIC RELATIONS

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List of Abbreviations

ADE	Adverse Drug Events
ADR	Adverse Drug Reactions
API	Active Pharmaceutical Ingredient
CDSCO	Central Drugs Standard Control Organisation
CDTL	Central Drug Testing Laboratory
CLCSS	Credit Link Capital Subsidy Scheme for Technology Upgradation
COPP	Certificate of Pharmaceutical Product
DCA	Drugs and Cosmetics Act, 1940
DCR	Drugs and Cosmetics Rules, 1945
DCGI	Drugs Controller General of India
EMA	European Medicines Agency
EUDRA	European Union Drug Regulatory Authorities
GMP	Good Manufacturing Practices
KMSCL	Kerala Medical Services Corporation Ltd.
MHRA	Medicines and Healthcare Products Regulatory Agency
MNC	Multinational Company
MoHFW	Ministry of Health and Family Welfare
MSF	Médecins Sans Frontières
NABL	National Accreditation Board for Testing and Calibration Laboratories
NADFC	National Agency for Drug and Food Control
NIC	National Informatics Centre
NIB	National Institute of Biologicals
NSQ	Not of Standard Quality
PTUAS	Pharmaceutical Technology Upgradation Assistance Scheme

PvPI	Pharmacovigilance Programme of India
QA	Quality Assurance
QC	Quality Control
SDRA	State Drug Regulatory Authority
SSFFC	Substandard/Spurious/Falsely-labelled/Falsified/Counterfeit
T&T	Track and Trace
TNMSC	Tamil Nadu Medical Services Corporation
TRIPS	Trade Related Aspects of Intellectual Property Rights
USFDA	United States Food and Drug Administration
WHO	World Health Organization
XLN	Xtended Licensing, Laboratory and Legal Node

Acknowledgments

We are extremely grateful to all our national and international respondents who devoted their valuable time for detailed interactions with us, and were instrumental in enabling us to develop an understanding of the diverse set of issues in the area of drug regulatory reforms. The research team would like to acknowledge the invaluable insights received from the Advisory Committee of the Research Program on Drug Regulatory Reforms in India throughout the duration of this study. Finally, we are extremely thankful to participants of the Consultative Workshop on *Drug Regulatory Reforms in India*, held on 1st of May 2015 in New Delhi, where a draft version of this paper was presented. Their comments have been of immense help in improving this paper to its current form.

This paper was sent to several experts for review. In particular, we are thankful to Dr Aditya Bhattacharjea, Professor and Head, Department of Economics, Delhi School of Economics and Ms Susan Winckler, Managing Partner, Leavitt Partners LLC, Washington, DC, former Chief of Staff at USFDA, for their very helpful review and comments.

Abstract

Today, the global pharmaceutical product value chain is becoming increasingly complex and this has led to the emergence of 'multiple quality standards' for medicines. But this non-uniformity in the quality of medicine is also contingent upon both the regulatory milieu in the country of manufacture and the export destination of a pharmaceutical product. The focus of this paper is upon the domestic pharmaceutical market in India, where policy makers often face a trade-off between what has been called 'high quality' and 'affordable quality' medicines. With India being recognised as the pharmacy of the developing world, it is believed that there is need for strict quality specification and enforcement within the country in the first place. Against this background, there have been several reports where doubts have been raised regarding quality of medicines available in India. This paper, by mapping the perspectives of several stakeholders, attempts to bring clarity on issues related to poor quality medicines and suggest institutional reforms in the Indian regulatory regime, looking at good and bad practices followed both domestically and internationally.[α]

Keywords: *Regulation, Public Health, Government Policy, Pharmaceuticals Manufacturing, Economic Development*

JEL classification: *I15, I18, L51 L65*

Date*: September 2015*

[α] **Disclaimer**: This paper is part of ICRIER's Research Program on Drug Regulatory Reforms in India under the Health Policy Initiative, and reflects the views of its authors, and not that of any other individual or institution, including ICRIER.

DRUG QULAITY AND SAFETY ISSUES IN INDIA

Maulik Chokshi, Rahul Mongia, Vasudha Wattal*

1. Introduction

1.1 Context

With the exception of pharmaceuticals,[1] consumers, in most cases, are able to *ex ante* ascertain the quality of goods. At the heart of this statement is the very peculiar nature of pharmaceuticals as credence goods – those whose quality can rarely be ascertained even *ex post* (Ray & Bhaduri, 2003) - and therefore, often result in inefficient outcomes for public health. The dynamic and complex nature of pharmaceuticals and the cumulative effects of the production processes from manufacturing to packaging, and conditions of distribution such as handling, transport and storage, warrant quality assurance at all nodes of the pharmaceutical value chain. As such, effective regulation of these processes can largely ensure delivery of safe and high-quality medicines to consumers.

Poor quality of medicine resulting from intentional or negligent lapses in manufacturing, often leads to disastrous consequences. The immediate effects of poor-quality medicines include, adverse effects of incorrect active ingredients, loss of confidence in health systems and health workers and economic loss for patients as well as the producers and traders of good quality medicines (Newton, Green, & Fernández, 2009). More worrisome are cases where medicines for fatal, neglected diseases are of inferior quality since they tend to put tremendous burden on public health and defeat the purpose of several programmes specifically targeted towards the elimination of such diseases (Dorlo, Eggelte, Schoone, de Vries, & Beijnen, 2012). In addition, the prevalence of a subset of poor quality drugs does much damage to the reputation of the industry as a whole (Clarke & Berkrot, 2014).

There have been several reports where doubts have been raised regarding the quality of medicines available in India, which have been debated with a lot of 'emotive concern', rather than factual understanding of the situation. This paper attempts to address these issues, firstly, by bringing to fore the differences in the definitions of poor quality medicines and their varied implications. Secondly, the aim is to critically analyse existing views of diverse stakeholders and to look at good and bad practices followed domestically and internationally, in order to suggest technical and institutional reforms to the Indian regulatory regime.

* Maulik Chokshi is External Consultant and Rahul Mongia and Vasudha Wattal (vwattal@icrier.res.in) are Research Associates at ICRIER. The names have been placed in alphabetical order and do not reflect the contributions of individual members of the research team. All members contributed substantially to this paper.

[1] For the purpose of this study, the terms drug, medicine, pharmaceutical product and pharmaceuticals are used interchangeably to refer to medicinal products intended for prophylactic, diagnostic or therapeutic use.

1.2 The concept of 'Pharmaceutical Quality'

The uni-dimensional concept of quality[2] of medicine in standard economic theory has evolved to one with multiple complex dimensions,[3] including that of therapeutic efficacy and safety, impurity profile and environmental issues (Ray & Bhaduri, 2003).The rising complexity is due to the participation of numerous agents in the entire process of production and distribution of pharmaceuticals, including physicians and other dispensers of medicine, thus warranting comprehensive regulatory oversight.

One way in which these complexities are internalised across countries is through codification of standards with detailed quality parameters laid out in pharmacopoeias, ensuring uniform quality of the product being produced. However, because of the lack of harmonised standards, hurdles exist for setting up a pharmaceutical product common market (with universal recognition of quality standards), leaving each market zone to establish its own specifications (Layoff, 2012). These then tend to differ from one another in some aspects, for example, tolerance for impurity, which may be set at 95 or 99 per cent (Abbott & Dukes, 2009). Thus, depending upon where a manufacturer intends to market his product, there may be differences in what may be considered acceptable quality. This issue is further compounded by global differences in the definition and interpretation of 'poor quality medicine', an issue discussed in detail in section 3.1.

In mature regulatory jurisdictions, poor quality medicines in large part arise due to complex drug distribution chains. Additionally, in maturing regulatory jurisdictions like India, the problem is attributed to the existing regulatory mechanism, one that is ill-equipped with financial, technological and human resources (Fernández, et al., 2011).

1.3 Pharmaceuticals – The Indian scenario

The pharmaceutical sector is one of the fastest growing sectors in India and, with a 19 per cent compound annual growth rate (CAGR) during the 11th plan period, it is estimated to grow at a CAGR of 20 per cent over the next five years.[4] It accounts for 8 per cent of global production and is currently exporting to over 200 countries the world over. India has an immense advantage as a global player in generic formulations due to its cost effectiveness and, has the potential to further enhance its competitiveness in years to come.

In India, the monitoring of pharmaceutical quality is the responsibility of the health ministry and is governed by the provisions of the Drugs and Cosmetics Act, 1940 (DCA). Over the

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[2] In standard economic theory, quality is assumed to be a uni-dimensional concept, where better quality means more product services relative to the cost of production. See, for instance, Grossman & Helpman (1991).

[3] A comprehensive definition of drug quality should describe all conceivable quality parameters as perceived by different sets of economic agents (producers, pharmacists, physicians, patients and the government) involved in the specification of quality standards for medicines.

[4] See position paper presented at India Pharma Summit 2014-15 organized by WHO India, Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India and FICCI, on 23rd March 2015 in Chennai. Available at http://www.searo.who.int/india/mediacentre/events/2015/position_paper_pharma_summit_2015.pdf.

years, the act has been amended several times and according to the amendment of 1988, the licence holder is required to strictly comply with the requirements of Good Manufacturing Practices (GMP) as codified in Schedule M of the Drugs and Cosmetic Rules, 1945 (DCR). Further, specific standards for identity, purity and strength of drugs are prescribed in the Indian Pharmacopoeia (IP), which has a legal status under the second schedule of the DCA and DCR. To continuously improve the quality of medicines, the IP is updated with new as well as revised monographs under the aegis of the Indian Pharmacopoeia Commission (IPC).

The regulatory structure for pharmaceuticals is such that the responsibility of licensing and regulation of manufacturing facilities lie with the state governments -the State Drug Regulatory Authorities (SDRAs) - while the central government- the Central Drugs Standard Control Organization (CDCSO) - has greater involvement in new drug approvals and to a limited extent, laboratory testing of drug samples. Given the rapid growth of the pharmaceuticals industry in India over the last 45 years, the number of manufacturers has grown manifold, leading to the need for further strengthening of the regulatory mechanism while keeping the increased administrative cost of monitoring quality under control. The idea is to create a culture of quality amongst all stakeholders by ensuring that they have the correct incentives and opportunities that drive self-regulation.

1.4 Scope of the present paper

Bennett, David and Yin (2014) highlighted several factors that are responsible for the lack of a uniform quality of medicines available within India. These include the challenges posed by heavy investment required in quality control equipment, the inventory required to protect drugs during transportation and storage in extreme temperatures as well as the possibility of spurious and authentic products being mixed by corrupt wholesalers. All the factors identified by the authors have a definitive impact on the overall quality and safety of a product, but prevalence of certain categories of poor quality medicine may be affected more by some and less by other factors.

In order to address the problem of drug quality more accurately, this study distinguishes two main categories of poor quality drugs. One is that of substandard drugs[5] – those that do not meet the specifications given in the accepted pharmacopeia or a national regulation. The other main category is that of spurious drugs[6] – those that carry a false representation of

[5] For the purpose of the study, the drug shall be deemed to be Not of Standard Quality (NSQ) or substandard if it fails to comply with the standard as per Chapter V, The Second Schedule, sec 5(a), (b) of the DCA.

[6] Spurious Drugs are mainly the products that are deliberately and fraudulently mislabelled and manufactured to mislead patients by concealing their identity, source of manufacture and its content to profiteer on the popularity of fast-moving branded or generic medicines. It may or may not contain the active ingredients in the manner mentioned on the label. For the purpose of the study, the drug shall be deemed to be spurious if it falls within the definition specified in Chapter IV, Sec. 17B of the DCA:

a) If it is manufactured under a name which belongs to another drug; or
b) If it is an imitation of or is a substitute for another drug or resembles another drug in a manner likely to deceive or bears upon it or upon its label or container the name of another drug unless it is plainly and conspicuously marked so as to reveal its true character and its lack of identity with such other drug; or
c) If the label or container bears the name of an individual or company purporting to be the manufacturer of the drug; which individual or company is fictitious or does not exist; or

identity or source or both.[7] This paper narrows down the canvas of analysis and restricts the discussion only to the 'manufacturing' and 'distribution'[8] phases of the entire product value chain so as to focus on the issue of poor quality medicines[9] in the Indian domestic market. This narrowing is warranted because the 'manufacturing' and 'distribution' phases of the product value chain serve as portals of entry or entry points for both substandard and spurious drugs.[10] Restricting ourselves to the realm of quality of drugs manufactured within the country, we do not discuss issues that arise from drug approval processes and clinical trials. Nor do we address concerns of intellectual property rights and pricing issues.

This study finds that in order to address any issue in the context of ensuring availability of quality medicine in India, dedicated efforts will be required, from both the regulator as well as the manufacturer, towards improving existing mechanisms. It, therefore, is recommended that the manufacturing and inspection procedures be streamlined through the adoption of 'quality by design' and a 'risk' based approach respectively. Simultaneously, among other things, there is also need to strengthen the current regulatory infrastructure by having a more rationalized work distribution among regulatory personnel. Creating a comprehensive database to effectively monitor and regulate the sector is another vital reform and this can be accomplished using key IT interventions.

This paper is divided into four sections. The following section describes the research methodology adopted for identification of stakeholders and collection of primary data, selection of provinces in India and international jurisdictions for field study. Section three brings out the thematic analysis of findings from the ground along with implementable policy recommendations. This section is further subdivided into five themes – the first theme crystallises defintional issues with respect to the SSFFC framework and its impact on prevalence studies on poor quality medicines. The second theme discusses compliance issues with respect to GMP in India and the factors that drive its adoption and impact on drug quality. The third theme looks at the national (routine) drug sampling and testing capacities

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d) If it has been substituted wholly or in part by another drug or substance; or
e) If it purports to be the product of a manufacturer of whom it is not truly a product.

7 Buckley et al., (2013), make a similar distinction in their report. They use the term 'falsified' instead of 'spurious'. As will be explained later in this paper, the two terms are synonymous under the SSFFC framework, WHO.

8 The phase of 'distribution' is largely governed by Good Distribution Practices (GDP). Distribution of pharmaceuticals involves maintaining conditons of ambient temperature, humidity, exposure to sunlight, etc., which play a massive role in ensuring potency of the formulation downstream to the manufacturing phase. It is not the aim of the paper to look into supply-chain management issues of the pharmaceutical distribution chain. Only factors that affect potency of the drug and that allow the entry of spurious drugs in the chain are explored.

9 The use of the term 'counterfeit drugs' has deliberately been avoided from this paper to mark a clear distinction between spurious and substandard drugs, but wherever used, only the narrow legal connotation of wilful trademark infringement should be attributed to it as defined in the Trade Related Intellectual Property Rights (TRIPS) documentation. As explained later in this paper, interchanging these terms can lead to hurdles estimating the prevalence of each of these classes of drugs and create confusion during discussions and interpretation of data.

10 It will be later explained in the paper that the manufacturing phase plays a wider role for entry of substandard drugs while distribution phase plays a wider role in the entry of spurious drugs in the market. But these entry points are not mutually exclusive for poor quality medicines.

and compares the approach to post-market sampling and testing in the developed vis-à-vis the devloping world. The fourth theme examines the system of drug alerts in India and abroad. It also looks at how pharmacovigilance programmes across the globe are feeding into such alert systems. Also examined are the ground realities linked with the process of a product recall from the retail market. Finally, the fifth theme closely looks at the state of IT interventions like track and trace systems in India and analyses its feasibility as perceived on the ground. Section four concludes the paper with a brief summary and a discussion on the moot points that affect drug quality and safety in India.

2. Research Methodology

A list of potentially key stakeholders was drawn up based on an extensive survey of literature on drug quality issues in India and subsequently interviews were conducted –nationally and internationally – across several experts using a semi-structured questionnaire. For the national round of the study, apart from Delhi, interviews were conducted in four states, i.e. Maharashtra, Gujarat, Kerala and Tamil Nadu; for international benchmarking, USA, UK, Indonesia and China were selected.[11] Some interviews were also conducted at a pharmacovigilance conference[12] held in India while others were conducted at an international conference for the revision of the Drug Administrative Law of China.[13] A total of 121 experts were interviewed; their break up is provided in the Table 1 below. We were also able to visit three manufacturing facilities, one each of large, medium and small scale, and had the opportunity to interact with personnel at both the management as well as the shop floor, but these have not been included in the number of experts given below.

Table 1: Break-up of Interviews Across States and Countries

	Number of Interviews	Number of Group Interviews (GI)
STATES		
Delhi	12	2 (2 to 3)
Maharashtra	5	3 (2 to 3)[14]
Gujarat	7	0
Kerala	11	2 (2)
Tamil Nadu	8	1 (Workshop)[15]
COUNTRIES		
US	8	3(2 to 7)
UK/Europe*	6	3(4 to 5)
Indonesia	6	2 (2 to 3)
China	3	2 (3 to 5)
Workshops/Conferences/Roundtables	4	1 (2)

*Legend: The figure in the parenthesis reflects the number of persons per group interview. *We interviewed officials at the European Medicines Agency (which is headquartered in London, UK) as well as the national regulatory agency of the UK, i.e., Medicines and Healthcare Products Regulatory Agency (MHRA). In addition, we were also able conduct a telephonic interview with a Dutch drug inspector.*

The key interviewees belong to a broad spectrum of expertise including government regulators, retired government officials/policymakers, academicians, industry representatives,

[11] The selection criteria for states as well as international jurisdictions are elaborated in Annexure I. For states, the selection was made on the basis of drug inspectorate strength and number of manufacturing facilities/sales premises.

[12] The 14th Annual Conference of Society of Pharmacovigilance, India, was hosted by Aligarh Muslim University from 1–3rd December, 2014.

[13] Pharmaceutical Law Institute at the Tsinghua University School of Law, China Pharmaceutical Enterprises Association and China Pharmaceutical Industry Research and Development Association, co-organised an international conference on the Drug Administrative Law (DAL) revision and the improvement of China's drug regulatory system. This conference was held on May 29 and May 30, 2015, in Beijing.

[14] FICCI–WHO organised 'India Pharma Summit 2014–15' under the aegis of the Department of Pharmaceuticals, GOI on March 23, 2015, in Mumbai

[15] A FICCI-WHO event on 'Regional GMP Strengthening Workshop for Indian Pharmaceutical Manufacturers and State Regulators' was held on February 19, 2015, in Chennai.

drug inspectors, laboratory technicians, among others aligning with the scope of regulation of medicines. This division is given in Table 2 below.

We started with the exercise of building a stakeholder directory, which included various experts as mentioned above. Our final list of interviewees was obtained after several rounds of communication with the initial experts from our stakeholder directory and the use of the snowballing technique. All key informants were briefed about the objective of the study and their potential role. In the process, a total of 204 experts were contacted. Each respondent was assured that their confidentiality would be maintained and their quotes, if used, would not reveal their identity.

Table 2: Cross-section of Respondents Across Disciplines and Occupations

Representative Category of Interviewees		Number of Interviewees
Drug Regulators	State	10
	National	2
	International	20
Drug Inspectors		7
Laboratory Analysts/ Technicians		4
Industry Representatives	Large Companies	15
	Small and Medium Enterprises	3
	Industry Associations	13
Academicians		24
Legal Experts		10
Retired Government Officials/Erstwhile Policymakers in Health		8
Representatives from Civil Society Organisations		5

We would like to acknowledge the strengths and weaknesses of this study. The present study attempts to examine the regulatory bottlenecks in ensuring quality in India that go beyond the estimation of prevalence of poor quality drugs or the definitional issues with regard to such drugs, which has been the centre of attention in many previous studies. It does so by mapping multiple stakeholder perspectives and thereby identifying various nodes that have a crucial bearing upon drug quality. By conducting interviews across more than 100 stakeholders from various categories, it is built on a reasonably large canvas that ensures comprehensive representativeness. However, we identify the following two factors that may have contributed to imposing some limitation on the findings of the study.

1. We used qualitative technique of snowballing, which might have resulted in bias towards one particular group of stakeholders.
2. In the criteria used for selection of states for the field research (for more details, refer to Annexure 1), some states had to be left out at the outset due to absence of data on a number of parameters used in the said criteria. This may have led to potential bias in the selection of states.

The following six sections elaborate on the various factors/processes that affect the quality of pharmaceuticals. While some other processes may seem relevant in the context of drug quality, we focus solely on those aspects that emerged as crucially important from our desk and field research. Finally, while attempting international benchmarking for drug regulatory reforms in our study, we have made efforts to carefully contextualise those issues that are most relevant and feasible for the Indian system.

3. Research Findings, Analysis and Recommendations

3.1 Defining Quality Medicines

In several countries, the term 'counterfeit drugs' has come to represent poor quality medicines and is used in common parlance, although there are major differences in definitions and connotations. On account of these differences, there is great difficulty in exchange of information between countries as well as in estimating the global problem of poor quality medicine. To address this concern, in 2009, the World Health Organization (WHO) came up with a definition that was considered by many to be broad and ambiguous as it failed to distinguish substandard medicines from counterfeits.

> *"A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."*
>
> - WHO, 2009

Substandard medicines, although illegal, may be erroneously manufactured or may be a result of insufficient resources such as technical expertise, manufacturing infrastructure (Caudron et al., 2008); it may also be deliberate. There is thus a very thin line that differentiates medicines intentionally falsified from those which are substandard due to negligence or otherwise.

A broad definition often creates confusion between legitimate generics and dangerous fakes; therefore, it has been suggested time and again in several reports that that the term 'counterfeit' should not be used in the context of medicines (See, for example, Oxfam, 2011). Instead terms such as 'fake' should be used as they render greater precision towards understanding the nature of the problem.[16]

Responding to the above criticism, during the 63rd World Health Assembly, it was proposed that until a consensus could be reached on how medical products should be defined, the following acronym should be used: 'substandard/spurious/falsely-labelled/falsified/ counterfeit medical products' or SSFFC.

3.1.1 Defining SSFFC in India

There have been several unverified reports of spurious medicines in the Indian market. Hence, in order to map the magnitude of the problem of poor quality medicines, two surveys were undertaken in India recently.[17] Both studies mentioned at the outset that the issue of

[16] The NGO, Médecins Sans Frontières (MSF), for instance supports this view. Available at: http://www.msfaccess.org/spotlight-on/substandard-counterfeit-medicines.

[17] The first survey was funded by the WHO and was carried out by SEARPharm Forum, in collaboration with Delhi Pharmaceutical Trust with technical assistance from the Apothecaries Foundation in 2007. A second survey, titled 'Countrywide Survey for Spurious Drugs', was carried out by the CDSCO in 2008–09 based on

spurious drugs is invariably debated with 'emotive concern' rather than a factual understanding of the situation. During the course of the study, it was realised that depending on how poor quality drugs are defined and how these definitions are interpreted, all these reports may or may not be talking about the same class of drugs. This subsection aims to crystallise the factual understanding of the situation in terms of the nomenclature of poor quality medicines under the SSFFC framework.

Key respondents felt that loose, interchanging use of terms from the SSFFC framework leads to confusion. To add to the confusion, there are multiple iterations for a single term and in order to understand the issue in the Indian context, it is helpful to see how Indian laws view the terms in the SSFFC framework (see Table 3).[18]

Spurious Drugs: This refers to the term in common parlance in South Asia for fake or falsified drugs. In India, these are defined in subsections (a) through (e)[19] under section 17B of the DCA, as amended by the Drugs and Cosmetics (Amendment) Act, 1982.

Substandard Drugs: In India, these translate into Not of Standard Quality (NSQ) Drugs which do not meet the Indian pharmacopeia standard. Legally speaking, a drug is deemed to be NSQ or substandard if it fails to comply with the standards specified in the second schedule, Section 5 (a) and (b), Chapter V, of the DCA.

Falsified Drugs: Spurious and falsified are synonymous to each other. All the subsections under 17B of DCA, hence also apply to this term, although the act does not expressly mention this term.

Falsely labelled Drugs: This term refers to a product that may be of acceptable quality but with false packaging (which does not infringe on any trademarks held by other manufacturers). Subsections (a), (c) & (e) of Section 17B of the DCA, which defines spurious drugs, also effectively subsume falsely labelled drugs, although the act does not expressly mention this term.

Counterfeit Drugs: This term is not defined under the DCA, but in India, a narrow legal sense is attributed to it, i.e., wilful trademark infringement as defined in Trade Related Aspects of Intellectual Property (TRIPS) documentation.[20] Hence, 'counterfeit drugs' in India

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statistical methodology (for determining the sample size) advised by the Indian Statistical Institute, Hyderabad. During field visits, the research team was informed that a similar exercise is underway for conducting a scientific study on the extent of problems of spurious drugs and 'Not of Standard Quality' drugs, under the aegis of National Institute of Biologicals (NIB).

[18] The Drugs & Cosmetics Act, 1940, and its latest iterations do not mention the terms counterfeit, substandard or falsified drugs; instead, Sections 17, 17A and 17B of the act mention misbranded, adulterated and spurious drugs, respectively.

[19] These subsections have been defined in Section 1 on p. 4.

[20] The TRIPS Agreement defines 'counterfeit trademark goods' as goods that bear, without authorisation, a trademark that is identical to, or which cannot be distinguished in its essential aspects from, a registered trademark. Article 61 of TRIPS says that criminal counterfeiting activities involve trademark infringement that is wilful and is carried out on a commercial scale. Criminal trademark infringement or counterfeiting, can be distinguished from the so-called 'civil' trademark infringement in that it involves the intentional

refers to the unauthorised use of a registered brand name even when the product is of acceptable quality.[21] Subsections (a) (b) & (e) of Section 17B of the DCA, which defines spurious drugs, also effectively subsume the narrow legal definition of counterfeit drugs. Hence, counterfeit drugs are equivalent to spurious drugs, but spurious drugs are not just counterfeits but other fake products as well.

From the field research, it emerged that the umbrella framework of 'SSFFC' or substandard/spurious/falsely-labelled/falsified/counterfeit medicines acts as a surrogate to the ground perceptions (all these are interchangeable, see Figures 1 and 2) as opposed to how the elements of SSFFC are defined individually,[22] the only exception being the stakeholders who are in the regulatory sphere or have retired from it. Stakeholders outside the regulatory sphere interchangeably used the terms from SSFFC nomenclature. For a majority of the respondents, the terms 'spurious', 'counterfeit', and 'substandard' were synonymous with 'fake drugs' (very few individuals mentioned the term 'falsified' or 'falsely-labelled'). For example, a division head from an MNC said:

> *"Substandard drugs[23] or pass offs are typically targeted against the big brands and for big brands, almost 15 per cent of (the) sales are lost on account of these substandard products."*
>
> - Division Head, MNC

Respondents within the regulatory sphere (CDSCO officials and officials in SDRAs) or those retired from these institutions, unlike other stakeholders, were able to make a clear distinction between 'substandard/NSQ', 'spurious', 'misbranded' and 'adulterated' medicine.[24] But even in these interactions, the terms 'spurious' and 'counterfeit' on some occasions were used synonymously (see Fig. 1 & 2). But officials higher in the hierarchy clearly stated the absence of the term 'counterfeit' in the DCA and hence refrained from its use.

Recommendation 3.1.1: Include clear description of SSFFC terms in any ongoing or future studies instituted to quantify the extent of poor quality medicine in India and abroad.

misrepresentation of the product as the trademarked article, when in fact, it is an unauthorised copy. For a more clear exposition, refer to the Oxfam Briefing Paper 143 (2011).

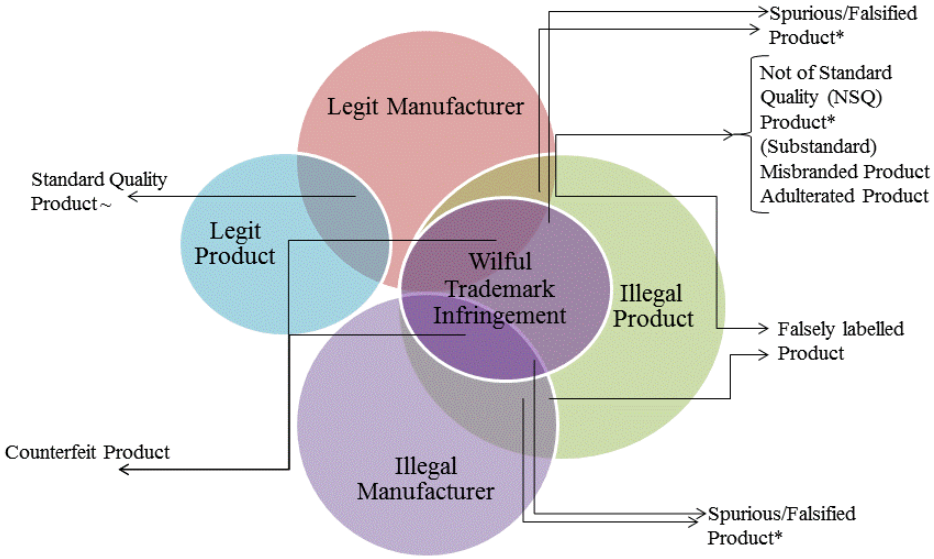
[21] Parliamentary Committee 59th Report on The Functions of the Central Drug Standards Control Organisation (CDSCO). Available at http://164.100.47.5/newcommittee/reports/EnglishCommittees/ Committee%20 on%20Health %20and%20Family%20Welfare/59.pdf

[22] For a more detailed insight on how substandard and counterfeit medicines are defined worldwide, see Table 1-1 to 1-5, pp. 34–47, Buckley et al. (2013).

[23] Later in the discussion, the respondent clarified that he was referring to spurious drugs and not substandard drugs in the statement.

[24] Sections 17, 17A and 17B of the DCA mention misbranded, adulterated and spurious drugs, respectively.

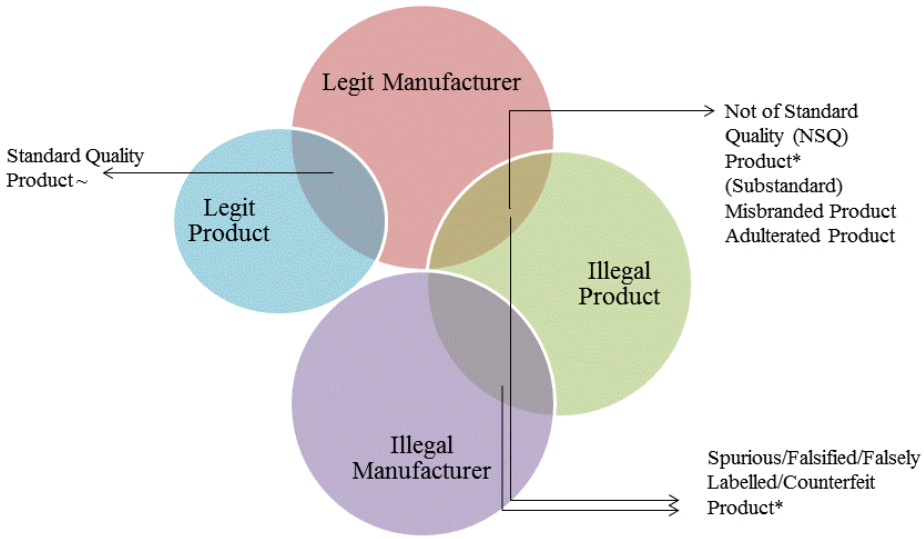
Figure 1: Depiction of SSFFC terms and terms used in the Drugs & Cosmetic Act on the basis of documented definitions in iterations reproduced over the years



*Legends: *NSQ and spurious products are distinguished only after an investigation by a drug inspector. The starting point of this investigation is the presence of the word 'substituted by' in Form 13, i.e., drug test report issued by a government analyst in a government drug testing laboratory. The term 'substituted by' acts as a surrogate to establish the intent of the manufacturer (in a case where the active pharmaceutical ingredient is found to be in deviation with the prescribed pharmacopeia standard), distinguishing it from a lapse in Quality Assurance or poor handling. A product with 0 per cent API is referred to as spurious, while a product with even 1 per cent API can be considered as a grossly substandard depending upon the contents of Form 13 provided by a government analyst, which is followed by an investigation to ascertain the true nature of the faulty product. (Based on the above interpretation a spurious product may be produced both as a legal as well as an illegal entity.); ~ Standard quality product refers to those samples that meet the standards prescribed in the Indian Pharmacopeia.*

Source: Authors' own compilation from literature and field study.

Figure 2: Depiction of SSFFC terms and terms used in the Drugs & Cosmetic Act as perceived on the grounds based on the field study



*Legends: * The Drugs & Cosmetics Act, 1940, and its latest iterations do not mention the terms counterfeit, substandard or falsified drugs. Instead Sections 17, 17A and 17B of the act mention Misbranded, Adulterated and Spurious Drugs, respectively.*

Source: Authors' own compilation from field study data.

Table 3: Interpretation of the 'SSFFC' framework in India

Packaging & Labelling[×]	Wilful Trademark Infringement	Right Active Pharmaceutical Ingredient (API)	Right Dose of Active Pharmaceutical Ingredient (API)	WHO definition of Counterfeit[25]	Type of Drug (as defined in India)
Fake	✓	✓	✓	Counterfeit	Counterfeit/Spurious*
Fake	✓	x	✓	Counterfeit	Counterfeit/Spurious[#]
Fake	✓	✓	x	Counterfeit	Counterfeit/Spurious[#]
Fake	✓	x	x	Counterfeit	Counterfeit/Spurious[#]
Fake	x	✓	✓	Counterfeit	Falsified/Falsely-labelled/Spurious[~]
Fake	x	x	✓	Counterfeit	Falsified/Falsely-labelled/Spurious^
Fake	x	✓	x	Counterfeit	Falsified/Falsely-labelled/Spurious^
Fake	x	x	x	Counterfeit	Falsified/Falsely-labelled/Spurious^
Genuine	-	x	✓	Counterfeit	Falsified/Spurious[+]
Genuine	-	x	x	Counterfeit	Falsified/Spurious[+]
Genuine	-	✓	x	Counterfeit	Substandard/ Spurious[§]

Legends:[×]*A packaging may be called fake if it purports to be the product of a manufacturer of whom it is not truly a product by virtue of either a wilful trademark infringement or simply if the label on the product bears the name of an individual or company that is fictitious or does not exist (without any trademark infringements);*
Refers to the definition of spurious drugs under Section 17B (a), **(b) & (e) of the DCA only and hence is equivalent to counterfeit.*
[#]*Refers to the definition of spurious drugs under Section 17B (a), **(b),** (d) & (e) of the DCA only and hence is equivalent to counterfeit.*
[~]*Refers to the definition of spurious drugs under Section 17B (a), **(c)** & (e) of the DCA only and hence is equivalent to falsified but are not counterfeit.*
^*Refers to the definition of spurious drugs under Section 17B (a), (c)**, (d)** & (e) of the DCA only and hence is equivalent to falsified but are not counterfeit.*
[+]*Refers to the definition of spurious drugs under Section 17B **(d)** of the DCA only and hence, is equivalent to a falsified but are not counterfeit product.*
[§] *Substandard and spurious products may be distinguished by the presence of the word 'substituted by' in Form 13 or certificate of test or analysis, i.e., drug test report issued by a government analyst in a government drug testing laboratory pending investigation by the drug inspector (application of these criteria was not found to be uniform across the states studied.). The ultimate onus of classification of the sample lies on the drug inspector who investigates the matter.*

Source: Authors' own compilation from literature and field research.

The key finding from stakeholder interviews is that even with a clear distinction between 'substandard/NSQ drugs' and 'spurious drugs' as two separate classes based on the DCA, the interpretation of these terms was not uniform across states because NSQ and spurious products are distinguished only after an investigation and is based on interpretation by a drug inspector. In some cases, the starting point of this investigation is the presence of the word 'substituted by' in Form 13,[26] i.e., drug test report issued by a government analyst in a government drug testing laboratory. The term 'substituted by' acts as a surrogate to establish the intent of the manufacturer (in a case where the active pharmaceutical ingredient is found

[25] See CEBR, 2002, *Counting counterfeits: defining a method to collect, analyse and compare data on counterfeiting and piracy in the single market"*, Final report for the European Commission, Directorate-General Single Market, p. 60.
[26] A sample copy of the same can be found in Annexure 4.

to be in deviation with the prescribed pharmacopeia standard), distinguishing it from a lapse in quality assurance (QA) or poor handling. A product with 0 per cent API is referred to as spurious, while a product with even 1 per cent can be considered as grossly substandard depending upon the contents of Form 13 provided by a government analyst, which is followed by an investigation to ascertain the true nature of the faulty product. Hence, depending upon the interpretation of Form 13, a drug sample[27] may be labelled as either of the two by the investigating drug inspector who is responsible for taking a call on the matter. The responses from the different SDRAs are described below.

One of the southern states in India uses the term 'substituted by' in Form 13 as the first step to ascertain whether the sample is spurious or substandard. But this is finally ascertained based on the investigation by the drug inspector in charge. Two other states, in western and southern India respectively, use the API content to ascertain whether the sample is spurious or grossly substandard, a product is considered 'spurious' only if there is complete absence of API. A product with some API may not be considered 'spurious' but 'adulterated' and 'substandard'. But in all cases, the investigation by drug inspector in charge finally ascertains it.

Making these distinctions have a strong bearing on pinpointing the extent of the problem of poor quality medicine. The Indian definitions under Sections 17, 17A and 17B of the DCA do not conform to international nomenclature. The various studies on prevalence of spurious medicines might be talking about an entirely different set of drugs depending upon the author's selection of the definition.

Recommendation 3.1.2: Training directed at a clear understanding of these definitions should be imparted to stakeholders across the country and especially to regulatory officials.

3.1.2 Spurious vs. Substandard Drugs in India

With the subtle distinctions between these two groups made explicit in the above section, a comment about their prevalence in the Indian context is warranted. Most of the stakeholders interviewed refrained from putting a number (or percentage) to the prevalence of poor quality medicines in India for want of a more rigorous study on the same. It was pointed out to the research team by a huge spectrum of stakeholders that even if anyone from the research team were to try to procure a spurious drug, he would fail because spurious drugs are typically nonexistent in the metros and big cities (except for a few recreational drugs), but can be easily spotted in semi-urban and rural settings. Besides, major studies estimating poor quality drugs in India have so far focused on a small number of fast moving brands/ generics, while makers of poor quality drugs might target slow moving brands/generics in order to evade detection.

A leading international civil society body, which is also a mass procurer of drugs from India, claimed that while debating about the drug quality in India, substandard drugs receive a lot less attention than spurious drugs. They argued that the real cause of worry is substandard drugs rather than spurious drugs. This viewpoint was also shared by individuals from the

[27] The term "sample" here refers to a single unit of packaging such as a strip or blister pack of tablets or capsules, a tube of ointment, a cream or gel, a bottle of syrup, a vial or ampoule of injection.

regulatory sphere. It was argued by many in the field that punitive action on spurious drugs was far more stringent than for substandard drugs. Several state drug regulatory authorities informed the team of various punitive actions that are taken after a substandard product is discovered. These included warnings, token suspension of manufacturing licences or civil suits, etc. But in most instances, the attempt is to settle the matter by rectifying the source of the substandard product. It was recommended by a few stakeholders that punitive action for grossly substandard drugs should be brought in line with that for spurious drugs.

Recommendation 3.1.3*: *Any ongoing or future study instituted to quantify the extent of poor quality medicine in India should focus equally on sampling from both urban and rural settings.

A staggered sampling strategy should be adopted where both fast and slow-moving branded and generic drugs may be included in the sample set from both urban and rural settings. Besides, generics from small and medium manufacturers should receive as much importance as products from larger manufacturers.

3.2 GMP Compliance - the Indian Context

One of the reasons for the prevalence of substandard medicinal products is failure at the manufacturing level. This could arise from human error or lack of resources to monitor the production process. While it is largely in the hands of the manufacturer to minimize the risks in the initial phases, we cannot rule out the fact that the quality of product may be compromised at other points of the supply chain. The GMP guidelines have been laid down precisely for this purpose; lack of effective implementation, however, is still an issue.

In India, the GMP guidelines followed by the manufacturers vary from Schedule M and WHO GMP to those of United States Food and Drug Administration (USFDA), Medicines and Healthcare Products Regulatory Agency (MHRA) and several others. As per the norms laid down in the Drugs and Cosmetics Act, 1940, all Indian manufacturers have to comply with the GMP guidelines as per Schedule M. In addition, those who wish to export have to comply with international GMP guidelines such as the WHO GMP or specific GMP requirements of the importing country (such as those of US FDA and MHRA). Generally, at the international level, WHO GMP guidelines are considered general and minimum technical requirements for quality assurance. The following table shows data for plants certified in India as per different guidelines.

Table 4: Number of Manufacturing Facilities with Different GMP Certifications

GMP Type	WHO	USFDA	UK MHRA	CEP with EQDM
No. of facilities	1295	546	857	804

Source: Pharmaexcil.[28]

Buckley and Gostin (2013) state that the instability in the market for drugs and the resultant shortages drive up the demand for drugs outside regulated markets. They, therefore,

[28] This data is compiled and released by Pharmaexcil in 2012. For more information see : http://www.pharmexcil.com/circulars/list-of-whogmp-usfda-mhra-edqm-approved-indian-companies-products/893/239f2813416daf5c3ef5c8ed90734a0d.html

recommend that for building a strong generics industry, regulatory authorities (especially in low and middle income countries) should adopt the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) format for product registration and reduce application costs for manufacturers. In light of the above, we asked our respondents whether having harmonised standards ICH guidelines (e.g., Common Technical Document (CTD), etc.)[29] will be more useful. A number of international respondents were of the opinion that the ICH guidelines, though scientific, run into a number of systemic bottlenecks. So while these guidelines may be cost-effective eventually, implementing them will take a long time as harmonisation is a very slow process. In addition, ICH guidelines serve as standards for the interpretation and application of technical guidelines and requirements for pharmaceutical product registration. But they do not standardize the way in which inspections are conducted, which differs across countries due to differences in the training provided to individuals. Some national respondents were unaware of the CTD, but those who did know were of the opinion that it would be useful to improve buyer confidence in the export market. However, one of the most immediate problems in the Indian context is the lack of uniform and effective implementation of domestic regulations.

The Indian GMP guidelines as written in Schedule M of the DCA were initially based upon the 1982 WHO GMP guidelines, and were subsequently renewed in 2001. However, its effective implementation remains an issue of concern till date. There remains some debate about fine gaps in the specific details of Schedule M vis-à-vis WHO-GMP guidelines, although the broad principles remain the same.[30] It should be noted, however, that as per the current system, the adoption of WHO GMP guidelines by the manufacturers is not aimed at improving quality domestically but rather to reach out to markets that explicitly require adherence to these norms. Therefore, it was argued by some respondents that smaller players and especially those supplying only within the domestic market need not necessarily adhere to WHO GMP guidelines, when the legal requirement is to comply with Schedule M. Nevertheless, at the same time, there efforts should be made towards increasing quality standards in the larger interest of ensuring access to good quality and safe medicines to the patients.

Several recent cases of non-compliance on part of the Indian companies with international quality norms have arisen from breach of protocol and problems of record-keeping, which may or may not affect the quality of product. However, such instances often result in casting doubt on the reliability and credibility of the Indian pharmaceutical industry.

The response of various stakeholders indicates that while the rules and guidelines are quite well in place, their interpretation is not uniform. Schedule M guidelines have to be read along with the DCA as well as the DCR, and without access to a reference document, non-legal

[29] ICH is an international agreement between US, EU and Japan to harmonize the technical guidelines and requirements for pharmaceutical product registration thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.

[30] A broad comparison of WHO-GMP guidelines with those of Schedule M and GMP guidelines in US, EU, Indonesia and China was carried out and is detailed in Annexure 2. However, we were told by some respondents that specifications such as those of ‘man machine movement’ are absent in Schedule M guidelines.

experts often find it difficult to interpret the strict legal terminology within these documents. This also often results in differences in the expectations of regulatory officials from manufacturers, while the latter seem to be quite unaware of the precise requirements.

Recommendation 3.2.1: In order to ensure uniform understanding and interpretation by all stakeholders, there is a definite need for a guidance/reference document for Schedule M on the lines of those for WHO–GMP guidelines.

To ensure the highest standards of quality, it is not only important to have the right set of policy guidelines and processes in place but also ensuring adherence to these as efficiently as possible. To achieve this goal, the Mashelkar Committee Report (2003) recommended a ratio of one inspector for every 50 manufacturing facilities and one inspector for every 200 retail facilities. Our situational analysis of states (some of which comprise the best functioning regulatory offices in this sphere) revealed that none of them seems to have met the recommended ratios (see table 5). The 59th report of the Department Related Parliamentary Committee on Health and Family Welfare notes that going by this rule, there should be 3200 inspectors in the country as opposed to the currently sanctioned 1349 posts, of which only 846 are filled. Further, it should be borne in mind that in any given state, the distribution of inspectors in each district is based on the number of facilities in that district. But the number of facilities in a district is a matter of state policy, since licensing is a state subject.

Table 5: Inspection Data from State Drug Regulatory Authorities

State	Total Number of Inspectors (1)	No. of Sr. Drug Inspectors (2)	No. of Drug Manufacturing Facilities to be Inspected~ (3)	No. of Facilities other than Drug Manufacturing Facilities to be inspected* (4)	No. of Licensed Sales Premises (5)	No. of Inspectors Required** (6)
Tamil Nadu	146	14	494	395	43218	234
Gujarat	126	42	2226	994	30887	218
Kerala	47	6	101	286	16598	174
Maharashtra[31]	124 (161)[32]	NA	1523	NA	80417	432

*Legends: ~ Only Allopathic Units; *Does not include retail/wholesale outlets; ** Calculated as per Mashelkar Committee Report*[33]

Source: Authors' own compilation from data collected during field research.

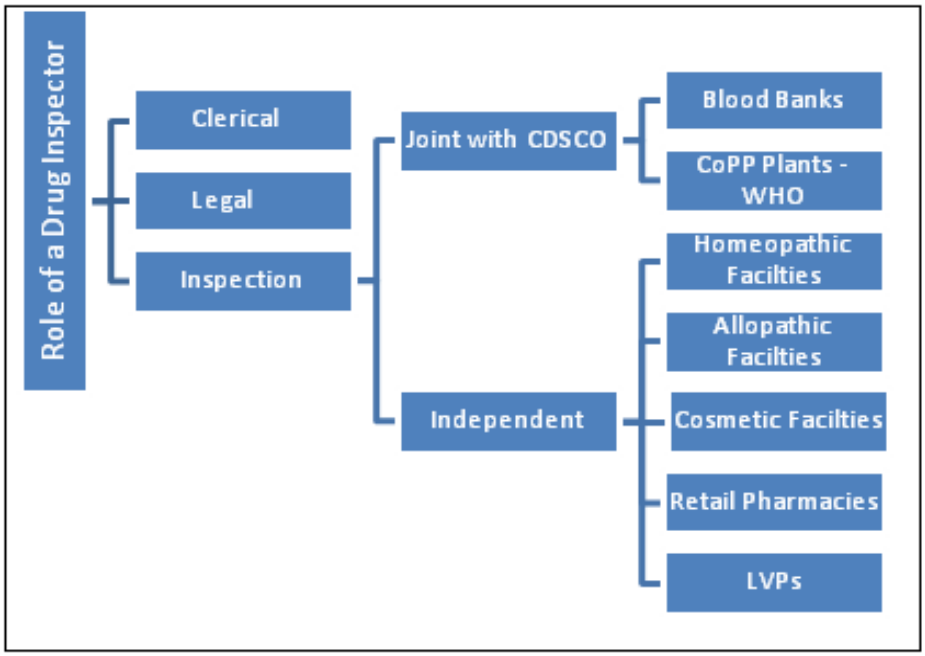
[31] Figures substantiated from: Kadam et al. (2013).

[32] The figure in the parenthesis shows the number of posts sanctioned while the number outside shows the number of posts filled. These figures were obtained from the regulator's office while conducting the field study.

[33] Note on the rationale behind Mashelkar Committee Requirements: While there seems no document that spells out the rationale behind the Mashelkar Committee requirements, the GMP inspectors from WHO (as told to the research team during an interaction at a FICCI-WHO event in February 2015, in Chennai) recommend that in any given year, an inspector should spend 100 working days at manufacturing sites (with two and a half days spent for preparation and follow-up for every day spent on the site). If we assume there is a reasonable probability that each inspection on an average takes two days, this would translate into the inspection of 50 manufacturing facilities in a given year or roughly one inspection cycle (preparation, inspection, follow- up, submissions) per week for 52 weeks in a year. This might render some support to the requirements posited by the Mashelkar Committee.

While division of labour based on the skills has been propagated by economists from as early as 1776, with Adam Smith's Wealth of Nations, and its immense benefits in terms of efficiency cannot be emphasized enough; however, this idea does not seem to have been received well and incorporated in the field of drug regulation. We found that each drug inspector was burdened with the responsibility of inspecting various kinds of facilities including allopathic, homeopathic, cosmetic, large volume parenterals, blood banks, etc., and there is no focus on specialists in each of these fields (see Fig. 3).

Figure 3: Responsibilities of a State Drug Inspector



Source: Authors' own compilation from field study data.

Recommendation 3.2.2: We recommend that the state drug regulatory authorities impart more specialised skills to their inspectors and government analysts, either product-based or process-based. This can be achieved by ensuring that each inspector is trained in a niche segment and develops specialty in it through continuous experience (see Box 1).

Box 1: Specialization Among Drug Analysts in Gujarat

We came to learn that such a practice is being used for government analysts in the state of Gujarat, where each analyst repeatedly carries out tests within a certain class of drugs and becomes adept at the process. This has led to a reduction in the time taken to carry out these tests as well as the pendency of number of cases for sample analysis.

In addition to having effective guidelines in place, there is also an active need for voluntary compliance with the guidelines to achieve the greater goal of ensuring a continuous supply of good quality medicine. There are broadly two ways to address the issue of compliance with norms (the carrot and stick model).

Create incentives for voluntary compliance (Carrot)
and
Impose severe punishments as deterrents to non-compliance (Stick)

In order to have a set of incentives to ensure quality, we first examined whether scale mattered to guarantee a given standard of quality. It has often been suggested that smaller firms tend to produce lower quality drugs as compared to larger firms, yet there is no conclusive evidence to this effect.[34] Nevertheless, a number of state drug procurement agencies have put in place pre-qualifications and criteria in terms of a turnover clause to ensure that only quality drugs enter the system. The assumption behind this seems to be that suppliers of high-volume products, since they would invest more in improving in-processes, are more likely to have higher quality (Singh et al., 2013).

A large fraction of our respondents did not explicitly mention a minimum scale of operations required to ensure quality. However, they did believe that Schedule M compliance, if met, is the minimum requirement as per the Indian law. The government has in the past offered support in the form of subsidised loans to small and medium enterprises to upgrade their operations to meet Schedule M/WHO-GMP or other international requirements for both the domestic as well as the export market. Initially launched in the form of a credit linked capital subsidy scheme (CLCSS) for the small-scale enterprises, this scheme did not find many takers because the loan amounts under the scheme were considered insufficient to upgrade operations. Later, a new scheme was proposed for medium enterprises, which, due to their larger production volumes, could avail of the benefits of moving to higher standards required for export.[35] However, the scheme has yet to receive the required approvals.

Alternatively, to encourage firms to comply with the norms, one could also put in place mechanisms (such as prosecutions and criminal punishments that instil the fear of law) to deter non-compliance. Under the current system, inspectors notify the manufacturers of the lacunae if they fail meet the requirements under Schedule M through the Corrective Action and Prevention (CAPA) report after which the latter is supposed to file a response to the CAPA report. In case of failure to correct or repeated instances of non-compliance, the manufacturer's product licence is suspended and, in extremely rare circumstances, may even be cancelled. However, in case a given manufacturer has multiple production lines, then a short-term suspension of a single production licence may not be an effective deterrent.

Recommendation 3.2.3: Stringency with regard to GMP non-compliance should be increased. A fixed time frame for submission of response to a CAPA report should be made mandatory and failure to do so should trigger strict punitive action such as financial

[34] There is no study, as of date, that substantiates this argument in the Indian context but some respondents did believe smaller firms can be quality drivers in the market.

[35] This is called the Pharmaceutical Technology Upgradation Assistance Scheme (PTUAS). Under the scheme, it is proposed to increase the loan amount to Rs.2 crore for enterprises with a turnover of Rs.5-10 crore. For further details, see http://archive.expresspharmaonline.com/sections/market-section/2261-dop-calls-for-comments-on-soft-loan-scheme-for-mid-sized-pharma-cos.

penalty on the defaulter (found to be in use in USA and China) as an alternative to the existing system of suspending a single production licence.

Recommendation 3.2.4: Use of 'reputation effects' as a deterrence mechanism can be carried out by regularly updating non-compliance data and making it available in the public domain. This exercise is already being done by the European Medicines Agency (EMA) through the European Union Drug Regulatory Authorities (EUDRA) GMP database.

For good-quality drugs to be manufactured, a lot also depends upon the quality of the raw material used, most importantly, the Active Pharmaceutical Ingredient (API). Since it is not possible to trace the failure of a product to the quality of the API at the end of the process, it is imperative to address the issue at the source itself. The bulk of our API is imported from countries such as China, Taiwan, Korea; it thus becomes important to check the processes put in place to ensure GMP compliance in the manufacture of these raw materials. Some of our respondents, who were manufacturers of finished formulations, stated that they conduct GMP audits of their suppliers before they place their order. However, this may not be a necessary practice followed across all manufacturers.

Recommendation 3.2.5: Ensure the setting up of a permanent office of the CDSCO in countries that are high volume sources of API for the purpose of drug audit and quality certification. This initiative can be strengthened if the CDCSO comes out with an alert warning Indian manufacturers against suppliers of API who have repeatedly failed to meet the required standards.

During the course of our study, we found that a consolidated national list of manufacturers and the total number of licences granted did not exist. While there are private datasets such as Prowess, which gives firm-wise data, and IMS data, which is listed product-wise, they too do not capture the market in its entirety. At various points during our field research, we were given rough estimates to the tune of 10,000+ manufacturers, but there seemed no formal list that documented the names and numbers. The last known attempt by the public sector at generating such a list was in 2011, when the Department of Pharmaceuticals under the Ministry of Chemicals and Fertilisers consolidated information from various state regulatory bodies. However, this list too remains incomplete as information from a number of states is missing. The absence of a comprehensive state-wise list also stems from incomplete digitisation and computerisation of regulatory offices. Recently, some efforts have been made in this direction by setting up the Xtended Licensing Laboratory and Legal Node (XLN) system in a few states (this aspect is elaborated in detail in the Section 3.5). But the biggest problem created by the absence of a consolidated list is the difficulty in devising any concrete national or state policy for regulation of this sector.

Recommendation 3.2.6: The consolidation and building of a national registry of pharmaceutical manufacturers through an online database is a necessary exercise in order assess and revise distribution of human and financial resources across regulators within the country.

3.2.1 Contract Manufacturing and Loan Licensing

In India, at present, manufacturing of drugs is done in three ways – own licence, loan licence and third-party agreements. In case of the loan licence, any company which does not have its own arrangements for manufacturing can use the facilities of another manufacturer. In this scenario, the applicant of a loan licence often provides the necessary raw material to the manufacturer and maintains strict oversight during the entire process. Third-party agreements, on the other hand, just entitle a manufacturer to undertake the manufacturing process on behalf of another entity that would only market the product, with greater autonomy of operation to the former. We found an absence of clarity among respondents on the legal liability with regard to the quality of products that enter the market through contract manufacturing (or third-party manufacturing). While some of the respondents told us that the law puts the burden of penalisation on the marketing entity in case of third-party agreements, several manufacturers believed that the liability was borne equally by both parties and sometimes, possibly more by the manufacturer. There is less clarity on this aspect as third party agreements are not really covered under the law.[36]

As mentioned earlier, there is no established relationship between the quality of drug and the size of the firm. However, given that a number of products are manufactured by smaller firms through contract manufacturing/loan licensing, it is important for the consumers to be clear on all parties who are liable for ensuring quality. In this context, the present labelling requirements, particularly of product produced under a loan licence, is a matter of some concern. Currently, a product manufactured under a loan licence does not require the name of the loan licensee but only the manufacturing licence number to be printed on the product label. Hence, consumers are not even aware of the true manufacturer of the product, making it difficult for them to identify the responsible parties for a substandard product.

Recommendation 3.2.7: There should be more refined guidelines for labelling requirements and liability in the case of both loan licensing and third party manufacturing. This can be done by preparing an elaborate guidance document on the lines of those drafted by the US FDA and the ICH.

3.3 Drug Sampling and Testing Capacities

As mentioned previously, there is no consolidated list of the total number of manufacturing facilities for drugs in the allopathic tradition in India. This number was quoted to be from as small as 10,000 to in excess of 25,000.[37] The only consensus seems to be that the top 1,000 firms churn out over 90 per cent of the business by value of trade. In contrast, the national regulator for medicinal products in Indonesia (NADFC) reported a total of 217 manufacturers for allopathic medicines and a market size one- third (in terms of value of trade) of that of India, dominated mostly by 25 to 30 firms. Even if one takes the supposedly underreported figure of 10,000 manufacturers in India and compares the situation with that in Indonesia,

[36] However, we were told by senior regulatory officials that it is not an illegal activity as per the law.

[37] A leading industry association mentioned that the official figure of around 10,500 manufacturers is an underestimate of the number of firms; the actual number of firms may be in excess of 25,000 manufacturers.

extensive fragmentation[38] in the Indian pharmaceutical industry is apparent. A finite number of drug inspectors have to cover a lot of ground given the large number of manufacturers in this sector.

3.3.1 National Drug Testing Capacities

In India, the national drug testing laboratories[39] comprise eight central government laboratories (six for drugs, one for vaccines and one for r-DNA and diagnostic kits), state laboratories[40] (for most states) and more than 500 private laboratories.[41] According to the 59th Parliamentary Standing Committee report on the functioning of the CDSCO, out of the six national drug testing laboratories, Central Drug Testing Laboratory, Hyderabad, was not fully equipped (in 2012) and the other five central drug testing laboratories at Kolkata, Mumbai, Chennai, Guwahati, and Chandigarh were reasonably equipped but required upgradation with state-of-the-art facilities for testing/analysing complex formulations and detecting spurious, misbranded, substandard and adulterated drugs. The present drug testing capacity of the six laboratories is around 8,000 samples per annum, which is targeted to be increased to 24,000 samples per annum.[42]

According to World Health Organization Regional Office for South-East Asia (2013), 28,157 samples from four national laboratories in Mumbai, Chennai, Kolkata and Chandigarh, were collected during 2010-2013, of which, 24, 014 samples were tested. During 2007–2012, a total of 2, 21, 274 samples were tested in all central and state government laboratories of which 11, 426 were not of standard quality and 579 were declared spurious or adulterated. Around 856 prosecutions were launched but only 96 were decided and 641 people were arrested. The value of substandard/spurious/falsified/falsely-labelled/counterfeit (SSFFC) medicines was INR 3, 83, 621,721 during 18, 264 raids.[43]

The team visited two state drug laboratories in the states of Kerala and Tamil Nadu to gauge the sample capacity that the states could handle (see Table 6). It is important to note that for both laboratories, the equipment was procured by their respective states' drug and medical equipment procurement agencies, i.e., Kerala Medical Services Corporation Ltd. (KMSCL) for Kerala and Tamil Nadu Medical Services Corporation Ltd. (TNMSC) for Tamil Nadu. In both states, the equipment was found to be up to date, but there was lack of staff to operate the equipment. This was more acute for the lab in Thrissur in Kerala, which had opened quite recently.[44] But interestingly, in both the cases, there were posts lying vacant from the pool of

[38] Fragmentation here refers only to the large number of pharmaceutical firms in the Indian industry and not the nature of integration present in the industry.

[39] National laboratories analyse drugs and cosmetics sent by CDSCO branch offices at ports and airports and also by state drug regulatory authorities as appellate labs.

[40] State laboratories analyse samples sent by the state regulatory authorities.

[41] See World Health Organization Regional Office for South-East Asia. (2013).

[42] 59th Parliamentary Standing Committee report on the function of the CDSCO, 2012

[43] Ibid

[44] It was noticed that the laboratory staff from the main state drug laboratory in Trivandrum was partially shunted to the Thrissur facility in order to transfer both capabilities and capacities.

total sanctioned posts, while both laboratories reported shortage of hands required to meet the annual targets.

Table 6: Capacities of State Drug Labs Visited During Field Study

Location of Laboratory	In-house sample -processing capacity/year*	Average number of samples received/year~	Pendency build up^
Kerala	5,000 - 6,000	7,000–8,000	2,000–3,000
Tamil Nadu	6,000 - 6,500	8,000–8,500	1,000–2,000

*Legends: * Capacity was reported for entire state and not a particular facility; ~ Samples received are for an entire state and not a particular facility; ^ Existing pendency for the entire state and not a particular facility*
Source: Authors compilation from field research.

Two completely divergent views emerged from the field research at the national and the international level regarding routine drug testing in the post-marketing phase.

The stakeholders at the international level (in both the USA and Europe), doubted the sustainability of sampling in the post-marketing phase because of the limited budgets of regulators[45] to undertake such an exercise and stressed the importance of quality assurance or quality by design approach.

The above view is in contrast to that taken by stakeholders in India, who held that there is need to increase sample collection and simultaneously increase medicine testing capacity to process (test) samples in the country in a timely manner.[46] The most plausible argument provided to support and even upscale this activity by several stakeholders was that the Indian regulatory system is yet to mature. Therefore, until a robust culture of quality is ensured in the country, abandoning post-market drug sampling would only lead to deterioration of drug quality in India. Moreover, stakeholders in India stressed the need to bolster existing capacity of state drug testing laboratories to process more samples quickly. They also felt that random samples should be lifted more frequently from different agents in the drug distribution chain.

Interestingly, the exception to the above consensus came from a few retired officials (from the regulatory sphere), who talked about the futility of such post-shipment sampling and testing. The major reason cited was that depending upon the batch size and volume use, a single batch may be consumed within three to six months or less.[47] With extended timelines in receiving reports on drug quality, most of the products from that production batch may already have been consumed. From the day a drug is sampled by a drug inspector until the

[45] This view was taken by USFDA, which in 2013 had a budgetary request of approximately USD 4.5 billion. See http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM291555.pdf. Last accessed on 17th April 2015.

[46] This view was taken by a majority of stakeholders in India across the board, although a few pointed to the futility of such an exercise.

[47] Reported during several interviews.

time one receives the analysis report, the timeline is two to five months;[48] this varies across states. The extended timelines were there due to build-up of pendency from unprocessed samples earlier received by the labs. Both the Kerala[49] and Tamil Nadu state drug labs had the capacity to process more than 6,000 drug samples/annum but a build-up of 1,000-2,000 pending samples were tacitly reported for both (see Table 6). In both these labs, the pendency was ascribed to two main factors:

a. A mismatch in the number of drug samples being received for processing and the current in-house capacity; the former exceeds the latter by a few thousand samples.

b. The in-house capacity was not being fully exploited due to lack of technical hands to process samples. Although the existing staff was meeting individual targets prescribed by their superiors, both labs were running at less than full capacity on account of lack of personnel to man the available equipment. In the case of Tamil Nadu, even the sanctioned posts for government analysts were not completely filled.

A reform measure suggested by several experts was to reinforce the drug sample processing capacity by exploiting the capabilities available in the private space. The 500 odd labs in the private domain have a subset of National Accreditation Board for Testing and Calibration Laboratories (NABL) accredited labs, which were reported to be on par with or had higher capacity than government drug testing labs. Many public drug procurement agencies including TNMSC (Tamil Nadu Medical Services Corporation) have empanelled such labs for pre-shipment quality check.

Recommendation 3.3.1: As a short-term measure, National Accreditation Board for Testing and Calibration Laboratories (NABL) accredited private labs should be used to ease the backlog of drug samples in public drug testing laboratories. This measure should only be resorted to until the in-house testing facilities of central and state drug testing labs are established.

The capacities of these labs may be used for drug testing with adequate checks and balances. A double blinded[50] two-phased drug test could be instituted where only the drug samples which fail testing in the first phase should be sent to the state drug testing laboratories for the second phase.[51] This measure should only be resorted to until in-house testing facilities of central and state drug testing labs are established. This measure is recommended to bring

[48] A timeline of 15 days (providing for sterility check) is considered sufficient for a comprehensive drug analysis. Out of the battery of tests performed based on the monographs listed in the Indian Pharmacopeia, most tests can be completed in less than a week, except for the sterility check.

[49] The state of Kerala has recently opened a new drug testing facility at Thrissur, in order to bolster the capacity already available in the main laboratory at Trivandrum. There reportedly were plans to open two more zonal labs. But interestingly, the decision to establish the Thrissur facility was taken almost a decade back and on the time of visit, it was not running at full capacity, largely due to lack of personnel.

[50] TNMSC instituted a software-based double blinding mechanism for pre-shipment quality checks in the mid-1990s. Other public drug procurement agencies were reportedly performing only single blinding or manual coding.

[51] The second phase of testing is absolutely necessary because only a drug analysis report generated by a government analyst is admissible in a court of law.

down the already existing pendency with labs and to reduce the time taken to generate drug test reports.

The views taken by stakeholders at the international level vis-à-vis the stakeholders in India as discussed above, bring out the contrast in the approach taken by international regulatory agencies in US and the EU and those in India. The latter approach is likely the result of a highly fragmented nature of the pharmaceutical sector, where a majority of the pharmaceutical manufacturers are small enterprises.

3.4 Drugs Alerts and Product Recall

While product recall is a system that, on the one hand, may be essential to make sure that there are no poor quality or expired products available in the market, in practice it can be quite costly to carry out. Hence, regulators in developed countries, for example in the USA, do not initiate the process of recall themselves but expect the responsibility to be taken up by the manufacturer. But voluntary recall can be tricky as firms have to carefully weigh the costs versus the benefits of carrying out the recall, given that it is an expensive and tedious process. Moreover, recalls can also have a damaging effect on the reputation of a firm.

International regulators also face the dilemma of such recalls leading to market shortages, more so in the case of drugs with no immediately available alternatives.[52] This is a major problem that has been on the rise in the EU and US for the last few years. Having said that, we have found that appropriate mechanisms are in place in these countries to ensure that any suspected product can be reported to the authorities and necessary action taken after investigation. In the UK, for example, there is a system called the Yellow Card Scheme that allows any person – a doctor, consumer, pharmacist or healthcare professional – to report a suspected product via phone, email or by filling up an online form.

In India, at present, while there is a detailed process for product recalls outlined on the website of the CDSCO, there are no mechanisms for identifying the products for which a recall process has been initiated. There are lists of drug alerts that have been reported by the state and central authorities; however, information about which of these drugs have been recalled is not available in the public domain. This creates lack of clarity as to how the recall process is being carried out.

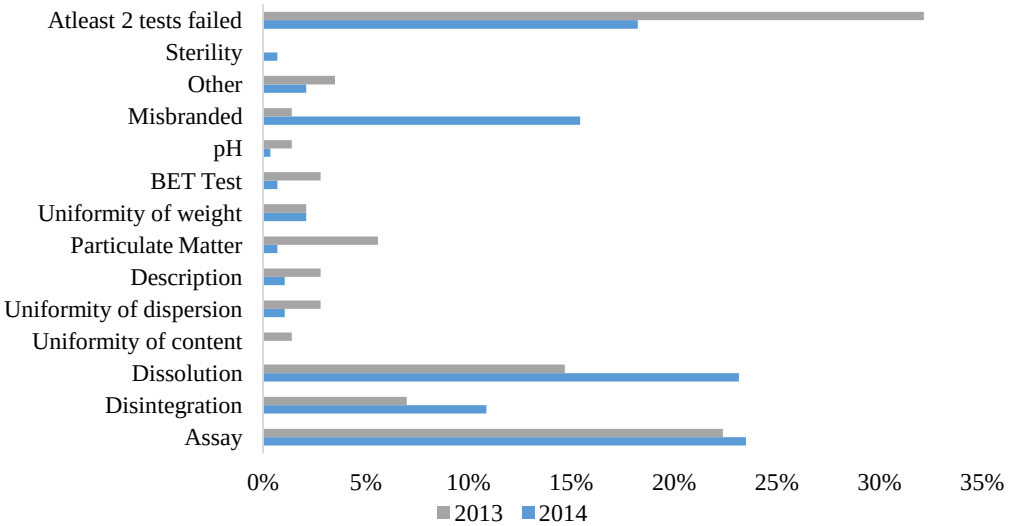
The recalls often have to be carried out at various levels, depending upon how far in the supply chain a poor quality batch has reached. For effective recall, at times the product may have to be recalled from the retail level, which means from thousands of retailers across the country. This poses a problem in cases if a laboratory report identifying a faulty product takes three to four months to process – by then, a large portion of the batch would have already been consumed in the market, especially if they are fast moving products.

[52] See also http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf. Last accessed on 18th April 2015.

Recommendation 3.4.1: Introduce an online monitoring system for product recalls that requires a manufacturer to provide real-time information about the progress of the recall process. This information should then be made to available to the public through various media.

The system of drug alerts in India is part of post-marketing surveillance – every month, drug inspectors both at the centre and states randomly sample drugs to be tested at government laboratories. Subsequently, a list is generated of those drugs that fail one or more of these tests. While the CSDCO has been posting lists of drug alerts since mid-2012 on its website, not all states have made this list available in a continuous and updated fashion to the public at large. Our analysis of the data available on the CDCSO website for the years 2013 and 2014 (the only two years for which complete data was available) reveals that the total number of NSQ drugs doubled from 2013 to 2014. One reason for this could be that a higher number of samples were collected in the second year or possibly, improved testing procedures were used. However, the broad pattern in causes of drug alerts remained the same. Figure 4 below shows that in 2013, the greatest fraction of drug alerts came from samples that failed two or more tests; the number fell in the following year. The year 2014 saw a rise in the share of misbranded drugs[53] implying that were more cases of labelling errors or those of colour and coating. The other main causes were dissolution, assay and disintegration test[54], for each of which the proportion of cases increased in 2014.

Figure 4*:* Causes of Drug Alerts



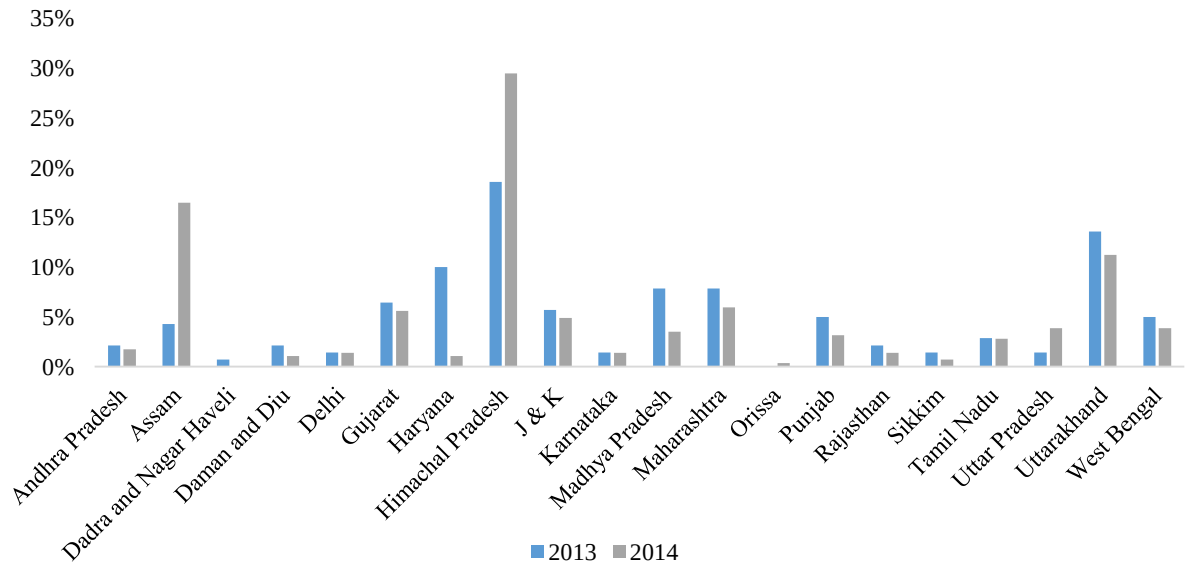
Souce: Authors' own compilation from CDSCO data.

[53] Under the DCA, misbranded drugs are defined as
(a) if it is so coloured, coated, powdered or polished that damage is concealed or if it is made to appear of better or greater therapeutic value than it really is; or (b) if it is not labelled in the prescribed manner; or (c) if its label or container or anything accompanying the drug bears any statement, design or device which makes any false claim for the drug or which is false or misleading in any particular

[54] A drug assay refers to the measurement of absolute API concentration in a formulation. A dissolution test measures the rate of dissolution of select dosage forms (tablets/capsules) which mimics the drug dissolving in the fluids of the gastrointestinal tract prior to absorption in the systemic circulation. A disintegration test determines whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium under prescribed standard experimental conditions.

We also analyse drugs alerts according to the location of the manufacturer of such drugs (shown in Figure 5 below). For this purpose, we assume at the outset that the sample drawn is random. In 2013, the highest number of NSQ drugs seems to have come from Himachal Pradesh and Uttarakhand. In 2014, Assam was the second-highest source of NSQ drugs, although Uttarakhand's share is still relatively high at around 12 per cent. Other major sources of such drugs are Maharashtra, Gujarat and J&K. This seems interesting since despite being a reasonbly large pharmaceutical manufacturing hub, Himachal Pradesh has a small inspectorate of 14 people (see Table 1 in Annexure 1). This could be a probable reason for the high incidence of NSQ drugs in the state.

Figure 5*:* Drug Alerts – Manufacturer Locations



Souce: Authors' own compilation from CDSCO data.

Recommendation 3.4.2: A system that integrates the drug alerts generated by the states and the centre should be developed to allow effective tracking of such poor quality products.

In addition to the system of drug alerts, the Pharmacovigilance Programme of India (PvPI) was set up in 2010 with the explicit purpose of monitoring adverse drug reaction (ADR) or an adverse drug event (ADE). Although its mandate includes detection of substandard quality, it functions independently of the CDCSO. Lack of awareness about the PvPI system has led to underreporting of ADRs. The data collected by the system is currently shared only with the WHO, and neither with the concerned companies nor the public at large; hence, awareness is limited and this prevents the adoption of corrective steps.[55]

Recommendation3.4.3: The PvPI data also needs to be integrated with the system of drug alerts even though both may operate independently (see box 2).

[55] For more details see http://archive.expresspharmaonline.com/sections/market-section/2507-pharmacovigilance-the-way-forward-for-india. Last accessed 10th April 2015.

Box 2: Pharmacovigilance Programme in the UK and China

While the UK does not carry out random sampling of drugs, its ADR reporting mechanism allows patients as well as healthcare professionals to report ADRs either telephonically or through an online portal. On the other hand, in China, the ADR reporting is based on 11 criteria used to identify the seriousness of the case. Further, whether a particular drug has quality issues is identified through a cluster-based approach (if they are being repeatedly reported from the same source), which is then reported to the China Food and Drug Administration (CFDA), and an enquiry is set up. In a similar fashion, an integrated network for reporting and collection of data could be developed in India to have a well-functioning pharmacovigilance programme.

3.5 Role of Technological Interventions – the Case of Track and Trace Technology & XLN Software

3.5.1 Role of Track and Trace Technologies

Track and Trace technologies (referred to hereafter as T&T) are touted to be the game changer in ensuring safe drug distribution chains and instituting quality and expiry recalls. T&T systems allow regulators, manufacturers, consumers and others to track products in the drug distribution chain, improving the visibility of the product movement.[56] They also allow patients or pharmacists to verify its authenticity and past locations. T&T systems rely on serialisation, the assigning of unique identifying numbers to products. When fully implemented, products that lack identification numbers, or products with identification numbers that cannot be accounted for throughout the distribution chain must be treated as falsified and removed from the market, even if they come from licensed manufacturers.[57] The unique identifier may be stored in a barcode, electronic product code, a radio frequency chip or it may be a human-readable number It is interesting to note that track and trace systems may also be deployed to solve many more long-standing problems in pharmaceutical regulation in India[58].

3.5.1.1 T&T in India

In 2011, the Government of India instituted a task force for studying T&T that examined three hardware and seven solution providers, after which they found that there was not much difference across hardware providers as hardware essentially consisted of barcode readers, computers and printers. It was suggested that stakeholders at the lower end of the supply chain can also use their existing computers and internet connection to be part of the T&T

[56] See Altunkan, S. M., A. Yasemin, I. T. Aykac, and E. Akpinar. 2012. *Turkish pharmaceuticals track & trace system.* Paper read at Health Informatics and Bioinformatics (HIBIT), 2012 7th International Symposium, April 19-22, 2012.

[57] Ibid

[58] Integration of a 'track and trace' system with the newly launched "Integrated Pharmaceutical Database Management System" or IPDMS by NPPA, is a case at hand. A T&T system may be used to extend IPDMS into a real time monitoring system for CDSCO and NPPA.

system, thus ensuring that no added costs are imposed. But at the same time it was acknowledged that being a system that is not widely used within the pharmaceutical industry, the cost estimated by stakeholders and solution providers varied greatly. This is in line with findings from the field study. Many of the stakeholders interviewed were not technically competent to comment on the viability concerns of the system and quoted costs that varied greatly.

One of our respondents, who was part of the above committee, revealed that a cloud based solution instituted at National Informatics Centre (NIC) would not cost the exchequer a very hefty amount, given that the software for deployment is ready. The only task left would be for manufacturers to upload the data from each of their production lines to the servers at NIC and print unique identifiers on the primary packs.[59] A consumer can access the server containing the data about the source of the product by punching in the unique identifiers on the primary packing and gain knowledge about the authenticity and source of the product procured.[60]

In early February 2015 there were media reports regarding an immediate roll-out of a track and trace system for the domestic market[61] and by April 2015, the discussion on T&T rollout on primary packing had entered into policy circles.[62] The speculation on T&T implementation ended by early June 2015, with the release of a draft notification containing the draft rules to implement bar-coding of medicines at the primary packing level in the domestic pharmaceutical market.[63]

A small section of stakeholders was sceptical of the idea of making such a system mandatory as this may pose difficulties in implementation (at the primary level packaging) for all the manufacturers and may drive out marginal players, in particular. A majority of stakeholders were of the opinion that although, in principle, T&T systems are needed to enhance consumer confidence and improve overall drug quality, the viability of mandating the printing of unique identifiers on primary packing in the domestic market would run into significant challenges.

If this provision is made mandatory and implemented at the primary packaging level, then India would become the first country to do so. One of the major concerns is that its deployment in the current form would result in steep learning curves for pharmaceutical firms leading to huge compliance costs for manufacturers both big and small. Secondly, since such a system requires the database structure to establish a parent-child relationship (where the former is the central node enforcing T&T, while the latter represents the firms feeding data to this node), requiring constant movement of data both towards the central node and away from it when accessed by downstream supply chain participants and consumers, raising challenges

[59] Primary packaging level means the package which is in physical contact with the drug.

[60] But this stakeholder also declined to comment on the feasibility of the system from the point of view of cost to be borne by manufacturers to install printers for primary packing.

[61] See for instance, Rupali Mukherjee "Soon retail drugs will be 'barcoded' for genuineness", The Times of India, Feb 3, 2015

[62] See Agenda No. 1 of "Minutes of the 69th meeting of drugs technical advisory board held on 22nd April, 2015 at CDSCO, HQ, FDA Bhawan, Kotla Road, New Delhi", p. 3-4.

[63] On June 3, 2015, MoHFW also released a draft notification (GSR449E) containing the draft rules to implement bar-coding of medicines supplied domestically to authenticate the genuineness of the drugs.

in maintaining a secure database. When printed on primary packs this information would be available in the public domain, which may allow illegitimate products to enter into legit pharmaceutical product supply chains by making use of legitimate serialization numbers, further compounding the problem of spurious drugs in the country. A view taken by some key stakeholders was that serialization at the secondary packing[64] level, by contrast, may result in a relatively more secure database, allowing only those managing the supply chain of medicines to authenticate the fidelity of the serialization information. Lastly, bar-coding at primary packs runs into several issues, like that of artwork standardization which many a time has to be accommodated onto extremely small sized packaging; exemption of the inventory that is already labelled without the proposed provisions, etc. These issues might lead to a situation where consumers may discard legitimate products because of problems with accessing the database or with packaging variations. Hence, the move for deploying T&T to the primary packs has its due set of challenges which need to be adequately addressed before they are made mandatory to comply with.

After having several discussions, deliberations and demonstrations of the T&T technology, the research team is of the view that, in the long run, benefits to be derived from the roll-out of T&T bar-coding on primary packaging would be beneficial from the perspective of providing safe and efficacious medicine to the patients. But at the same the onus of resolving the challenges the system brings should be borne by the regulator. The system can be implemented in a staggered fashion (by introducing barcodes on secondary packs for the domestic market to begin with) and slowly be retrofitted into every pharmaceutical production line. Hence, sufficient time should be provided to the manufacturers for a primary pack level implementation. Also, this would only be within the reach of manufacturers if the entire life cycle management cost of deploying the T&T system (software development, cloud deployment, database security/management, artwork standardisation, bar code standard selection etc.) is borne by the exchequer.

Recommendation 3.5.1: Rule 96 of the Drugs and Cosmetics Rules, 1945, should be amended to make a provision for bar coding on primary, secondary and tertiary packings of drugs.

Recommendation 3.5.2: A centrally located T&T solution is highly recommended as an addition to the function of track and trace. A centrally located database relying on global data standards for reporting can be used to create the much-needed national registry of active pharmaceutical manufacturing firms with details in the country. Although, sufficient time should be provided for a full blown implementation.

A T&T system will require every manufacturer to periodically upload (to NIC servers using the online portal) a standard data 'file' containing the unique identifiers on the primary packs, before each batch of the product is shipped. The standard data 'file' would be automatically generated from the software provided by NIC and would have no bearing on intellectual

[64] Secondary packaging level means the carton containing multiple primary packs including a mono carton.

property for the firm. This periodic data collection can be used to fulfil the following purposes:

i. A consumer can access the server via an SMS by punching in the unique identifiers on the primary packing and gain knowledge of the authenticity and source of the product procured and hence, help track and trace spurious medicines from the supply chain. Additionally many consumers are duped and deceived while purchasing medicines, as the true site of manufacture may not be necessarily revealed on the primary pack. (The brand of a medicine acts as a proxy for good quality for many consumers in the market.). However, the voluntary nature of feeding in data may limit the actual effectiveness or outcome of T&T.

Recommendation 3.5.3: Use T&T in providing complete information to consumers with respect to products manufactured via contract manufacturing.

ii. NIC can periodically forward this data to CDSCO, which should use this data to formulate a national registry that enumerates all active manufacturing firms in all Indian states along with data on what all pharmaceutical products are being manufactured by these firms including fixed-dose combinations. This in itself would serve as a real time monitoring system for CDSCO, and can be used to define the true quantum of duties for the national regulator to institute further reforms. It will also be possible to remove any irrational drugs from the market smoothly using such a registry.

Recommendation 3.5.4: The T&T system should be integrated with the newly rolled out Integrated Pharmaceutical Database Management System (IPDMS), also developed by NIC for the National Pharmaceutical Pricing Authority (NPPA), acting as a pharmaceutical monitoring and information system.

3.5.2 Role of XLN Software

Another major technological intervention has been the introduction of XLN software (XLN - Xtended Licensing, Laboratory & Legal Node). XLN is a software for transparent and speedy disposal of various licensing applications; it helps reduce the time lag between the collection of samples to declaration of results to dissemination of information to stakeholders. Apart from online processing of manufacturing and sales premises licences, the software maintains an online database of batches of spurious and substandard drugs which fail testing at various government approved laboratories.[65] A complete deployment of the tool was aimed at ensuring end to end transparency and a streamlined drug distribution chain.

Even though it was claimed that it has been implemented in 10 states and five more states were in the process of implementing the software, it was found that in states other than Gujarat and Maharashtra, XLN was being used only to track licensing of retail pharmacy

[65] During the course of our study, we attempted to carry out an analysis of the XLN data on NSQ drugs in one state, however the data, due to being poorly maintained and without any source files to provide explanation as to how the data had been consolidated, proved to be quite unusable.

outlets, i.e., the entire capabilities the software were not being exploited. Our research teams were told that full implementation of XLN can bring about more efficiency in the day-to-day functioning of SDRAs and is a key reform area which could have a massive bearing on the quality of drugs in India.

Recommendation 3.5.5: There should be speedy implementation of XLN software across all states.

XLN should be uniformly implemented pan India and the data on spurious and substandard samples should be made public in a precise and cogent fashion. Warnings regarding spurious samples and firms manufacturing substandard products should be issued online, and this should be disseminated using all electronic and print media channels.

4. Conclusions

To secure their health, consumers who have no means for verifying the authenticity or potency of drugs, need to be assured at all times that medicines made available to them are of good quality and safe to use. It, thus, falls upon other participants at various nodes of the supply chain to provide the much needed assurance. Since provision of good quality medicine is ensured through a participative process, the issues linked with it are intertwined and cannot be dealt with in isolation.

One of the major obstacles that both the industry and regulators face is related to the definition and interpretation of quality standards of the manufacturing process. The fact that domestic quality assurance parameters in India are not entirely harmonised with international norms, although in principle they are broadly aligned with each other, further complicates problems since the quality parameters applied to manufacture for the domestic and international markets may not be the same. During our study, we found that the domestic quality assurance parameters, even though broadly aligned with international norms, provide comparative elbow-room to both the industry as well as the drug regulatory regime.

The federal structure further increases complexity since states have differing regulatory capacities and their own interpretations of the guidelines set by the central government. This varied regulatory capacity in turn is the result of insufficiency of trained personnel as well as testing capabilities. Currently, none of the states in our study has adequate number (as mandated) of personnel to monitor the entire pharmaceutical industry. Besides, these regulators are entrusted with responsibilities other than quality assurance. They also need continuous training to help them keep up with the ever evolving international quality standards. Lack of drug testing infrastructure at state levels warrants the use of accredited private sector for service delivery, at least in the short term. The present system of monitoring manufacturing processes needs to be made more streamlined by following a risk-based approach, which provides cogent and specific corrective and prevention action points to manufacturer to ensure quality of products. Unless this is done, penalising manufacturing firms alone may not ensure effective compliance. Greater stringency in punitive action (while also deliberating upon the specific type of punitive action – financial penalty or suspension of licence) needs to be brought about for them to act as a deterrent.

The process of assuring quality of drugs to the consumer continues even beyond the production process and thus requires that necessary regulatory mechanisms be put in place. It is essential that the regulator is in a position to assess the quality of the product even after it has been marketed. Even though the regulator may not be able to assess all the formulations available in the Indian market, due to the sheer volume, under no circumstances should it be unable to assess the quality of product and identify its manufacturer. In order to have a system that makes consumers more vigilant and helps them participate in the quality assurance process, there is need for a comprehensive, product level database that should accessible to regulators as well consumers. This becomes a particularly crucial issue in the case of loan licensing, where the consumer has little knowledge of the true manufacturer of the product in the absence of clear packaging regulations. It is in such instances that the use of information technology/barcode-based track and trace mechanism can play a pivotal role. Such a mechanism can be used to address a number of challenges that we are at present faced

with, including effective recall of poor quality medicines, tracking the true manufacturer in order to weed out spurious medicines and the consolidation of national database for formulation of evidence-based policy action. This mechanism, if integrated with existing databases, can play a decisive role in ensuring better quality of drugs. This will also enable the government to initiate necessary actions to incentivise investment in therapeutic categories, of which there are fewer manufacturers. This being said, it should be noted that there is a link between health and the industrial policy and the industry can only be incentivised if they have the assurance that the policies are aligned to their needs. In the past, a few policies that had been put in place to encourage smaller manufacturers to upgrade their facilities remain unutilised due to the insufficiency of the loan amount. Therefore, there may be need to devise an innovative mix of policies that can drive self-regulation.

While the quality of medicines produced in India currently is under scrutiny, the good news is that the Indian regulator as well as industry are aware of the areas that need to be focused upon. Some recent reform efforts in this direction include the cabinet approval of a proposal to strengthen the drug regulatory system both at the level of the centre and the states.[66] The said proposal, among other things, seeks to upgrade both equipment and manpower in the existing drug testing laboratories as well as set up new laboratories, make provision for a training academy for regulatory and laboratory staff, and foster greater use of information technology enabled services. In addition, a recent report of the task force on enabling private sector to lead the growth of pharmaceutical industry recognizes that there is greater need for creating a conducive policy and operating environment which fosters growth of the industry.[67] Among its several recommendations, the task force highlighted the need to strengthen regulatory support by increasing the available manpower for effective monitoring and control of manufacturing and retail facilities. The present study adds to these reform efforts by bringing out the need for not only enhancing the capacity of the regulatory systems but also for improving upon the precise mechanisms for monitoring the sector (such as inspections, testing, etc.) with the aim of making them more effective. By channeling resources in these areas and actively engaging various stakeholders, India can become a widely acknowledged source of safe and efficacious medicines for all.

[66] See press release by the Ministry of Health and Family Welfare, Government of India, available at the following link http://pib.nic.in/newsite/PrintRelease.aspx?relid=124950 . Last accessed September 16th 2015.

[67] *Recommendations of the Task Force on Enabling Private Sector to Lead the Growth of Pharmaceutical Industry*. Government of India, 2015. Retrieved from available at http://pharmaceuticals.gov.in/taskforce1.pdf . Last accessed September 16th 2015.

THEME WISE LIST OF POLICY RECOMMENDATIONS

Defining Quality Medicine

1. A clear description of SSFFC terms should be included in the any ongoing or future study instituted to quantify the extent of poor-quality medicine in India and abroad.

2. Training directed at a clear understanding of these definitions should be imparted to stakeholders across the country and especially to regulatory officials.

3. Any ongoing or future study instituted to quantify the extent of poor quality medicine in India should focus equally on sampling from both urban and rural settings.

GMP Compliance

4. There is a definite need for a guidance/reference document for schedule M on the lines of those for WHO–GMP guidelines and its uniform application by all stakeholders.

5. We recommend that the state drug regulatory authorities impart more specialised skills to their inspectors and government analysts, either product-based or process-based. This can be achieved by ensuring that each inspector is trained in a niche segment and develops specialty in it through continuous experience.

6. Stringency with regard to GMP non-compliance should be increased. A fixed time frame for submission of response to a CAPA report should be made mandatory and failure to do so should trigger strict punitive action such as financial penalty on the defaulter (found to be in use in USA and China) as an alternative to the existing system of suspending a single production licence.

7. Use of 'reputation effects' as a deterrence mechanism can be carried out by regularly updating non-compliance data and making it available in the public domain. This exercise is already being done by the European Medicines Agency (EMA) through the European Union Drug Regulatory Authorities (EUDRA) GMP database.

8. Ensure the setting up of a permanent office of the CDSCO in countries that are high volume sources of API for the purpose of drug audit and quality certification. This initiative can be strengthened if the CDCSO comes out with an alert warning Indian manufacturers against suppliers of API who have repeatedly failed to meet the required standards.

9. The consolidation and building of a national registry of pharmaceutical manufacturers through an online database is a necessary exercise.

10. There should be more refined guidelines for labelling requirements and liability in the case of both loan licensing and third party manufacturing. This can be done by preparing an elaborate guidance document on the lines of those drafted by the US FDA and the ICH.

National Testing Capacities

11. In the current situation, NABL accredited private labs should be used to ease the backlog of drug samples in public drug testing laboratories until public testing facilities of central and state drug testing capacities are strengthened

Drug Alerts and Product Recalls

12. Introduce an online monitoring system for product recalls that requires a manufacturer to provide real-time information about the progress of the recall process. This information should then be made to available to the public through various media.

13. A system that integrates the drug alerts generated by the states and the centre should be developed to allow effective tracking of such poor quality products.

14. The PvPI data also needs to be integrated with the system of drug alerts even though both may operate independently.

Role of Technological Interventions

15. Rule 96 of the Drugs and Cosmetics Rules, 1945 should be amended for making a provision for bar coding on primary, secondary and tertiary packings of drugs.

16. A centrally locatedT&T solution is highly recommended as an addition to the function of track and trace. A centrally located database relying on global data standards for reporting can be used to create a much-needed national registry of active pharmaceutical manufacturing firms with its details in the country.

17. Use T&T in providing complete information to consumers with respect to the products manufactured via contract manufacturing.

18. The T&T system should be integrated with the newly rolled out Integrated Pharmaceutical Database Management System (IPDMS), developed by NIC for National Pharmaceutical Pricing Authority (NPPA) acting as a pharmaceutical monitoring and information system.

19. There should be a speedy and uniform implementation of XLN software across all states.

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Annexure 1

Rationale for State Selection for Field Study

In order to select the states for our study, we used a criterion based on parameters that define the pharmaceutical manufacturing and regulatory landscape in various states of India. In this context, three parameters seem to be of paramount importance – the burden of work upon state regulators, the export orientation of the sector and the state resources devoted to regulation of the sector. The first parameter, i.e., the burden of work upon the state regulator is defined as the ratio of the number of inspection facilities to the strength of the inspectorate in the given state. This parameter takes cognizance of the Mashelkar Committee recommendations for the ideal work distribution which is described below.

The Mashelkar Committee in 2003 undertook a comprehensive examination of drug regulatory issues in India and looked into the issue of shortage of manpower in state drug regulatory authorities (SDRA). The committee states:

"Earlier, the norms suggested were one drug inspector for 25 manufacturing units and one drug inspector for 100 sales units. In view of the amended requirement of statutory inspections (only once a year instead of twice a year and five-year validity of licence instead of two years), the requirement of appropriate inspectorate staff could now be considered as one inspector for 50 manufacturing units and one inspector for 200 sales units."

- Mashelkar Committee, 2003, p. 49

The committee's recommendation of maintaining a ratio of one drug inspector to 50 manufacturing units and one inspector for 200 sales units has been considered as the minimum benchmark that SDRAs are expected to maintain to efficiently monitor the entire product value chain. In order to augment the inspectorate staff keeping the recommendations of Mashelkar Committee in mind, the Planning Commission's (2011), "Report of the working group on Drugs & Food regulation for the 12th Five-year plan", calculated the additional budgetary requirements for every state to hire additional drug inspectors to meet this minimum benchmark.

In other words, the 1:200 ratio for a drug inspector to pharmaceutical sales units and 1:50 ratio of a drug inspector to manufacturing units crudely signifies that inspecting one manufacturing unit is four times the work for the inspectorate vis-à-vis inspecting a single pharmaceutical sales unit. In our analysis for the state selection, we seek to compare the existing work distribution across both manufacturing facilities and retail pharmacies, based on the Mashelkar committee recommendations. The data that we have at present does not reflect the inspectorate staff inspecting manufacturing facilities and retail pharmacies separately. Hence, we have assigned weights to each of the two. The ratio of total number of facilities that have to be inspected to the number of available inspectors is calculated as follows:

$$\left(\frac{\sum_i^n w_i x_i}{Total\ No.of\ Inspectors}\right)$$

where:
w= weights assigned to inspection facility of type i
x= the number of inspection facilities of type i
n= different types of facilities to be inspected

For simplicity, we assume here two types of inspection facilities, i.e. manufacturing units and retail pharmacies. If we assign the weight w_1 to manufacturing facilities as 1, then as previously stated, w_2 i.e. the weight assigned to retail pharmacies would be 0.25.

Thus, the last column of Table 1 below reflects this ratio which we then use to crudely identify states that are close to meeting the minimum prescribed ratio by the Mashelkar Committee. This ratio serves as one of the primary criteria to select states. Given that the data was missing for a number of states and that there is some probability that the numbers may even be under-reported, especially those of retail pharmacies, we remain suspicious of the extremely low values such as those of Odisha, Madhya Pradesh, Bihar and Goa. On the higher end, i.e., states that appear to be overburdened with close to 200 facilities (both manufacturing and retail units) per inspector, include Tamil Nadu, Punjab and Maharashtra , and those with more than 300 facilities (both manufacturing and retail units) per inspector include Delhi and Karnataka. For the purpose of our study, we wish to evaluate cases that are representative of both, overburdened and moderately burdened states. For the latter, one could consider the states of Andhra Pradesh, Gujarat and Kerala.

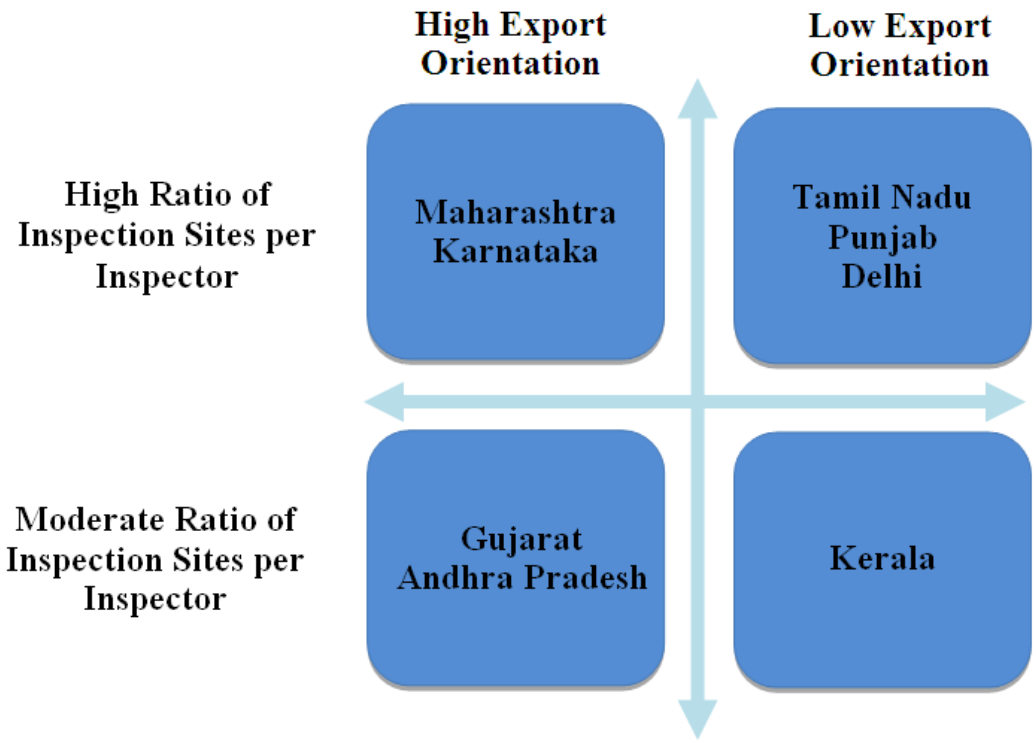
The second parameter is the export orientation of the sector in a given state, which is captured by the number of WHO-GMP compliant (COPP) plants in the state. While Schedule M is the minimum requirement mandated in order to obtain a licence and to supply within India, the manufacturer may be required to meet additional criteria depending upon where he chooses to market his product. In order to export to the US, manufacturers are required to meet with cGMP guidelines of the USFDA; the UK has its own MHRA guidelines, and there are other countries which recognise the Certificate of Pharmaceutical Product (COPP) that is issued to WHO GMP compliant plants. Since there is no data available for distribution of USFDA, MHRA and other country-wise certified plants in individual states, we rely on COPP certification data (which is given by the CDSCO) to assess the export orientation of the sector. This is given in the third column of Table 1 below. Among all states, Gujarat seems to have the highest export orientation followed by Andhra Pradesh and Maharashtra. While a number of states have no WHO compliant plants, among those on the lower end are Punjab, Rajasthan, Bihar, Kerala and Tamil Nadu. Again for the purpose of effective comparison, we focus on selecting states with high as well as low export orientation. Based on the above two parameters we thus narrow down our selection to the states of Gujarat, Andhra Pradesh, Maharashtra, Kerala, Tamil Nadu and Punjab.

Table 1: State-wise Distribution of Drug Inspectorate and Indicative ratios of Inspectorate to Inspection Sites

State	Total no. of Drug Inspectors[+]	Total No. of Manufacturers^	WHO GMP Units*	Number of Pharmacies ~	$\sum_{i}^{n} w_i x_i$	$\frac{\sum_{i}^{n} w_i x_i}{Total No. of Inspectors}$
Andhra Pradesh	130	1071	138	33938	9555.5	73.5
Arunachal Pradesh	6	0	0	347	86.75	14.4
Assam	NA	21	1	2429	628.25	NA
Bihar	56	209	5	4163	1249.75	22.3
Chhattisgarh	NA	10	NA	NA	NA	NA
Goa	5	72	42	255	135.75	27.1
Gujarat	84	874	307	20948	6111	72.7
Haryana	30	317	19	874	535.5	17.8
Himachal Pradesh	14	537	NA	2818	1241.5	88.6
J&K	64	69	NA	NA	NA	NA
Jharkhand	NA	67	NA	NA	NA	NA
Karnataka	49	231	52	71736	18165	370.7
Kerala	47	87	14	7531	1969.75	41.9
Madhya Pradesh	41	294	24	1381	639.25	15.5
Maharashtra	126	888	136	99614	25791.5	204.6
Manipur	NA	0	0	NA	NA	NA
Meghalaya	NA	1	0	150	38.5	NA
Mizoram	NA	0	0	382	95.5	NA
Nagaland	NA	0	0	NA	NA	NA
Odisha	41	69	1	1259	383.75	9.3
Punjab	45	170	7	35290	8992.5	199.8
Rajasthan	60	299	4	18214	4852.5	80.8
Sikkim	NA	27	NA	3082	797.5	NA
Tamil Nadu	138	446	5	101240	25756	186.6
Tripura	NA	3	NA	257	67.25	NA
Uttaranchal	NA	341	1	NA	NA	NA
Uttar Pradesh	88	499	21	30276	8068	91.6
West Bengal	NA	165	6	89630	22572.5	NA
A&N Islands	NA	0	0	NA	NA	NA
Chandigarh	NA	8	NA	NA	NA	NA
D&N Haveli	NA	36	NA	NA	NA	NA
Daman &Diu	NA	56	26	NA	NA	NA
Delhi	17	79	12	20978	5323.5	313.1
Pondicherry	NA	20	10	1716	449	NA
Lakshadweep	NA	0	0	NA	NA	NA
Total	**1041**	**6966**	**814**	**548506**		

Source: +Individual SDRA Websites, Press Releases, Media Reports; ^ CDSCO 2011 Data, Available at: www.cdsco.nic.in; *Iyer (2008); ~ Indiastat.com (2005); NA = Not Available.

If we categorise the states according to their export orientation and the inspection sites to inspector ratio, we arrive at the four-quadrant diagram shown below. In order to have a broad canvas for our case studies, we have chosen one state (apart from Delhi) from each quadrant. Such selection is based on our last parameter, that is, the resources dedicated by the state to the health sector.



For some of the states identified above, we look at the per capita health expenditure and drug expenditure as a percentage of health expenditure (see table 2 below). We also note safety alerts (for NSQ drugs) generated by the national regulator (CDSCO) based on the products sampled from various locations across the country. In the last column of Table 2, the locations of the manufacturers of such products for which alerts are generated during 2012-13, have been reported. The location of the manufacturer where the products for which safety alerts This acts as a proxy to assess the stringency of regulation in the state in which manufacturers of such NSQ drugs are located. Amidst all the selected states, we wish to narrow down our selection to two states with good resources and greater stringency and two others with moderate resources and relatively weaker regulatory stringency. It can be seen that Tamil Nadu and Kerala come across as those states well-endowed with resources in this sector, since they have the highest health expenditure per capita as well as the highest drug expenditure as a percentage of health expenditure, simultaneously least number of alerts have been reported for products manufactured in both states. On the other hand, there is Maharashtra with one of the lowest per capita expenditure but the highest number of drug alerts, and Gujarat, which has moderate per capita health expenditure and drug expenditure as a percentage of health, and a high number of drug alerts. In this way, Gujarat seems to be a particularly interesting case study with its high export orientation and relatively moderate inspection sites to inspector ratio.

Therefore, the four states that we select for the state study (other than Delhi) are Tamil Nadu, Kerala, Gujarat and Maharashtra. It should be noted that an attempt at having a comprehensive selection process has been made to select case studies that enable views from diverse stakeholders in various scenarios. However, we do acknowledge that the absence of data or limited data on a number of parameters may have resulted in some bias during the selection process.

Table 2: Health Expenditure Statistics for Selected States

S.No.	State	Overall government expenditure. (in Rs. Lakh)	Per capita expenditure (in Rupees)	Drug expenditure as a % of health expenditure	No. of safety alerts by manufacturer in the state 2012–13
1	**Maharashtra**	20882	18.7	5.2	11
2	**Gujarat**	15431	26.4	7.6	10
3	Punjab	1545	5.6	1	6
4	Andhra Pradesh	23458	27.9	10	3
5	**Tamil Nadu**	43657	65	12.2	3
6	Karnataka	14831	25.1	6.3	3
7	**Kerala**	24861	72.3	12.5	0

Sources: 1. The data on government expenditure on drugs was taken from the report of the high- level expert group on Universal Health Coverage, 2011.
2. The data on safety alerts was collated from the website of CDSCO.

Annexure 2

Rationale for Selection of International Jurisdictions for the study

The international study was carried out to facilitate a comparison of existing mechanisms for addressing quality issues in other countries and to draw lessons for India from their experience. We, therefore, have looked at countries which are either highly evolved in terms of their regulatory structure in this sector or are emerging and have issues similar to the ones that India faces. As Figure 1 below shows, issues of fake medicines and quality/effectiveness is most worrying in Asia and Africa and are not major issues in North America or Europe. With this is mind, we consider USA and EU for international benchmarking since these are also two of the largest markets for pharmaceuticals. Even though the IMS study (2011)[68] forecasts that pharmaceutical spending by the US will go down by 2015, its rank as the top market remains unchallenged. With regard to spending, the US is closely followed by several member states of the EU such as Germany, France, Italy, Spain and UK. While USFDA is known to be one of the strictest regulatory agencies across the world, the EMA also has a highly evolved regulatory system with a federal structure that is similar to that in India. The similarity with India is apparent since in EU, while the marketing authorisation for a drug product is centralised through the EMA,[69] the responsibility for licensing manufacture rests with the competent regulatory authorities within individual member states.

The case for China as an emerging leader in the pharmaceuticals sector is also quite interesting since it is the largest producer and supplier of API in the Asia-Pacific region. However, it also faces some of the issues that are relevant in the Indian context. One of the major challenges in the context of drug regulation being currently faced by China is the absence of strict regulatory requirements for chemical manufacturers who may be producing API instead of bulk chemicals. This is worrying since overseas manufacturers of finished dosage forms may purchase API from such chemical manufacturers.

Finally, we select another Asian country with an entirely different framework. In a major revamp of its healthcare system, Indonesia is the first Asian country to launch the world's largest health insurance system starting 2014 with full implementation expected by 2019. It proves to be a compelling case study since it promises to open up opportunities for the pharmaceutical sector, especially for domestic generics manufacturing companies that have a 70 per cent share by volume.

Thus, for the purpose of international benchmarking, we have selected USA, EU, China and Indonesia.

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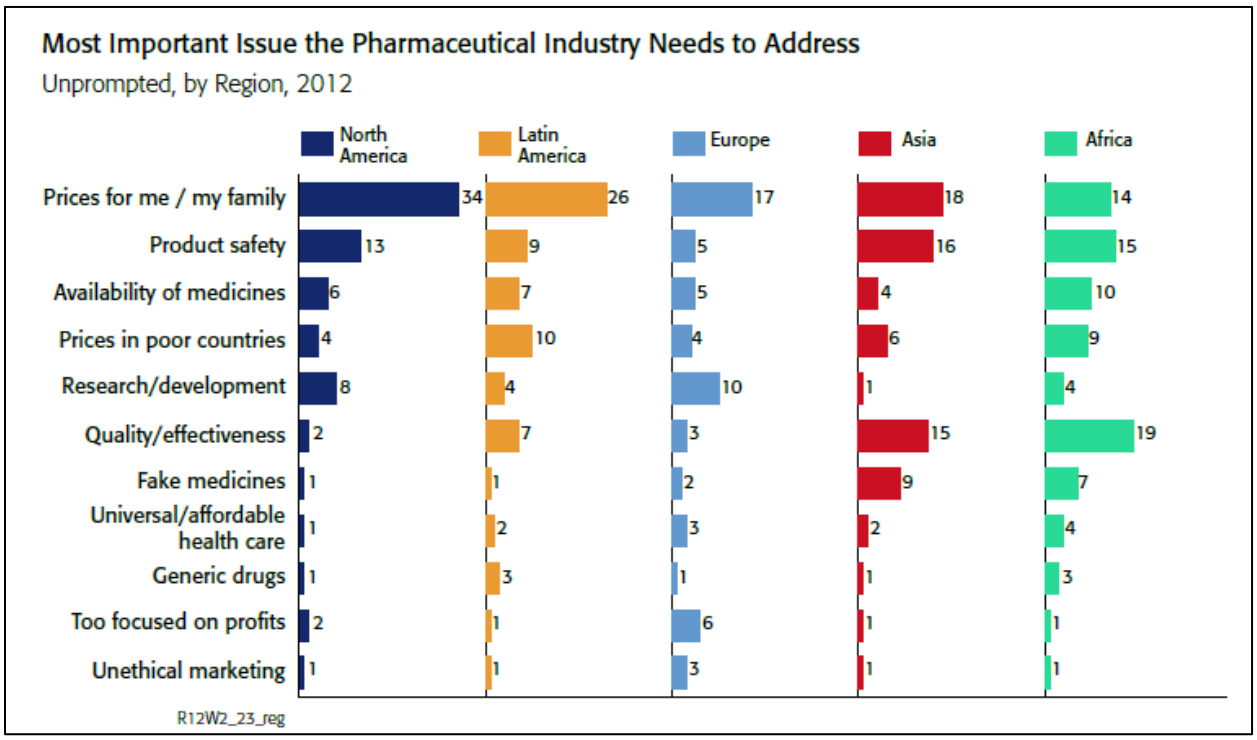
[68] The Global Use of Medicines: Outlook Through 2015 Report by the IMS Institute for Healthcare Informatics

[69] Alternatively, an applicant may also apply through the *decentralised* route to any particular member state or through *mutual recognition procedure* where the applicant may apply in various member states to recognise the market authorisation granted by a 'reference' member state.

Figure 1: Important Issues in the Pharmaceutical Sector across the World



Source: GlobeScan Stakeholder Intelligence eBrief

Annexure 3

Cross Country GMP Norms Comparison

GMP Norms	US	EU	China	Indonesia	Schedule M
1. **All manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.**	N.A.*	✓	✓	✓	✓
2. **Instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided.**	N.A.*	✓	✓	✓	✓
3. **Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by methods and personnel approved of by the quality control department.**	✓	✓	✓	✓	✓ Specific SOPs are to be maintained on who can draw samples from the production line.
4. **Operators are trained to carry out the procedures correctly.**	N.A.*	✓	✓	✓	✓
5. **Records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviation is fully recorded and investigated.**	✓	✓	✓	✓	✓
6. **Records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form.**	N.A.*	✓	✓	✓	✓
7. **There is proper storage and distribution of the products that minimises any risk to their quality.**	N.A.*	✓	✓	✓	✓
8. **There is a system to recall any batch of product from sale or supply.**	✓	✓	✓	✓	✓ Complete SOP is established.
9. **Complaints about marketed products are examined; the causes of quality defects are investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.**	N.A.*	✓	✓	✓	✓
10. **The aspects of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, and qualified and validated.**	N.A.*	✓	✓	✓	✓
11. **There is an annual review of qualification and validation.**	N.A.*		At defined	✓ Internal ☒ External	✓

GMP Norms	US	EU	China	Indonesia	Schedule M
			intervals		
12. **There is a quality manual or validation master plan in place.**	N.A.*	✓	✓	✓	✓
13. **The responsibility for performing the validation is clearly defined.**	N.A.*		✓	✓ Roles of QA and QC heads are explicitly listed. Their spheres of influence are independent of each other.	✓
14. **The validation studies conducted are in accordance with predefined and approved protocols and stored properly.**	N.A.*		✓	✓	✓
15. **There is a person responsible for handling complaints and deciding on the measures to be taken designated, together with sufficient supporting staff.**	N.A.*	✓	✓	✓	✓ This duty is assigned to the head of the QA team.
16. **There is a written procedure describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.**	✓	✓	✓	✓	✓ Complete SOP has to be established.
17. **The complaint records are regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.**	The records are reviewed but regularity is not specified	✓	✓	✓	✓
18. **All responsible staff have their specific duties recorded in written descriptions and have adequate authority to carry out their responsibilities.**	✓	✓	✓	✓ he GMP guideline explicitly mentions an Organogram and the scope of each individual's duty to be assigned.	✓
19. **All personnel are aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.**	✓	✓	✓	✓	✓
20. **The heads of the production and quality control generally have some shared, or jointly-exercised, responsibilities relating to quality.**	N.A.*	✓	✓	✓ The duties are explicitly defined.	✓
21. **Are batch processing record kept for each batch processed, based on the relevant parts of the currently approved specifications on the record.**	✓	✓	✓	✓	✓
22. **The batch packaging records are being kept for each batch or part batch processed. It should be based**	Batch production records	✓	✓	✓	✓

GMP Norms	US	EU	China	Indonesia	Schedule M
on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors	include both processing and packaging information.				
23. **The finished product contains the information on ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorisation; the ingredients are of the required purity, in their proper container and are correctly labelled.**	✓	✓	N.A.	✓	✓
24. **Therecordsaremadeoftheresultsofinspectingandtestingthematerialsand intermediate, bulk and finished products against specifications. The product assessment includes a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.**	✓	✓	Only the first part is found.	✓	✓
25. **There are procedures for no batch of product to be released for sale or supply prior to certification by the authorised person(s), that it is in accordance with the requirements of the marketing authorisation.**	✓	✓	Requires the signature of the qualified person.	✓	✓
26. **There is availability of sufficient samples of starting materials and products retained to permit future examination of the product, if necessary. The retained product is kept in its final pack unless the pack is exceptionally large.**	✓ Section on reserve samples mentions that double the quantity of sample that is required to conduct the quality tests should be kept.	✓	✓	✓	✓ Same as in case of US; maintain double the sample required for conducting all quality tests.

Notes: N.A. refers to 'Not available in the main GMP document'. The asterisk denotes that supplementary documents might contain the specific GMP norms. While for most countries, several of the WHO–GMP guidelines are recorded verbatim in their respective GMP guidelines, in the USA, most of the guidelines are distributed over multiple sections and several details such as those for qualification and validation as well as responsibilities of key personnel could not be found in the Code of Federal Regulations. Hence, N.A. in the case of the USA does not signify that GMP norms are not adhered to but simply that they were not located in the main GMP document.

Annexure 4

FORM 13

(*See* rule 46)

Certificate of test or analysis by Government Analyst under section 25 (1) of the Drugs and Cosmetics Act, 1940

1. Name of Inspector from whom received .....
2. Serial No. and date of Inspector's memorandum.....
3. Number of sample .....
4. Date of receipt .....
5. Name of drugs purporting to be contained in the sample .....
6. Condition of seals on the [1][packet or on portion of sample or container] .....
7. Result of test or analysis with protocols of test or analysis applied .....

In the opinion of the undersigned the sample referred to above is of standard quality as defined in the Drugs and Cosmetics Act, 1940 and Rules thereunder
is not of standard quality as defined in the Drugs and Cosmetics Act, 1940 and Rules thereunder

for the reasons given below:-

Date..... *Government Analyst.*

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1. Subs. by G.S.R. 59(E), dt. 7.2.1995.

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