A STUDY ON THE INDIAN PHARMACOPOEIA AND HOW IT IMPACTS DRUG QUALITY

By Priyanka Pulla
Reviewed by: Shirish Kulkarni, Ph.D.

FUNDING SUPPORT
THAKUR FOUNDATION

INDEX - A Study on The Indian Pharmacopoeia Commission and Its Impact On Drug Quality

Contents

Executive Summary

The Indian Pharmacopoeia (IP) plays a critical role in ensuring the safety and efficacy of drugs sold in India. It does so by setting chemical and physical specifications for drugs – an important task because the safety and efficacy of drugs are often dependent on these specifications. Once the IP sets specifications, they are enforced by India's central drug regulator, the Central Drugs Standards Control Organisation (CDSCO) and 36 state and union-territory regulators.

However, the IP does not set all specifications for all drugs sold in the country. It comes into the picture mainly in two scenarios: (1) when the IP has an "individual monograph" for a drug, which contains all quality specifications for that drug, and (2) when it has a "general monograph for a dosage form", which covers all specifications for that dosage form, such as tablet, powder or injection.

As per the Second Schedule of the Drugs and Cosmetics Act, when the IP has an individual monograph for a drug, this monograph defines the standard quality for this drug in India. When neither the IP, nor any other global pharmacopoeia has an individual monograph for a drug, the drug is called a "patent or proprietary medicine". In this case, Schedule V of the Drugs and Cosmetics Act, 1940, defines a drug of standard quality as one which complies with the general monograph for the dosage form.

Given this scenario, a serious lacuna is created in two situations: if the IP or any global pharmacopoeia lacks an individual monograph or a general monograph for a drug or dosage form, or if an individual monograph or general monograph exists in the IP, but doesn't comply with international standards. In both cases, the manufacturer, CDSCO and state regulators are left with too much discretion in setting specifications, a situation that has had troubling consequences historically.

This study, the first independent study to look into this issue, finds the IP to be lacking on both counts. It finds that the number of drugs covered in IP's individual monographs are too few, while individual and general monographs are frequently not in line with global benchmarks. (This study did not look into whether IP general monographs covered all dosage forms available in India).

For instance, this study estimates that out of all drug formulations approved in India since 1961, the 2022 edition of the IP contains individual monographs for approximately 34.5%. A key deficiency of the IP 2022 lies in the area of fixed-dose combinations, or FDCs. This study finds that out of an estimated 4046 FDCs

approved by CDSCO and state regulators in India as on today, the IP 2022 has individual monographs for only 157 --- a coverage of 3.8%.

The lack of IP monographs for widely used drugs has triggered several quality problems in the past, as illustrated by two cases discussed in this study. The first case is that of injectable liposomal amphotericin B, a drug used to treat the deadly and disfiguring disease, mucormycosis, and other fungal infections. Even though this drug is included in India's National List of Essential Medicines, testifying to its criticality to India's health priorities, neither IP 2018, nor the latest 2022 edition of IP have an individual monograph for this drug formulation.

This is a problem because liposomal amphotericin is a complex drug, whose quality specifications are inextricably linked with the drug's safety and efficacy. Challenges in manufacturing safe and effective liposomal amphotericin came into the spotlight in 2016, when the CDSCO asked state regulators to suspend the manufacturing licenses of 10 companies making liposomal amphotericin, because these products were found to be toxic.

For such a complex drug, an IP monograph would have gone a long way in helping manufacturers adhere to minimum quality requirements. The lack of such a monograph would have been especially significant during the 2021 epidemic of Covid-associated mucormycosis, which led to widespread shortages of liposomal amphotericin. In response, the CDSO gave licenses to six new manufacturers initially, a number that grew further later. Some of these manufacturers lacked the skills to set the right specifications for their product, as the case study shows. This, in turn, would have impacted the safety and the efficacy of the drugs they made, a possibility that needs to be investigated further.

Another illustrative case is that of itraconazole capsules, for which IP 2022 lacks a monograph as well. In 2018, doctors from New Delhi's Ram Manohar Lohia Hospital documented widespread quality problems with the itraconazole formulations sold by Indian manufacturers. They found that the capsules varied widely on key quality parameters that impact the efficacy of this drug, such as number of pellets in each capsule and the pellet size. This variation could lead to a smaller dose of this drug to be delivered to the patient, the doctors observed. The small dose, in turn, could provide the ideal ground for deadly pathogens like *Aspergillus to* become resistant to itraconazole.

Such drug resistance is already a challenge in Indian hospitals and out-patient settings, given India's high burden of fungal disease. As per one 2014 estimate, the country was seeing between 27,000 and 0.17 million cases of chronic pulmonary aspergillosis each year, a disease caused by *Aspergillus* genus of fungi, with up to 15% mortality.

Apart from the poor coverage of drugs sold in India, an equally concerning problem is that both individual and general monographs in the IP are frequently not in line with guidelines from the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH). ICH guidelines are considered a global benchmark for drug quality today, with many countries, as well as the World Health Organisation (WHO), relying on them to ensure drug quality.

Yet, even though ICH guidelines recommend dissolution tests for all solid oral dosage forms, and impurity tests for all dosage forms, many IP monographs are missing these tests.

The Indian Pharmacopoeia Commission (IPC), the autonomous government agency that writes the IP, did not disclose how many individual monographs in IP 2018 and IP 2022 lacked dissolution tests or impurity tests, although its scientific director Rajeev Raghuvanshi acknowledged that this problem exists.

However, the author found that only 2 out of the 14 general monographs for solid oral dosage forms in IP 2018 carried a dissolution test, while only one of 42 general monographs for all dosage forms carried an impurity test (this calculation is specific to tests for related substances, that are formed due to degradation or through the interaction of the active ingredient and excipients. Tests for sterility and bacterial endotoxins were not counted as impurity tests). These numbers show that the IP has historically not given dissolution tests and impurity tests the importance they deserve.

The lack of dissolution tests in some medicines can directly impact their efficacy. One example is albendazole, an anti-helminthic drug, which has been shown in several studies to lose efficacy against hookworm infections when its rate of dissolution is poor. Even though this fact was first uncovered as early as the 2000s, the IP did not introduce a dissolution test for albendazole until 2019.

Albendazole is used widely in Indian deworming programs to protect children against helminthic infestations, and adults against lymphatic filariasis. This means that the lack of a dissolution requirement in IP for many years could have been partly responsible for India's continued high burden of helminthic infections, and its repeated failures in meeting filariasis eradication deadlines. Overall, the case of albendazole illustrates how the incompleteness of an IP monograph can directly impact the country's public-health goals.

Meanwhile, if the lack of impurity tests in some monographs is concerning, it is equally concerning that for the IP monographs that do require impurity tests, the limits are far more lenient than those recommended by ICH. This is worrying because impurities do not just interfere with the stability of drugs, but can also be toxic to patients.

One example is nitrosamines, a class of potentially carcinogenic impurities that most ICH regulators today impose limits on. IP 2022 has not imposed any mandatory limits on nitrosamines for all drugs, as ICH countries have. What's more, IP 2022 has also not mandatorily limited nitrosamines in the small subset of widely used drugs, such as valsartan and ranitidine, which are known to be vulnerable to nitrosamine contamination. This gap in the IPC is putting Indian patients at risk of developing cancer from the very medicines they consume.

In 2021, the IPC appointed a new scientific director, who has indicated that he plans to bring the IP more in line with ICH requirements. In doing so, he has taken a different stance from several of his predecessors, who had argued that India need not comply with ICH guidelines. These predecessors, former members of the IPC's scientific body, were concerned that ICH was a protectionist agency, that was imposing arbitrarily stringent standards to stifle competition from the generics industry. However, whether this stance was entirely driven by ICH's shortcomings, or by the IPC's need to protect the small- and mid-sized Indian industry, which has historically struggled to meet ICH standards, is debatable.

Against this background, it is a good sign that IPC's new director, Rajeev Raghuvanshi, is speaking a different language. Still, his efforts to bring IP 2022 more in line with ICH guidelines haven't been aggressive enough. The IP 2022's line on nitrosamines is one example of this. Raghuvanshi has said that the reason behind the IPC's decision to not bring in mandatory limits on nitrosamines was that the Indian small- and mid-sized pharma industry lacked the skills and infrastructure to comply with these limits. This means that the historical challenges faced by Indian industry in meeting global standards remain even today.

This IPC stance --- to shy away from imposing stringent quality specifications unless the industry can comply --- has created a Catch 22 situation over the years. Global experience shows that few industries are capable of regulating themselves, because there is no economic incentive to do so. So, without the IPC taking the first step, the gap between ICH guidelines and the IP is likely to persist for a long time. This would mean the quality, safety and efficacy of Indian drugs would continue to be lower than those of drugs sold in ICH countries, like the USA, European nations or Japan.

It can also be argued that the IPC's stance to prioritise industry well-being over patient health is unethical. The organisation's foremost goal, after all, should be the safety of patients, rather than to protect the pharmaceutical industry. The only situation in which the IPC ought to lower quality specifications, is if higher specifications will impact drug supply enough to lead to shortages. Even in such a situation, the harm from poor quality drugs, such as nitrosamine-tainted drugs, or drugs that don't dissolve properly, must be weighed against temporarily reduced access.

There are ways out of this Catch 22. It is possible for other government bodies, such as the Department of Pharmaceuticals, to invest in building the skills and infrastructure of the small and mid-sized pharma industry. The Production Linked Incentive scheme of this department can be expanded to enable these companies to meet ICH standards. This will give the IPC the freedom to improve drug quality more aggressively.

To do this, however, the IPC needs to clarify its own vision. Since its inception, the IPC's vision has, controversially, been "to promote the highest standards of drugs for use in humans and animals within practical limits of the technologies available for manufacturing and analysis". It can be argued that the IPC has frequently used this consideration of "practicality" as an excuse to lower quality specifications, hurting patients in the process. The IPC must rewrite its vision statement in a way that patient health takes priority over industry growth. Only then will it be able to fulfil its primary purpose – to ensure that only safe and efficacious drugs are sold to Indians.

This study is the first independent attempt to identify key lacunae in the IP, which plays a central role in ensuring the quality of India's drug supply. However, this study suffers from several limitations. First, the ideal way to evaluate the completeness of the IP would have been to compare the number of individual monographs in it with the top selling drugs in India, by volume. However, this data wasn't available to the author.

Second, among quality specifications, this study focused primarily on dissolution tests and impurity tests, although the IP needs to be evaluated for its completeness for many other specifications. This study also doesn't delve deeply into IP monographs for active pharmaceutical ingredients, biologicals, blood products, vaccines etc, focusing instead on chemical formulations.

Finally, this study doesn't evaluate the IP's performance on reference standards and impurity standards – small highly pure samples of drugs and impurities – which the IPC is tasked with supplying to Indian manufacturers.

Further studies are required to evaluate how well the IPC does in these other areas.

Acknowledgements

Many individuals and organisations helped shape this report by sharing their insights and data. While it is not possible to name everybody, the author wishes to thank the following:

- Rajeev Raghuvanshi, scientific director of IPC, for explaining IPC's current and future plans.
- Anthony C Cartwright, former member of UK Medicines Control Agency (now the Medicines and Healthcare products Regulatory Agency) and former member of ICH working groups on impurities, for discussing the evolution of ICH impurity guidelines.
- Officials from India's state regulators in Maharashtra, Uttar Pradesh, Sikkim, Himachal Pradesh, Telangana etc for explaining how the state regulators interact with the IPC.
- Representatives from the Indian Drug Manufacturers' Association (IDMA), Indian Pharmaceutical Alliance (IPA), the Pharmaceuticals Export Promotion Council of India (PHARMEXCIL) for explaining their stance towards the ICH.
- Former members of IPC's scientific body, who explained the historical evolution of the IPC.
- Scientists from the domestic pharmaceutical industry, who explained how they use the IP.
- Officials from the US Pharmacopoeia and the US FDA who responded to questions on US quality standards and the ICH.
- The World Health Organisation's team on norms and standards for pharmaceuticals, for responding to questions on how they view the ICH.
- Patient advocacy group People's Health Movement, for explaining their stance towards the ICH.
- Several independent pharmaceutical quality consultants, who discussed the role of IP.
- Dinesh Thakur, director, the Thakur Family Foundation, for reviewing the completed report for accuracy, and offering suggestions.

- The Thakur Family Foundation, who funded this study. The report does not necessarily reflect the views of the Foundation.
- MONIMO LLP for designing the report and post-production editing.

Rationale and Scope of Study

The Indian Pharmacopoeia (IP), a text prepared by the Indian Pharmacopoeia Commission (IPC), plays a critical role in ensuring drug efficacy, safety and quality in India. It does so by defining standard quality for drugs sold in the country.

The IP publishes specifications in the form of two types of monographs. "Individual monographs" tell the manufacturer what chemical and physical parameters a specific drug formulation or API should comply with. "General monographs for dosage forms" do the same for the entire class of medicines that are sold in a particular dosage form, such as tablets or injections.

It is important for the IP to be complete in two ways.

First, it must have individual monographs for as many drugs sold in India as possible; if not, the CDSCO and state regulators allow manufacturers to set specifications by themselves. And because manufacturers have an incentive to cut corners, there is a risk that these manufacturer-led specifications could be inadequate to ensure the safety, efficacy and quality of the drug.

Second, for each individual monograph and general monograph, the specifications must be in line with international standards. A global consortium of drug regulators called the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) publishes guidelines on how to develop such drug specifications. These guidelines have today become the de-facto global benchmark for drug quality.

So, comparing IP monographs with ICH guidelines is a good way to assess the completeness of the IP.

Against this background, this report aims to assess the completeness of the IP in two parts:

Part A) How widely do individual monographs in the IP cover the universe of drugs sold in India?
Part B) When the IP has an individual monograph or a general monograph, are the specifications in line with ICH guidelines?

This report does not attempt to answer these two questions comprehensively. Instead, it aims to develop a broad perspective on the above questions by seeking data from IPC, through interviews with former and current IPC officials, pharmaceutical industry scientists, and case studies of IP monographs.

A Brief History of the Indian Pharmacopoeia Commission (IPC)

During the late-nineteenth century, when India was a colony of the British, drugs sold in India complied with the specifications in the British Pharmacopoeia. In the book, The British Pharmacopoeia, 1864 to 2014, author Anthony C Cartwright wrote that editions of the British Pharmacopoeia were frequently adapted for local use in India. For instance, given the tropical climate of India, the 1898 edition of the British Pharmacopoeia allowed the use of extra alcohol in liquid extracts to prevent degradation.

When India attained independence in 1947, the use of the British Pharmacopoeia came to an end. A new body, the Indian Pharmacopoeia Committee, was formed in 1948, which began preparing the IP, a pharmacopoeia exclusively for India, from then on. But over the next few decades, the Committee failed to keep up with the needs of the rapidly growing Indian pharmaceutical industry, and to ensure drug safety and efficacy.

India derecognized product patents in 1970, giving a boost to the local pharma industry, which could now reverse-engineer drugs developed and patented elsewhere in the world. This led to the industry expanding at a quick pace, and flooding the market with products. Meanwhile, the Committee was publishing new editions of the IP every ten years or so, while other global pharmacopoeias, like the British Pharmacopoeia and the US Pharmacopoeia, were doing so annually.

Further, the Committee did not develop reference standards: small and highly pure samples of drugs and impurities that manufacturers require while testing their products to ensure compliance with IP specifications. So, manufacturers had to turn to the British Pharmacopoeia and the US Pharmacopoeia to purchase these reference standards at a high cost. “We were lagging far behind,” GN Singh, a former scientific director of IPC, told the author in a January 2022 interview.

To remedy this situation, in 2005, the decision was made to establish a new, autonomous body, the IPC. The body began working unofficially in 2005 itself, publishing a new edition of the IP in 2007. However, the IPC was formally incorporated only in 2009.

From the very beginning, the goal of the new IPC was circumscribed by the limitations of the Indian pharma industry in the mid-2000s.

According to a 2007 presentation by Saranjit Singh, a member of the scientific body of the newly formed IPC, by this time, a gap had already formed between the quality specifications, skills and infrastructure of the small- and mid-sized industry that supplied to domestic consumers, and the large industry that exported to regions that followed ICH guidelines (US, Europe, Australia etc).

The latter group was rapidly acquiring the ability to make high quality products, while the former group operated at a lower level, lacking access to critical technologies like High Performance Liquid Chromatography (HPLC) . One estimate from 2007 puts the total number of licensed manufacturing firms in India at the time at 6000, with only 100 units exporting to ICH countries.

Against this background, the goal of the IPC was to publish more frequent editions, to develop reference standards, and to keep up with global standards as much as practically possible. The idea of not pushing the industry beyond what was "practically" feasible was baked into the IPC's vision. A statement from the IPC's 2010-11 annual report, its first annual report after the body was officially formed, says its vision was to "promote the highest standards for drugs for use in humans and animals within practical limits of the technologies available for manufacture and analysis". This vision statement remains the same in the IPC's 2020-21 annual report.

Since its formation, the IPC has been publishing the IP every four years, with addendums in between. According to GN Singh, the decision to publish the text every four years, instead of every year, was taken in response to requests from the small-scale industry, which communicated that buying a new edition every year would be too expensive. "The books cost about Rs 40-50,000 at that time. Then representatives of the small-scale industry approached Indian Pharmacopoeia Commission and the ministry (of health and family welfare). They pleaded that…bearing such a high cost is not feasible."

Today the IPC retains the three-tiered structure that was setup in 2009. These three tiers are the general body, consisting of 25 members, which include government officials, and industry representatives from manufacturing associations such as the Indian Drug Manufacturers' Association (IDMA) and the Indian Pharmaceutical Alliance (IPA). In addition, there is a governing body of a similar composition, including a mix of government and industry representatives. Finally, the scientific body contains 23 members with representatives from Central Drugs Standard Control Organisation (CDSCO), state regulators, experts in regulatory affairs, and government drug-development experts.

The latest edition of the IP was published on July 2022, and will become official in December 2022. It contains a total of 3284 monographs, which include 1245

formulation monographs. As on August 2022, the IPC was also supplying a total of 652 reference standards and 300 impurity standards.

The IPC's stance towards the ICH

i.) The Stance

Historically, the IPC's stance towards ICH was one of distrust.

The ICH was founded in 1990 by six bodies: the drug regulators of the US, Europe and Japan, and three industry associations representing new drug developers (frequently referred to as innovator firms) from the same regions.

The consortium's purpose was to harmonise the drug standards of the three regions, which were conducting 90% of the global pharmaceutical research at the time, and were the original developers of most drugs available around the world then. Most countries outside the US, Europe and Japan at the time, including India, were manufacturing generic versions of the drugs developed in ICH regions. This situation continues, by and large, even today.

As on date, the ICH has developed a total of 61 guidelines that advice regulators and manufacturers on how to ensure drug quality, safety and efficacy. Several of these guidelines pertain to drug specifications, which are the subject of this study.

Given the structure of the ICH in the 1990s and the 2000s, and the fact that it lacked both representation from low- and mid-income countries and from generics manufacturers, several members of IPC's 2009 scientific body believed the ICH represented innovator-pharma interests. In interviews with the author, these members argued that the ICH was a protectionist agency that was deliberately creating stringent quality guidelines to stifle competition from generics.

Further, IPC members said, the consortium's guidelines were driven by the technology that was available in the nineties to pharmaceutical innovators, rather than by public-health concerns like safety and efficacy. "Big pharma wanted to show that they were better than all others. So, they brought in lot of controls through standards. ICH was mostly foreign pharmaceutical companies. They wanted to capture the market, and (show that) they are the best, and (generics makers) are not the best," R Sridharan, a member of the IPC scientific body and vice-president of the Mumbai-based Lupin Limited in 2010, said in a May 2022 interview with the author.

One consequence of this belief among IPC members was that the Commission imposed more lenient drug-specifications on Indian manufacturers. This stance

led to a large gap between IP specifications and ICH guidelines, which remains even today.

Some of the IPC's distrust for ICH can be explained by the lack of transparency around the early ICH guidelines. Two examples of this are the ICH Q3A and Q3B, guidelines for controlling organic impurities in active ingredients and drug formulations. The ICH rolled these out in 1995 and 1996, respectively.

The basis of the reporting and identification thresholds in ICH Q3A and Q3B were never captured in any ICH documents, as the author reported in The Wire Science. This led to non-ICH regulators questioning whether these thresholds were based on the toxicity of these impurities. Instead, these regulators speculated that because innovator firms had access to advanced technologies, like High Performance Liquid Chromatography (HPLC), the ICH was treating these technologies as the baseline to set unnecessarily stringent standards.

ii.) A critique of IPC's stance towards the ICH

A closer examination of IPC's historic distrust towards ICH reveals that not all aspects of it were justified.

Firstly, even though the bases of the thresholds in ICH Q3A and Q3B were not spelt out in the original documents, some of these thresholds were later validated by independent researchers. In 2012 and 2017, two separate groups published peer-reviewed papers that provided support for the 0.1% identification threshold in ICH Q3A.

Secondly, subsequent ICH guidelines, like ICH Q3C for residual solvents, ICH M7 for mutagenic impurities and ICH Q3D for elemental impurities, provided transparent justification for the limits they proposed. Yet, as on 2022, the IP has not yet adopted the principles of ICH Q3A, Q3B, M7 or Q3D widely.

As for the structural shortcomings of ICH, the consortium subsequently remedied them through reforms that lasted between 2010 and 2015. At the end of the reforms, both generics manufacturers and low- and mid-income countries were invited to join. Today, the ICH has a total of 20 members, including regulators from the upper-mid-income countries China and Brazil, as well as one association of generics manufacturers, the International Generic and Biosimilar Medicines Association. In 2015, the Indian regulator CDSCO also joined as an ICH observer, although it hasn't yet pitched to become a member.

Moreover, even if the ICH's early lack of transparency and conflicted structure were valid concerns for India, it is pertinent to ask why India continued to rely heavily on the assessments of ICH regulators to approve new drugs in the country.

Many, if not most new drugs the CDSCO has historically approved, and which the IPC has published specifications for, were first developed in ICH countries. Further, under rule 101 of the New Drugs and Clinical Trials rule 2019, the CDSCO frequently waives off local clinical trials for any drug that has already undergone trials in the ICH regions Europe, US, Japan etc. Even before this rule came into being in 2019, the CDSCO was known for waiving off local clinical trials for drugs approved in ICH regions, as noted by the Parliamentary Standing Committee on Health and Family Welfare in its 59th report on CDSCO.

Given this excessive reliance both CDSCO and IPC have placed on the judgement of ICH regulators, the IPC's stance towards ICH drug-specifications is paradoxical.

The only explanation for this stance is that the IPC didn't wish to force stringent specifications on Indian manufacturers, not for reasons of patient safety, but because it could have hurt the Indian industry's growth prospects, and increased the cost of medicines. Indeed, even though the IPC has criticized ICH guidelines for not being motivated by patient safety, its own drug specifications aren't particularly mindful of patient well-being either.

For instance, as this author reported in The Wire Science, the 2007 edition of the IP set the identification threshold for organic impurities at three times the threshold suggested by ICH. The rationale behind the IP threshold wasn't that organic impurities were not toxic below this level. In fact, neither the IPC, nor Indian manufacturers evaluated any pharmacovigilance data to validate this threshold, as ICH had done for its 0.1% threshold. Instead, this limit was chosen because Indian manufacturers couldn't comply with anything more stringent. This points to the IPC's own double standards in accusing the ICH of not prioritising patient safety, even though the IPC was guilty of the same in India.

All this makes it clear that the IPC's main objective in setting lenient specifications for the Indian industry was to enable it to grow, much like the India's 1970 Patent Act did. This fact is acknowledged by several former IPC members too. "If we had implemented the 0.1% ICH identification threshold for organic impurities then, it would have been a killer of the small- and mid-sized industry at large," a former IPC scientific body member, who spoke to the author on condition of anonymity, said. He further added that the death of the small industry would have led to medicine shortages in India.

Another former IPC member in 2009, JL Sipahimalani, who was also a member of the IDMA at the time, said in a March 2022 interview that not just the Indian small-

and mid-sized industry, but also Indian state-drug regulatory labs lacked the HPLC and gas chromatography (GC) instruments that would be needed to comply with ICH standards in the 2000s.

The IPC's strategy, to protect the Indian industry, could have benefited patients too, if it had been time limited. In other words, if the IPC had planned a systematic transition to full compliance with global standards, the industry would have grown in size and revenue, while also improving quality. But the IPC never set any deadlines for such a transition.

As a result, IP standards continue to be lenient even to this day, thirteen years after the IPC was formally created. The 2018 edition of the IP, which is in force until December 2022, continues to have looser impurity standards than ICH Q3A, Q3B, Q3D and M7.

This leniency is also reflected in dissolution tests. The ICH Q6A, a guideline which lists specifications for new drugs, requires all solid dosage forms, such as film-coated tablets or prolonged-release tablets, to comply with dissolution tests. In contrast, IP 2018 doesn't impose dissolution tests on these dosage forms. *(This is discussed further in the An Assessment of the IPC: Part B)*

This IP's alignment with ICH standards may potentially improve in the future. In 2021, the IPC appointed a new scientific director, Rajeev Raghuvanshi, who previously headed a formulation development team at the Hyderabad-based Dr Reddy's Laboratories.

Raghuvanshi has since indicated that he intends to bring the IP more in line with ICH.

In a February 2022 interview, he told the author that including more dissolution tests and impurity tests for monographs in the IP was a priority for him. Indeed, the IP 2022, which was the first to be published in his tenure, does upgrade several monographs by adding dissolution tests and impurity tests.

However, the IPC has refrained from making several critical changes even after Raghuvanshi's tenure began. One such change relates to nitrosamines, a class of potentially carcinogenic compounds, that occur as impurities in several drugs. Even though the risk to public health from nitrosamines is clear, and ICH countries have introduced mandatory limits on nitrosamines in all drugs, the IP 2022 has failed to do the same.

Asked why the IP 2022 has taken a slow approach to such a worrying public-health concern, despite Raghuvanshi's pro-ICH stance, Raghuvanshi told the author in an August 2022 interview that it was because much of the industry was still in no

position to comply. He said the IPC's strategy was to introduce the industry slowly to nitrosamine-testing, instead of imposing mandatory limits suddenly.

"When it comes to policy, everyone has a different way of doing things. We are taking a stepwise approach. Today, if I put a nitrosamine test in monograph, people won't be able to analyse because of infrastructural and cost issues, and availability of reference materials. So, I have to take a safer approach, so that the industry gets sensitized, and has time to prepare."

Overall, the IPC's continued decision to go slow with harmonisation has led to two tiers of drug quality in India today. The large industry, which exports to ICH countries, complies with more stringent quality standards. Sometimes, the more stringent quality standards spill over to the products they sell domestically too. According to Sudarshan Jain, secretary general of the Indian Pharmaceutical Alliance (IPA), a lobby group for 24 export-oriented Indian companies, all IPA member companies make the same quality of product for all their markets. This claim is hard to verify independently, however, and other independent observers have questioned it.

Meanwhile, firms that do not export to ICH countries follow looser quality standards. For customers, this means that, depending on who they buy a drug from, the quality may differ greatly – an unethical and unsustainable scenario.

The next section discusses IP's performance in terms of number of monographs for drugs, and how well monographs comply with ICH standards.

An Assessment of the IPC

Part A:
How widely do individual drug monographs in the IP cover the universe of drugs sold in India?

i.) Discussion

An individual drug monograph in the IP is a monograph for a specific drug or an API. For instance, the monograph for metronidazole tablets and the monograph for the API amphotericin-B are individual monographs.

There are multiple axes along which the individual drug monographs in the IP can be compared with the universe of drug formulations sold in the country (See *Table 1*). The IP performs well when compared to some restricted lists of drugs, such as the National List of Essential Medicines (NLEM) but does very poorly when compared to others, such as the list of all fixed-dose combinations (FDCs) approved in India. The assessment of individual drug monographs for APIs is outside the scope of this study.

An important axis of comparison is that of the IP with the top-selling drug formulations in India, by volume. However, the IPC has never carried out this comparison, making this a key blind-spot in the organisation's assessment of itself.

IPC officials have also said that they have an internal framework which they use to prioritise drugs for inclusion in the IP. They have never published this framework, and so it is not known how the IP performs against it.

A detailed discussion of five such axes of comparison follows.

Axis	Number of individual drug monographs in IP 2022 that fulfil criteria	Number of individual drug monographs targeted for inclusion	%ge coverage	Notes
IP 2022 vs IP's internal prioritisation framework	Not known	Not known	NA	IPC has never published this framework, and says it doesn't plan to.
IP 2022 vs all drug formulations approved in India from 1961 to 2022	~2030	~5868	34.5%	Confidence in this data is poor since the CDSCO's lists of all approved drugs in India are of poor quality.
IP 2022 vs NLEM 2015	368	376	98%	NLEM 2015 has now been replaced by NLEM 2021.
IP 2022 vs top 300 brands by sales value	219	300	73%	300 brands cover top 35% of drugs by value, as per news reports.
IP 2022 vs WHO Model List of Essential Medicines	316	479	66%	
IP 2022 vs FDCs approved in India by CDSCO+ Kokate committee	157	4046	3.8%	

Table 1: How individual drug monographs in the IP perform against five lists of drug formulations

ii.) IP 2022 vs IPC's internal prioritisation framework

IPC officials say it isn't their goal to develop monographs individually for all drugs sold in the country. Instead, they have developed an internal framework to prioritise drugs for inclusion in the IP. According to them, this framework takes into the account the market value of the drug, how many manufacturers make the drug, whether it is present in the National List of Essential Medicines and whether it is present in the WHO Model List of Essential Medicines etc.

During a 26 August, 2022 workshop held at the Karnataka Drugs Control Department, IPC scientific director, Raghuvanshi, clarified that the sales volume of a drug was the ideal parameter on which to base inclusion decisions. This is because volume represents the true usage of the drug rather than sales value, which can be skewed by high prices.

However, Raghuvanshi added that the IPC has found it difficult to source sales-volume data. Because of this, IPC has had to rely more often on value data to decide on which drugs to include.

Raghuvanshi also clarified that IPC does not plan to publish its internal prioritisation framework. Nor has IPC ever shared its own performance against this framework. This means it is impossible for third parties to evaluate IPC's performance along this key axis of comparison.

iii.) IP 2022 vs all drug formulations approved by CDSCO and state regulators during 1961-2022

A key axis of comparison to evaluate IP 2022's completeness would be to compare the number of individual drug monographs for formulations with all drug formulations approved in India by CDSCO. According to a current member of the IPC's scientific body, such an evaluation has never been carried out by the IPC.

To make up for this data gap, a crude comparison is attempted in this study. An approximate estimate of the total number of drug formulations sold in India can be derived from documents uploaded on the CDSCO's website. According to these documents, 3260 drug formulations were approved in India since 1961 and 2022.

These documents seemingly include small molecule formulations, fixed-dose combinations (FDCs), biologicals, vaccines and immunosera, vitamins and minerals, herbal products, radiopharmaceuticals, phytopharmaceuticals, blood

and blood products, and veterinary drugs and vaccines. APIs are excluded from these documents.

In addition to the 3260 formulations approved by CDSCO, another 2608 FDCs were approved illegally by state drug regulators, but subsequently cleared for marketing by the Kokate committee. (See *vii: IP 2022 vs Fixed Dose Combinations* for further details). Put together, this means a total of 5868 drug formulations were approved in India until 2022 (See *Table 2*)

Approval authority	**Year of approval**	**Number**	**Source**
CDSCO	1961-1970	277	Link to CDSCO document
CDSCO	1971-1980	348	Link to CDSCO document
CDSCO	1981-1990	297	Link to CDSCO document
CDSCO	1991-2000	427	Link to CDSCO document
CDSCO	2001	41	Link to CDSCO document 1 + document 2
CDSCO	2002	56	Link to CDSCO document 1 + document 2
CDSCO	2003	38	Link to CDSCO document
CDSCO	2004	78	Link to CDSCO document
CDSCO	2005	121	Link to CDSCO document
CDSCO	2006	162	Link to CDSCO document
CDSCO	2007	189	Link to CDSCO document
CDSCO	2008	271	Link to CDSCO document 1 + document 2
CDSCO	2009	217	Link to CDSCO document
CDSCO	2010	224	Link to CDSCO document
CDSCO	2011	143	Link to CDSCO document
CDSCO	2012	44	Link to CDSCO document
CDSCO	2013	35	Link to CDSCO document
CDSCO	2014	63	Link to CDSCO document

CDSCO	2015	46	Link to CDSCO document 1 + document 2
CDSCO	2016	22	Link to CDSCO document
CDSCO	2017	37	Link to CDSCO document
CDSCO	2018	26	Link to CDSCO document
CDSCO	2019	26	Link to CDSCO document
CDSCO	2020	29	Link to CDSCO document
CDSCO	2021	25	Link to CDSCO document
CDSCO	2022	18	Link to CDSCO document
FDCs approved by state regulators and cleared by Kokate committee	1961-2022	2608	See *Table 3: Total number of FDCs approved in India as on 2022*
Total drug formulations approved in India 1961-2022		**5868**	

Table 2: Total number of drugs approved in India by CDSCO and state regulators/Kokate committee since 1961

However, there are many inconsistencies in the CDSCO's documents, and they are overall of very poor quality. Even though these documents list some FDC approvals by the CDSCO, it is clear that they do not list all.

For instance, the list of drug formulations approved by the CDSCO between 1961 and 1970 contains the contraceptive FDC norethindrone 1mg +mestranol 0.05mg, reportedly approved in September 1970. In contrast, a second list of FDCs approved by CDSCO between 1961 and 2019 shows no such contraceptive FDC approved in 1970. This is inconsistent with the first list, because the first list is supposed to be a subset of the second. Further, the second list shows the FDC fibrinolysin+desoxyribonuclease (used for debridement of dead tissue), reportedly approved in 1962. This second FDC doesn't appear on the first list.

Other inconsistencies and shortcomings in the CDSCO documents include a lack of data on revoked approvals and banned drugs, and a lack of sales data for drugs. Sales data is important, because many of the drugs approved since the 1960s are likely not in wide use anymore.

While being mindful of these limitations, if one were to treat 5868 as a crude estimate of the number of drug formulations approved in India till date, a comparable number of monographs in IP 2022 can be derived by summing the number of monographs for formulations, vaccines and immunosera, herbal products, biologicals, radiopharmaceuticals, allergen products, veterinary products, phytopharmaceuticals, blood products, and vitamins, minerals, amino acids and fatty acids (See *Fig. 1*).

The number of monographs for herbal products, radiopharmaceuticals, allergen products, phytopharmaceuticals, blood and blood products, and vitamins, minerals, amino acids and fatty acids in *Fig. 1* includes APIs, and so, is an overestimate for the number of formulation monographs. Still, if one were to add these monographs, the total number of monographs for formulations in IP is 2030. This means that IP2022 covers roughly 2030/5868 = 34.5% of all formulations approved in India by CDSCO and state regulators since 1961.

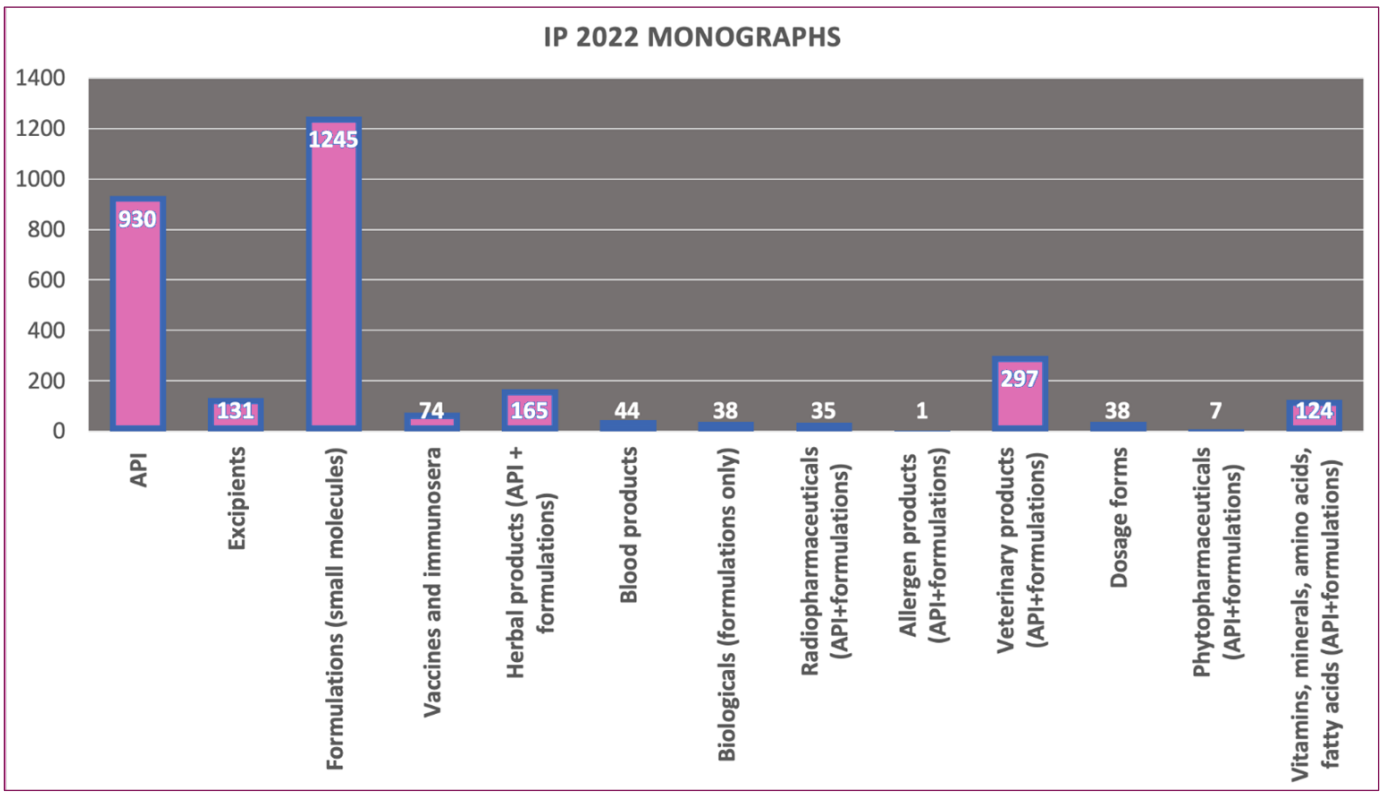

Fig 1. Breakup of monographs in IP 2022
Source: Rajeev Raghuvanshi, Director, IPC, July 1, 2022

iv.) IP 2022 vs National List of Essential Medicines 2015

According to data shared by Raghuvanshi in August 2022, monographs in the IP 2022 cover 98% of the drugs in the National List of Essential Medicines 2015 (NLEM).

The NLEM, which is prepared by a committee appointed by the Ministry of Health and Family Welfare, is a list of drug formulations that satisfy the priority healthcare needs of India. One of the goals of this list is to signal to policy makers that these medicines must be easily accessible, affordable and of assured quality. For this reason, these drugs are also subject to price control under the Drugs (Prices Control) Order, 2013. The 2015 edition of the list, which the IP was compared with, has 376 drugs on it.

Given that the NLEM aims to represent India's top public-health needs, it is important for the IP to maintain good coverage of it. However, aiming for coverage of the NLEM alone is a low bar for IPC to set, since the NLEM is a very small subset of the total number of drugs sold in the country. It does not include many drugs which the committee does not deem cost-effective, which are used in relatively rarer illnesses, and which have a relatively poorer risk-benefit profile in the treatment of-high burden diseases, but which can nevertheless benefit from the quality control that comes from inclusion in the IP.

Secondly, even though the committee that prepared NLEM 2015 recommended that it be revised every three years, in order to reflect the latest treatment trends, this has not been happening. For instance, NLEM 2022, which was published in September 2022, came out seven years after the previous edition.

The low frequency of updates suggests that the NLEMs are not always in line with India's healthcare needs. So, while it is important for the IPC to aim for high coverage of the NLEM, this is a necessary but not sufficient criterion for IP's completeness.

v.) IP 2022 vs top brands sold in India

According to data shared by Raghuvanshi in August 2022, monographs in the IP 2022 cover 73% of India's top-selling 300 brands (by value).

Raghuvanshi said these top 300 brands were the same as those which the CDSCO had directed to carry QR-codes for in a June 2022 gazette notification. The CDSCO,

in turn, relied on a list prepared by the National Pharmaceutical Pricing Authority (NPPA).

Since the NPPA has not clarified where it sourced its data from, it is unclear what percentage of market value they constitute. Pharmabiz and Livemint reported that these 300 brands were selected because they constituted 35% of the market-value for "lifesaving drugs". But the two publications do not specify the denominator of lifesaving drugs, and which therapeutic classes they include. The 300 brands span across antibiotics, analgesics, anti-diabetics, vitamins, acidity blockers etc.

If the 35% market value is correct, this number exposes major gaps in the IP 2022's coverage. If IP only provides individual monographs for only 73% of the top 35% of drugs, that would mean 25.5% of even this small subset of top brands lack IP monographs.

vi.) IP 2022 vs WHO Model List of Essential Medicines (MLEM)

According to data shared by Raghuvanshi in August 2022, monographs in the IP 2022 cover 66% of the 2021 edition of the WHO Model List of Essential Medicines (MLEM).

The MLEM is prepared by the WHO every two years, and is intended to guide member countries in preparing their own NLEMs. In order for a drug formulation to be included in the list, it must treat a disease of high prevalence globally, be cost effective, and should have strong evidence of safety and efficacy. The latest edition of the list, which was published in 2021, contains 479 drugs across a range of therapeutic indications.

Because the MLEM is not specific to India, it has a few drugs that may not be relevant to the Indian scenario, such as fexinidazole for the treatment of African human trypanosomiasis (sleeping sickness). On the other hand, because it is updated much more frequently than NLEM, the MLEM has new drugs and drug combinations which are highly relevant to India, but which NLEM has so far failed to include, such as the anti-tuberculosis drug rifapentine and the FDC rifapentine + isoniazid.

For this reason, a straightforward comparison of the IP with MLEM may be difficult to interpret. The IPC must prepare a more relevant list for India, based on usage and sales volume, to serve as a benchmark for comparison.

vii.) IP 2022 vs Fixed dose combinations (FDCs)

According to data shared by Raghuvanshi in August 2022, the IP 2022 has 157 monographs for FDCs. In comparison, the total number of FDCs legally approved in India as on 2022 is 4046, among the highest approved anywhere in the world (See *Table 3* for breakup of 4046).

This means that individual drug monographs in IP 2022 cover only 3.8% of the FDCs legally approved in India. The 3.8% does not include FDCs that are sold in India in contravention of the law, although such sales continue to happen due to poor surveillance by CDSCO and state drug regulators.

FDCs are an especially critical pain-point for quality control in India, because the Indian market is flooded with so many of them. State drug regulators are struggling to keep a check on these drugs, because they lack the appropriate specifications to do so. Against this background, an IP coverage of 3.8% is abysmal.

One reason for the historical proliferation of FDCs in the Indian market was the violation of the Drugs & Cosmetics Act 1940 by state drug regulators. The Act requires the CDSCO to approve any new FDC before state regulators give firms the permission to manufacture them. Yet, over the years, many state regulators green-lit FDCs that the CDSCO had never cleared.

Further, because state regulators had even lesser capacity than CDSCO does to evaluate the scientific rationale behind these FDCs, most of these state-licensed FDCs were irrational combinations. This meant that these FDCs offered no therapeutic benefit to patients and were possibly dangerous.

The scale of this problem became apparent in 2015, when the CDSCO revealed that state drug regulators had licensed as many as 6220 FDCs, while less than a quarter of this number were approved by CDSCO till then. To tackle this problem, the Union Health Ministry appointed a committee under the chairmanship of pharmaceutical scientist CK Kokate to evaluate state-licensed FDCs for safety, efficacy and rationality. As on today, the Kokate committee has declared a total of 2137 drug FDCs and 471 vitamin and mineral FDCs as rational (See *Table 1*). To this, if one adds the total number of FDCs approved by CDSCO until May 2022 (1438), the total number of FDCs approved for marketing in India today is 4046.

The Kokate committee exercise may not have solved India's FDC problem however; questions have been raised subsequently about how thorough the Kokate committee's evaluation was. A paper published in the 2022 Bulletin of the World Health Organisation identified a number of antibiotic FDCs which the WHO

has recommended against using, but which the Kokate committee cleared. These irrational FDCs may be ineffective, unsafe and may worsen antibiotic resistance, a major public health problem India is already facing.

Name of approving body	Total	Source of data
First list of FDCs approved by state licensing authority and classified as rational by Kokate committee	1687	CDSCO circular, 4 July, 2022
Second list FDCs approved by state licensing authority and classified as rational by Kokate committee	450	CDSCO circular, 28,Jan, 2020
List of vitamin/mineral FDCs approved by state licensing authoties and classified as rational by Kokate commitee	471	CDSCO circular 28 Dec, 2021
List of all FDCs approved by CDSCO between 1961 and 2019	1324	CDSCO document, 2019
FDCs approved by CDSCO in 2020	46	CDSCO document, 2020
FDCs approved by CDSCO in 2021	47	CDSCO document, 2021
FDCs approved by CDSCO in 2022	21	CDSCO document, 2022
Total FDCs approved in India as on 2022	**4046**	

Table 3: Total number of FDCs approved in India as on 2022

This means that the presence of only 3.8% of the FDCs sold in India in IP 2022 adds a double edge to India's irrational FDC problem. In addition to the presence in the market of irrational FDCs, even approved and rational FDCs may not comply with quality parameters, rendering them ineffective.

In an August 2022 interview with the author, Raghuvanshi said that the IPC has not yet set any goals for how many FDCs the IP must cover. One reason for this, he said, was that the CDSCO hadn't yet made it clear which FDCs were legally

approved in India. On the contrary, the CDSCO had told IPC that the lists of FDCs approved by the Kokate committee and published on the CDSCO's website were not yet final. "We have to reconfirm the list of drugs cleared by Kokate committee. There has been an instance when (CDSCO) have specifically told us not to pick an FDC, in spite of it being there (on the Kokate approved list)."

This lack of clarity from the CDSCO on which drugs are approved in India is an obstacle in IPC's way of prioritising FDC's for inclusion in IP.

Part A:
How does the Lack of Individual Drug Monographs in IP Impact Drug Quality?

The lack of individual monographs in IP 2022 for over 65% of the drug formulations approved in India since 1961 (See *Part A, section (iii) IP 2022 vs all drug formulations approved by CDSCO and state regulator*s *during 1961-2022*) is worrying.

When the IP lacks an individual drug monograph, Section 124, Schedule V and the Second Schedule of the Drugs and Cosmetics Act 1940 tell regulators and manufacturers what minimum specifications the drug must comply with. The Second Schedule requires manufacturers to comply with the monograph in the current official pharmacopoeia of any other country, if available. If unavailable in any other official pharmacopoeia, or its previous edition, manufacturers are allowed by regulators to develop their own specifications (*See Figure 2*).

Further, Schedule V requires these manufacturer-developed specifications to comply with, at minimum, the general monograph for the dosage form. Once the manufacturer develops their own specifications in accordance with this general monograph, the central regulator or state regulator vets them before approving the drug. (See *Figure 2*)

Overall, this situation, in which the manufacturer develops their own specifications, is fraught with risks to patient health. First, IP general monographs for dosage forms are often incomplete, as discussed further in *Part B* of this study. And since the manufacturer has an incentive to skip some technically difficult specifications that are crucial for safety and efficacy, the lack of both individual monographs and adequate general monographs allows them to do so. Further, both CDSCO and state regulators have been known to waive such specifications historically, putting patients and public health in danger (see *Case study 2: Itraconazole capsules*).

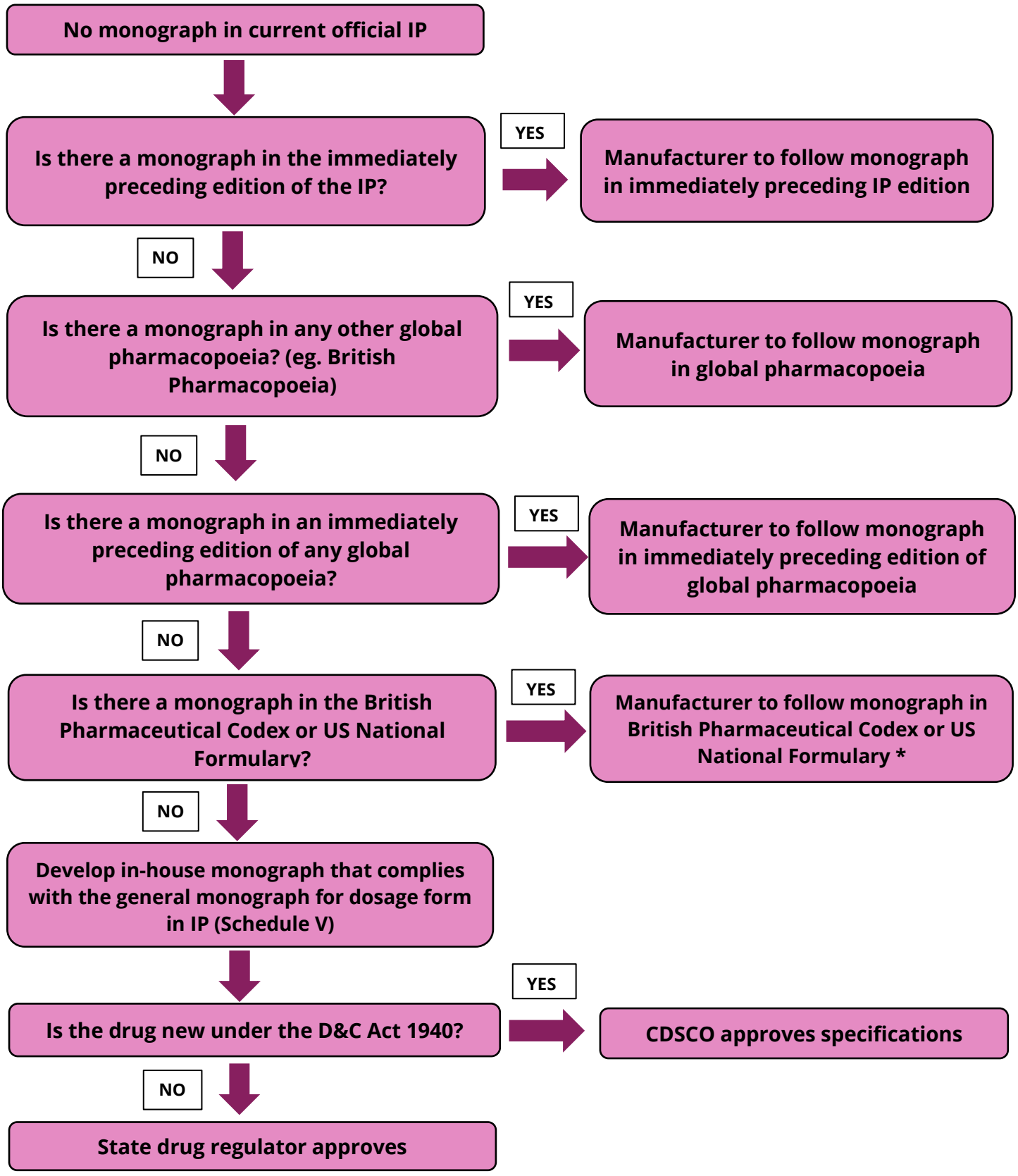

Figure 2: How manufacturers decide what specifications to comply with for drugs not included in IP, as per Rule 124, the Second Schedule and Schedule V of Drugs and Cosmetics Act 1940

It is unclear why Section 124 of the Drugs and Cosmetics Act 1940 refers to the British Pharmaceutical Codex or the US National Formulary, since these are not texts of drug specifications.

In a June 2021 blog post, Ganadhish Kamat, former global quality head for Dr Reddy's Laboratories, and current member of IPC's scientific committee , published results of a survey which show the laxity of state drug regulators when it comes to specifications. In the survey, also conducted in 2021, state regulators were asked what data they sought from manufacturers while awarding manufacturing licenses.

In response, three of eight surveyed state regulators, namely Himachal Pradesh, Jammu & Kashmir, and Sikkim, said they did not routinely ask manufacturers for specifications for either formulations or APIs. Further, Kamat noted on his blog, most regulators didn't ask manufacturers to include dissolution specifications for solid dosage forms, or to include impurity specifications for APIs and formulations, unless the IP explicitly asked for them. Both tests are crucial to ensure the efficacy, safety and quality of drugs.

The fact that state drug regulators do not understand the importance of quality specifications was also captured in a 2021 incident, when several batches of injectable remdesivir manufactured by the Gujarat-based Zydus Cadila were found to trigger adverse events among patients. Even though testing for a type of impurity, called endotoxins, is critical for the safety of injectable drugs, as this author reported in Mint, officials from both the Maharashtra and Uttar Pradesh regulatory labs did not conduct these tests on implicated batches from Cadila. (See *Part B, Case study 3: Bacterial Endotoxins in Injectables*)

Given that both state regulators and CDSCO frequently fail to set adequate drug quality specifications, the IPC's role is more crucial in India than it is in other regions like the US and Europe, where pharmacopoeias play a secondary role to regulators. If the IP lacks an individual drug monograph, and an equivalent monograph is not available in any other global pharmacopoeia, the task of setting drug specifications falls entirely upon the CDSCO and state regulators. This is not ideal.

Two case studies of drugs that were not covered in the IP or any other global pharmacopoeia at the time the drugs were approved in India are discussed in the next section.

Part A:
Case studies for drug formulations with no IP monograph

Case study 1

i.) Liposomal amphotericin for injection

For reasons that are not entirely clear, India has historically had the world's highest prevalence of the fungal disease, mucormycosis, at almost 70 times the global median prevalence. In its most common form, rhino-orbital-cerebral mucormycosis, the disease infects the nose, eyes and brain. Initial symptoms may include nasal discharge, and a black lesion in the affected region. If untreated, it can destroy affected organs or result in death.

In 2020, the arrival of the Covid pandemic, the wide use of steroids, and other factors led to India's biggest mucormycosis epidemic. Such a Covid-associated spike in this fungal disease was not seen in any other country, and the reasons behind it are still being investigated.

The most effective therapy against mucormycosis, which can kill up to 50% of patients, is the antifungal amphotericin B. In addition, amphotericin B is also effective against multiple other fungal diseases, including aspergillosis and candidiasis, as well as the parasite which causes visceral leishmaniasis (kala-azar), another prevalent disease in India. The importance of this formulation is reflected in the fact that both the WHO and India include it in their lists of essential medicines.

Out of all formulations of amphotericin, liposomal amphotericin B, first developed in the nineties by the US-based Gilead Sciences under the brand name AmBisome, is the least toxic to the kidneys and causes fewer infusion reactions, making it the most preferred treatment. In India, generic versions of liposomal amphotericin have been available since atleast 2003.

Gilead achieved this low toxicity partly by encasing the amphotericin molecule in a lipid sac (liposome), that prevents this drug from concentrating in kidneys. The manufacturing process for this product is extremely complex, requiring close tabs

to be kept on quality parameters throughout. As a Gilead-funded study demonstrated, in 2016, that even slight changes in the chemical composition or method of manufacture can lead to a more toxic product.

The challenges in manufacturing safe and effective liposomal amphotericin became abundantly clear in 2016, when the CDSCO asked state regulators to suspend the licenses of ten generics manufacturers in response to complaints of kidney toxicity. Further details of this incident are not available in the public domain, but complaints about the quality of generic liposomal amphotericin predate this incident, as Times of India reported in 2014.

However, a similar incident occurred in Argentina, when Anfogen, a generic liposomal amphotericin manufactured by Genpharma SA, was withdrawn from the market due to toxicity concerns. Prior to its withdrawal, in 2008, scientists published a study comparing the physicochemical specifications, preclinical toxicity and preclinical efficacy of Anfogen and AmBisome. They found that even though Anfogen had the same chemical composition as AmBisome, it was far more toxic and less efficacious in mice. The size of the liposomes in Anfogen were also much larger than those in AmBisome, a significant finding because the liposome size impacts the performance of the drug.

Against this background, it has become very important for drug regulators to guide manufacturers of liposomal-amphotericin on multiple counts: 1) how to prove bioequivalence with the innovator drug (AmBisome), 2) how to monitor critical process parameters during manufacture and 3) how to set final product specifications. The last element – setting final product specifications – falls within the ambit of the IP in India.

Yet, when the Indian mucormycosis outbreak occurred in 2020 and 2021, the IP did not have any monograph for liposomal amphotericin B. This was also the case with other global pharmacopoeias, including the British Pharmacopoeia and US Pharmacopoeia.

As cases of mucormycosis skyrocketed across the country, widespread shortages of liposomal amphotericin occurred, as only five Indian companies were making the drug at the time. To beef up production, the CDSCO handed out manufacturing licenses to six more companies, according to a June 2021 release from the Press Information Bureau. Subsequently, several other companies have also entered the market for this product.

The presence of a monograph in the IP would have helped manufacturers control the final product quality to some extent. The CDSCO has not issued any specific guidelines for liposomal products, and has instead asked manufacturers to rely on 2018 US FDA guidelines for the same.

That Indian manufacturers are struggling to comply with international guidelines and standards is evidenced by the 2016 suspension of licenses by CDSCO. After the incident, the CDSCO has become involved in the process of issuing new manufacturing licenses for liposomal amphotericin, even if this drug is decades old (normally, under the Drugs and Cosmetics Act, it is state regulators who issue licenses for drugs that are more than four years old).

Indian manufacturers continue to struggle with making quality liposomal amphotericin even today, as evidenced by an anecdote shared by IPC scientific director, Rajeev Raghuvanshi, during an August 2022 IPC awareness workshop. Raghuvanshi said that when CDSCO began issuing licenses for liposomal amphotericin during the 2021 mucormycosis outbreak, the IPC was tasked with testing the manufacturers' products as per their final product specifications.

However, according to Raghuvanshi, the specifications submitted by several manufacturers for liposomal amphotericin were those that are used for conventional amphotericin B, a completely different formulation. "We had to put our foot down, and say this is not the right liposomal specification. The specifications were then revised and sent to us for testing," Raghuvanshi said.

This incident highlights the low level of awareness and skill among manufacturers about the development of liposomal products. This, put together with the large number of manufacturers of liposomal amphotericin in India today, means that an IP monograph is critical to ensure the safety and efficacy of the drug Indians receive.

Case study 2

ii.) Itraconazole capsules

Itraconazole is another antifungal used in a range of conditions, including relatively benign skin infections like ringworm and high-fatality systemic infections like invasive aspergillosis. Its use was also investigated in mucormycosis during the 2021 Indian outbreak, as the country exhausted supplies of amphotericin B.

First developed by the US-based Janssen Pharma in the 1980s, capsules of this drug are difficult to formulate. Because the itraconazole molecule is nearly insoluble in water, it means it is unlikely to dissolve quickly in the human gut, making absorption difficult.

To counter this problem, the original manufacturers devised a sophisticated process. First, the drug is complexed with a polymer to improve its solubility. After that, the drug-polymer complex is coated over pellets. This gives the drug a

greater surface area than if it was in powder form, helping solubility even further. A large number of such uniformly-sized pellets are then administered in a capsule, improving dissolution, absorption and efficacy of the drug.

Even though a 100 mg capsule formulation of itraconazole was approved in India as early as 1993, and dozens of generic manufacturers today make this drug, the IP does not have a monograph for it. Further, according to a 2018 study conducted by officials from the US Pharmacopoeia, and published in the Bulletin of the World Health Organisation, up until 2017, even the British Pharmacopoeia and US Pharmacopoeia lacked monographs for this drug. Meanwhile the International Pharmacopoeia (published by the WHO) and the Japanese Pharmacopoeia lacked itraconazole monographs until 2016.

In the absence of a monograph in the IP or in any other ICH-conforming pharmacopoeia, the full burden of vetting the specifications for itraconazole capsules would have fallen for four consecutive years since 1993 on the CDSCO. After this, state drug regulators would have taken over. However, as this case study goes on to show, both the CDSCO and state regulators did a poor job.

The challenges of formulating itraconazole properly became increasingly evident in the mid-1990s, with reports from across the globe documenting the poor bioavailability of generic itraconazole compared to Janssen's product. The relatively poor quality of several generic itraconazole brands was also documented by Indian doctors in a 2018 study. After finding that their patients were getting repeated bouts of ringworm infection following use of generic itraconazole, doctors from new Delhi's Dr Ram Manohar Lohia hospital compared the physical characteristics of 22 itraconazole formulations. They found a vast variation in the size of pellets and number of pellets used by each manufacturer, with many formulations not matching the ideal characteristics designed by Janssen. Some manufacturers even filled their capsules with loose powder instead of pellets, explaining the lack of effectiveness of the drug.

How the CDSCO and state regulators allowed these formulations to proliferate, and whether they even required these formulations to comply with basic dissolution requirements, is unclear. But it raises questions about the ability of CDSCO and state regulators to design and enforce adequate quality specifications.

A second troubling episode in the itraconazole quality saga began in 2018, when the Australian firm Mayne Pharma developed a super-bioavailable (SUBA) version of itraconazole. The key to its increased bioavailability lies in the drug's formulation itself; Mayne Pharma created a solid-dispersion version of the drug, instead of the previous pellet formulation, that dissolved even better. The change

in formulation means the quality specifications of SUBA itraconazole would be significantly different from those of conventional itraconazole.

In December 2018, the US FDA approved a 65 mg dose of SUBA itraconazole for the treatment of various fungal infections, after Mayne demonstrated that this dose was bioequivalent to 100 mg of the older antifungal formulation. It isn't clear exactly when the CDSCO approved the SUBA version in India; the lists of new drugs approved in India between 2018 and 2021 do not mention this formulation. However, minutes of the Subject Expert Committee on Dermatology and Allergy, which advices CDSCO on approval of dermatological drugs, show that this committee had recommended two super bioavailable formulations by Indian manufacturers for approval in 2021. As on date, several Indian manufacturers are selling it.

Unfortunately, some Indian versions of SUBA itraconazole may be poor imitations of Mayne Pharma's product. In a disturbing revelation, Raghuvanshi said during a recent IP awareness workshop held in Bangalore that the IPC had found some makers of SUBA itraconazole to be testing their product against the specifications for the conventional itraconazole. Such a scenario would open a Pandora's box, because if Indian manufacturers are selling conventional itraconazole in a 65 mg dose, this would lead to patients receiving sub-therapeutic doses of the drug. This, in turn, could make deadly fungal pathogens such as *Aspergillus* resistant to itraconazole, making their treatment extremely challenging.

How and why CDSCO allowed manufacturers of SUBA itraconazole to get away with meeting specifications only for conventional itraconazole is unclear. CDSCO head, VG Somani, did not respond to this author's questions on this issue. But this is another indictment of the CDSCO's incompetence when it comes to setting quality specifications and enforcing them.

Raghuvanshi has said that the IPC has taken note of the several issues with itraconazole quality, and plans to introduce a new monograph for the drug soon.

PART B:
When the IP has an individual drug monograph or a general monograph, is it in line with ICH guidelines?

i.) Discussion

This study attempts to assess how many individual drug monographs and general monographs in the IP contain two important drug specifications: namely, dissolution and impurities. According to ICHQ6A, a guideline rolled out in 1999, all solid oral dosage forms require dissolution tests, while all oral dosage forms and parenterals require impurity tests. There are several ICH guidelines on impurities, but this study restricts itself to ICH Q3A, Q3B, Q3C, Q3D and M7.

The importance of general monographs to drug quality and how they are applied by manufacturers is described in *Figure 2* and *Table 4*.

Type of IP element	**How regulators and manufacturers use the element**
Drug monograph (Monograph for API or formulation)	(iv) Lists minimum specifications for API or formulation (v) CDSCO and state regulator must impose these specifications at minimum. They can also choose to impose more specifications, or more stringent specifications, if it is required for safety, efficacy or quality of the drug. For instance, even if a monograph for a tablet lacks a dissolution test, the CDSCO can demand that the manufacturer introduce a dissolution test. Further, if the monograph for a tablet allows 0.2% of unidentified impurities, CDSCO can lower this limit to 0.1%.

	(vi) Eg: Monograph for metronidazole tablets
General monograph for dosage form	1. Lists minimums specifications for all medicines in this dosage form 2. CDSCO and state regulator can impose more specifications, or more stringent specifications, if it is required for the safety, efficacy or quality of the drug. For instance, even if the general monograph for hard capsules lacks a dissolution test, the CDSCO can demand that the manufacturer introduce a dissolution test. Further, if the general monograph for a tablet allows 0.2% of unidentified impurities, CDSCO can lower this limit to 0.1%. 3. Eg: General monograph for film-coated tablets, general monograph for oral liquids, general monograph for powder for injection etc

Table 4: How individual drug monographs and general monographs work

Given the IPC's traditional stance towards the ICH (see The IPC's stance towards the ICH), both individual drug monographs and general monographs in IP 2018, the edition currently in force, frequently do not contain these tests.

IPC's present leadership has acknowledged this problem. In a February 2022 discussion with this author, scientific director Raghuvanshi said the lack of dissolution tests and impurity tests were two key areas of concern that the IPC was addressing on priority. In addition to the lack of impurity tests in several individual monographs and general monographs, the impurity tests that do exist are not in line with those recommended by ICH impurity guidelines. The IPC also plans to rectify this in due course, Raghuvanshi said.

A discussion of the importance of dissolution tests and impurity tests, and the extent of the lacuna in the IP, follows.

ii.) Dissolution tests: ICH vs IP

When a person ingests a tablet, the rate at which the tablet dissolves in the gut is key to the absorption of the drug in the body. ICH regulators first acknowledged this fact in the 1970s, when British doctors found that patients taking different formulations of the cardiac drug digoxin had widely varying levels of the chemical in their blood. Later studies showed that this variation was closely linked to differences in the rate of dissolution of each of these formulations, even though the amount of active ingredient in each formulation was the same.

These findings led to the US Pharmacopoeia introducing its first dissolution test for tablets in 1971, with the Indian Pharmacopoeia following up in 1985. Fourteen years later, in 1999, the ICH Q6A was rolled out, which recommended dissolution tests for all solid oral dosage forms.

While dissolution tests are an important quality attribute for all tablets and capsules, they are particularly important for two classes of drugs in the Biopharmaceutical Classification System (BCS): namely BCS Class 2 drugs and BCS Class 4 drugs. Class 2 drugs show low solubility in aqueous media, but are absorbed rapidly in the human gut (they have high intestinal permeability), while class 4 drugs show both low solubility and intestinal permeability.

For both classes, unless the formulation is designed to combat the low solubility, the drug will not get absorbed into the body, and will be ineffective. Therefore, every batch of the drug must be shown to meet dissolution parameters for the drug to be effective.

Yet, the IP has historically lacked dissolution tests for several BCS Class 2 drugs, such as albendazole, which is discussed later in the report.

While IPC has acknowledged the lack of dissolution tests in both individual drug monographs and general monographs, Raghuvanshi didn't share any data on how many individual drug monographs in IP 2018 or IP 2022 were affected, despite several requests. *Table 5* captures the status of dissolution tests in general monographs for solid oral dosage forms in IP 2018.

	General monograph for dosage form	Whether dissolution test is indicated Yes/No
	Capsules	
1	Hard gelatin capsules	No
2	Soft gelatin capsules	No
3	Modified release capsules	No
4	Gastro-resistant capsules	No
5	Oral powder	No
	Tablets	
6	Uncoated tablets	No
7	Coated tablets	No
8	Film-coated tablets	No
9	Dispersible tablets	No
10	Effervescent tablets	No
11	Enteric coated tablets	Yes, for tablets prepared from granules or particles already covered with an enteric coating
12	Prolonged release tablets	Yes, dissolution criteria to be defined at three or more time points
13	Soluble tablets	No
14	Tablets for use in the mouth	No

Table 5: Number of general monographs for solid oral dosage forms in IP 2018 that have dissolution tests

iii.)Impurity tests - ICH vs IP

Impurities are chemicals that are not supposed to be in drugs, because they offer no therapeutic benefit. But they get into drugs as a result of the manufacturing process, degradation of the active ingredient itself, equipment contamination and so forth. Often, impurities can be toxic to patients. Even if they are not, they can interfere with the stability of the active ingredient.

There are broadly three classes of impurities: organic impurities, elemental impurities and residual solvents. Any of these three classes of impurities can be mutagenic, which means they can potentially cause cancer. *Table 6* lists some common impurities and their toxicities.

Type of impurity	Examples of toxicity
Organic impurities	1. 4-aminophenol in the pain-killer paracetamol, which causes liver toxicity 2. Penicilloylated protein in the antibiotic ampicillin, which causes macropapular rash 3. Dimers/polymers in the antibiotic cefotaxime, which cause anaphylaxis
Elemental impurities	1. Aluminium in dialysis fluid, which causes dementia 2. Nickel in parenteral fluids is cardiotoxic
Residual solvents	1. Benzene is carcinogenic 2. Dimethylformamide in fluorescein (used by eye specialists) can trigger anaphylaxis and nerve pain
Mutagens	1. Nitrosamines can cause cancer 2. Hydrazine in the tuberculosis drug isoniazid can cause cancer

Table 6: Types of impurities and how they harm patients | Source: Anthony C Cartwright, International Pharmacy Journal, 1990

As this author reported in The Wire Science, the inability of India's small and mid-sized industry to comply with ICH guidelines led to the IPC rejecting several of ICH impurity standards for India. As recently as 2018, ICH Q3A and Q3B, which were rolled out in the mid-nineties, and ICH M7, which was rolled out in 2014, were not a part of the IP. Instead, IP adopted far more lenient standards.

Given Raghuvanshi's more pro-ICH stance, the IP did upgrade its general chapters on impurities to reflect ICH Q3A, Q3B and M7 for this first time in 2022. It also included a new general chapter on ICH Q3D.

However, there are major caveats to these inclusions. The updated general chapters are not mandatory for manufacturers, according to Raghuvanshi. This means it is entirely upto the CDSCO and manufacturers to implement new impurity limits proposed in IP 2022 (See *Table 7: IP 2018, IP 2022 and compliance with ICH impurity standards*)

This is a particularly worrying situation, especially when it comes to nitrosamines. Several drugs, such as valsartan, ranitidine and extended release metformin XR, which are sold widely in India, are known to be at high risk of nitrosamine contamination. Yet, IP 2022 allows manufacturers to get away without ensuring these drugs are nitrosamine-free.

Name of ICH standard	**Q3A**	**Q3B**	**Q3C**	**Q3D**	**M7**
Type of standard	**Organic impurities in APIs**	**Organic impurities in formulations**	**Residual solvents in AIs and formulations**	**Elemental impurities in formulations**	**Mutagens in API and formulations**
IP 2018	General chapter has more lenient limits than Q3A. These lenient limits are referred to in several individual drug monographs.	General chapter has more lenient limits than Q3B. These lenient limits are also referred to in several individual	General chapter is In line with Q3C.	General chapter has old heavy metal test with more lenient limits than Q3D. This test was also used in most individual	No guidelines for mutagenic impurities or nitrosamines

		drug monographs.		monographs and general monographs for dosage forms	
IP 2022	General chapter in line with ICH Q3A. However, the general chapter isn't mandatory. And these limits are yet to be incorporated in most individual monographs.	General chapter In line with ICH Q3B. However, the general chapter isn't mandatory. And these limits are yet to be incorporated in most individual monographs	General chapter In line with Q3C.	General chapter with old heavy metal test still widely used in individual drug monographs and general monographs for dosage forms. New general chapter In line with Q3D. However, the general chapter isn't mandatory. And these limits are yet to be incorporated in most individual monographs	General chapter makes a reference to ICH M7 for APIs. However, the general chapter isn't mandatory. Sartan monographs refer to general chapter. According to an IPC official, this doesn't mean that nitrosamine testing is mandatory even for sartans.

Table 7: IP 2018, IP 2022 and compliance with ICH impurity standards

As with dissolution tests, Raghuvanshi didn't share any data with the author on how many individual monographs in IP 2018 and IP 2022 lack impurity tests, or lack impurity tests in line with ICH guidelines. However, *Table 8* lists the general monographs in IP 2018, and whether they require impurity tests.

	General monograph for dosage form	Whether impurity test is indicated Yes/No
	Capsules	No
1	Hard gelatin capsules	No
2	Soft gelatin capsules	No
3	Prolonged release capsules	No
4	Gastro-resistant capsules	No
5	Hard cellulose capsules	No
6	***Creams***	No
7	***Ear drops***	No. Sterility test required when label claims sterile product.
8	***Eye drops***	No. Sterility test is required.
9	***Eye ointments***	No. Sterility test is required.
10	***Gels***	No. Sterility test is required when label claims sterile products.
	Granules	No
11	Effervescent granules	No
12	Coated granules	No
13	Modified-release granules	No
14	Gastro-resistant granules	No
15	Immediate-release granules	No
16	***Inhalation preparations***	No. Total viable aerobic bacterial count test required.
17	***Insulin preparations***	Yes, has test for related proteins, total zinc, sterility and bacterial endotoxins.
18	***Liposomal preparations***	No, has test for pyrogens and sterility.
19	***Powders for liposomal injections***	No, has test for pyrogens and sterility.
	Nasal preparations	No
20	***Nasal drops, solutions and sprays***	No
21	***Nasal powders***	No
22	***Ointments***	No. Sterility test required when label claims sterile product.
23	***Oral liquids***	No

24	***Oral powders***	No
	Parenteral preparations	
25	Injections	No, has test for sterility and pyrogens
26	Infusions	No, has test for sterility and pyrogens
27	Powders for injection	No, has test for sterility.
28	Concentrated solutions for injection	No, after dilution, concentrated solutions must comply with tests for injections and infusions, as appropriate.
	Implants	
29	Pessaries	No
30	Suppositories	No
	Tablets	
31	Uncoated tablets	No
32	Coated tablets	No
33	Film-coated tablets	No
34	Dispersible tablets	No
35	Effervescent tablets	No
36	Modified-release tablets	No
37	Gastro-resistant tablets	No
38	Prolonged-release tablets	No
39	Soluble tablets	No
40	Tablets for use in the mouth	No
41	Sublingual tablets	No
42	Chewable tablets	No

Table 8: Number of general monographs for dosage forms in IP 2018 that have impurity tests

Part B:
Case studies of drug formulations where individual monographs are not in line with ICH

Case study 1

i.) Albendazole

Albendazole is an anti-helminthic drug used in the prevention and treatment of a range of parasitic diseases. It is a key intervention against soil-transmitted infections caused by hookworms, whipworms and roundworms, as well as against the mosquito-borne lymphatic filariasis (elephantiasis).

This makes it a crucial drug for India, given that India has the world's highest burden of soil-transmitted helminthiasis. Around 435 million Indian children are at risk of helminthiasis, as per a 2020 estimate from the WHO. Meanwhile, filariasis, a disease characterised by swellings that result in long-term disability, is also a problem in India. Despite preventive treatment being available of it, India has repeatedly missed its elimination targets for filariasis, in 2015, 2017, and most recently in 2021.

The albendazole chemical itself, which was first synthesized by the British firm, Glaxosmithkline Plc (GSK) in 1975, is not very soluble in water, but is highly permeable. This means it is a BCS class 2 drug, like itraconazole. And like the antifungal, albendazole needs to be formulated in a way that improves its dissolution, because dissolution is key to its efficacy.

Scientists uncovered the importance of dissolution to albendazole's bioavailability as early as the 1990s. In a 1999 paper, German researchers compared the dissolution characteristics of multiple formulations available in the market. They found that while all passed the disintegration test, only GSK's product and a generic made by another firm passed the dissolution test as well. In a worrying 2011 survey to evaluate quality of medicines for neglected tropical diseases, the WHO also found that some 57% of tablet samples failed to comply with dissolution tests, with albendazole and mebendazole failing most often.

This poor dissolution seemingly translates to low bioavailabity and efficacy against some parasites. In a mid-2000s trial, researchers compared two albendazole formulations manufactured by the Nepali firms Royal Drug and Curex, and used in the country's mass-deworming program, with GSK's formulation. They found only GSK's drug to comply with the dissolution test and to be effective against hookworm infections. The dissolution test they had used was the one specified in the US Pharmacopoeia.

A 2015 study in Jimma Town of Ethiopia reinforced these findings. There, researchers compared the dissolution characteristics and efficacy of albendazole from Indian manufacturer Cipla and Korean firm DaeHWa Pharmaceuticals. Cipla's formulation not only failed the dissolution test, but also showed poor efficacy against hookworm infections.

By 2015, the WHO had also recognised the necessity of dissolution testing for albendazole. That year, it revised the monograph for albendazole chewable tablets in the International Pharmacopoeia to include this test.

But the Indian Pharmacopoeia, which has had a monograph for albendazole tablets for many years, did not introduce a dissolution test until 2019. Only after the WHO requested IPC to do so, in January 2019, did it amend the 2018 edition of the IP, mandating a dissolution test for this drug. The amendment resulted in the postponement of several state deworming campaigns across India. This was because several Indian manufacturers, who were not complying with dissolution tests until then, struggled to fall in line with the new requirements.

This incident raises the question of whether India's efforts to reduce the burden of soil helminthic infections and lymphatic filariasis have done poorly due to preventable reasons. After all, the IP did not impose a dissolution test for albendazole for almost a decade after scientists realised the test's importance. If India was using more effective anti-parasitic drugs, could the elimination target for filariasis have been achieved earlier? Could the burden of soil-helminthic infections have been reduced to a greater degree?

Case study 2

ii.) Nitrosamines

In July 2018, the European Medicines Agency found high levels of a potential carcinogen, called N-Nitrosodimethylamine (NDMA), in the widely used blood-pressure drug valsartan. The active ingredient had been manufactured by

Chinese firm Zhejiang Huawei. The incident triggered investigations by multiple ICH drug regulators, including the US FDA, Health Canada etc.

Together, these regulators found that not just valsartan, but multiple other blood pressure drugs in the sartan group were contaminated by NDMA and related compounds, called nitrosamines. As the author reported in Mint, these regulators later also found other drugs, such as ranitidine, metformin, and the tuberculosis drug rifampin and rifapentine, to contain unacceptably high levels of nitrosamines.

Nitrosamines in widely used medicines have the potential to unleash a cancer-epidemic. One American study calculated that if 100,000 patients took the highest dose of NDMA-tainted valsartan manufactured by Zhejiang Huawei for six years, between 40 and 125 of them would develop cancer. And as per 2018 data from the market research firm, IQVIA, Indians consumed 3078 million sartan pills that year. These numbers show why nitrosamines aren't a risk to be taken lightly.

Knowing this, ICH member regulators have brought in strict limits on the levels of nitrosamines in drugs. In fact, for ICH countries, control of nitrosamines was already mandated before 2018, as part of ICH M7. This guideline requires manufacturers to limit all mutagens in their products.

In addition to that, the US FDA, the European Medicines Agency, and other regulators have also published nitrosamine-specific guidelines for manufacturers. Further, in December 2021, the US-Pharmacopoeia published a general chapter, 1469, which described methods for testing for nitrosamines.

India had the option of controlling nitrosamines in two ways. Either the CDSCO could have set limits on nitrosamines, or the IPC could have done so. However, both agencies have chosen to take lenient approaches. More than four years after the European Medicines Agency first discovered NDMA in valsartan, neither IPC, nor CDSCO, have brought in mandatory limits on nitrosamines.

To be sure, the IPC took the first step in this direction with the introduction of a general chapter on nitrosamines in its 2022 edition, published on July 1, and due to become official in December 2022. But this general chapter is not mandatory.

In an August 2022 interview, Rajeev Raguvanshi said the general chapter on nitrosamines remains no more than a "guidance" document for manufacturers.

Asked why the IPC has desisted from mandating nitrosamine control even in drugs like sartans, metformin extended release tablets and rifampin, even though contamination in these drugs has been well documented, Raghuvanshi said the decision was mainly because large parts of the industry wouldn't be able to

comply with such controls. Testing for nitrosamines in drugs would require these manufacturers to upgrade from HPLC-UV (HPLC combined with an ultraviolet detector) instruments to HPLC-MS-MS (HPLC combined with tandem mass-spectroscopy) or HPLC-HRMS (HPLC combined with high resolution mass spectroscopy), which are expensive devices. In addition, they must also develop skills to do so.

This has been the main factor preventing IPC from forcing these limits on the Indian industry.

Case study 3

iii.)Bacterial endotoxins in injectables

Drugs that are administered as parenterals (via injections, catheters etc) need to be sterile because they enter the blood stream directly, without first encountering the gastrointestinal system, as oral drugs do. This means that they must not contain any microbial contamination, or even toxins produced by microbes, namely bacterial endotoxins. The presence of either of these contaminants can trigger deadly reactions in already sick patients, such as fever, chills and fatal sepsis.

Yet, a key general monograph in IP 2018 – the monograph for powder for injection – lacked an endotoxin test. This oversight was a significant one. When a drug is not present in the Indian Pharmacopoeia or any global pharmacopoeia, both the central and state drug regulators are required to ensure that manufacturers of the drug comply, at minimum, with the general monograph for the dosage form.

An incident in 2021, described in this Mint report drove home the impact of this lacuna in IP 2018. The incident concerns the antiviral drug, remdesivir, originally developed by the US-based Gilead Sciences for hepatitis C. After the drug failed to show efficacy against hepatitis C and multiple other viral diseases, it remained unused until 2021, when Gilead repurposed it for Covid.

Subsequently, an early clinical trial showed that remdesivir could be useful in Covid leading to wide use in India in 2021. Several Indian manufacturers began making it after entering voluntary licensing agreements with Gilead. The most widely used formulation for this drug was powder for injection.

Since remdesivir had never been used commercially before, no global pharmacopoeia, including the IP, had a monograph for this drug in 2021. This meant that when the central drug regulator approved the drug for use in India, it was required to follow, at minimum, the general monograph for powdered

injectables. What actually happened though, was that CDSCO adopted a more stringent specification for remdesivir, as it has the power to do. The CDSCO-approved specifications for this drug included bacterial endotoxins.

Against this background, in May 2021, hospitals across multiple Indian states, namely UP, Rajasthan, Maharashtra and Bihar, reported adverse events associated with remdesivir formulations manufactured by Zydus Cadila. In response, several state regulators, including the Maharashtra Food and Drug Administration (FDA), collected remdesivir samples for quality testing. However, instead of seeking CDSCO-approved specifications from Zydus Cadila, before testing if the product complied with them, the Maharashtra FDA merely tested the remdisivir for compliance with the general monograph for powder for injection. In doing so, the Maharashtra FDA was taking a cue from Schedule V.

Since this general monograph lacked a test for bacterial endotoxins, the Maharashtra FDA did not conduct an endotoxin test, but still pronounced the product to be of standard quality. However, another state regulator, the Uttar Pradesh Food Safety and Drug Administration (FSDA), did seek specifications from Cadila, which included an endotoxin test. The UP FSDA found the batch to fail the endotoxin test, providing a possible explanation for the adverse events experienced by patients.

This incident reveals the failings of the Maharashtra FDA – it ought to have sought the complete list of CDSCO-approved specifications before testing the remdisivir. But it also reveals the incompleteness of the IP, given how critical bacterial endotoxin tests are for injectable drugs.

Subsequent to this incident, the IP did introduce a monograph for remdesivir powder for injection through an amendment to its 2018 edition. However, it remains unclear today if the IP has added a test for bacterial endotoxin to the general monograph for powdered injectables.

As this incident shows, state regulators rely heavily on general monograph for dosage forms, when approving new drugs.

Conclusion

i.) Discussion

As the preceding assessment shows, the Indian Pharmacopoeia does not perform very well on two counts: 1) the number of drug formulations sold in India covered by individual monographs in IP 2022, 2) the number of individual monographs and general monographs that contain dissolution and impurity tests. By any measure, these two shortcomings have a material and consequential impact on the country's drug supply.

Clearly, this situation is a consequence of the strategy explicitly chosen by the IPC in 2009, the impacts of which are being seen even today. The IP chose to follow ICH guidelines only as far as they would not interfere with the growth of the Indian pharma industry. In other words, economic growth of the pharma industry superseded public health when it came to IPC's priorities.

IPC has argued in the past that if it had adopted ICH guidelines early, it would have hurt the Indian industry so badly that it would have led to medicine shortages. This, in turn, would impact public health.

But this claim is highly debatable, because it doesn't consider the public-health benefits of quality-assured medicines. There is little doubt that the proliferation of poor-quality drugs also hurts people.

India has around 8,500 drug manufacturing units today. And, according to a 2020 estimate from the IDMA, only 1,000 of these facilities comply with the Good Manufacturing Practices recommended by the WHO, raising questions about the quality of drugs they make.

This data point also casts into question various past estimates of the rates of substandard drugs sold in India. For instance, a 2014-2016 survey by the Uttar Pradesh-based National Institute of Biologicals had found only 3% of surveyed drugs to be substandard. If 11% of the manufacturing units in India follow WHO Good Manufacturing Practices, and if Good Manufacturing Practices are critical for the development of standard drugs, then the 3% substandard-rate is unlikely to be representative of the real situation in the country..

A 2021 report in Mint by this author documented how poor compliance with Good Manufacturing Practices led to the production of adulterated cough syrup which killed 13 children in Jammu and Himachal Pradesh. As the case study of albendazole tablets shows, a poor-quality drug can also ineffective. And as the case study of itraconazole shows, a poor-quality drug can worsen anti-fungal resistance.

This raises the question of whether companies that don't comply with Good Manufacturing Practices are really benefiting patients. If they are not, then the benefits to patients of more stringent standards will outweigh the harm of medicine shortages.

ii.) Recommendations

1. While it is commendable that the IPC's current leadership has committed to better alignment with the ICH, the IPC's progress has been too slow. This is evidenced by the fact that the IP 2022 has chosen not to impose mandatory limits on nitrosamines even in drugs such as valsartan and ranitidine, where clear evidence of a high risk of contamination exists. Further, the health impact of this contamination is well documented, thanks to analysis conducted in ICH countries. To ignore this data, and allow the Indian industry to continue without imposing mandatory controls on nitrosamines, is unethical, not to mention short-sighted.

   Arguably, the control of nitrosamines is better addressed by CDSCO, rather than the IPC. In the US, for example, limits on nitrosamines are being imposed by the US FDA, rather than by the US Pharmacopoeia. Even though the US Pharmacopoeia has published a chapter on nitrosamines, this chapter serves more as guidance, rather than being mandatory.

   However, the Indian scenario is different for the US scenario. The Indian drug regulatory landscape is highly fragmented. And as this report notes, there are vast differences in the abilities of state regulators and CDSCO to impose quality specifications. In fact, state regulators have little ability to vet quality specifications, and rely heavily on the IP.

   This means that the Indian Pharmacopoeia plays a bigger role in controlling impurities like nitrosamines in India, relative to pharmacopoeias elsewhere in the world. Therefore, it is important for it to take a more aggressive stance in controlling quality.

2. Since its inception in 2009, the IPC has repeatedly argued that imposing stringent quality specifications on the small- and mid-sized industry will impact access to medicine, and ultimately public health. Yet, the IPC has never shared a formal analysis providing evidence for this argument.

   The other side of this argument is that lower quality specifications hurt patient health. Further, access to a poor-quality drug is often worse than no access at all. For instance, an antibiotic or antimicrobial that dissolves poorly in the body can be sold at a lower cost than one that complies with dissolution tests. But it can also make pathogens more resistant to these drugs, imposing a high cost on society as a whole.

Given that the IPC's stance has always been a controversial one, the IPC must be pushed to publish evidence that supports this argument.

3. IPC officials have publicly said that they follow an internal prioritisation framework to choose which monographs to include in the IP. However, they have only shared the bare bones of this framework publicly *(see An Assessment of the IPC: Part A)*. It isn't fully clear what weightage is assigned to each element in the framework either. Nor has the IPC ever shared its own assessment of how the IP performs against this internal framework.

   In the absence of this information, it is difficult for external assessors to evaluate the IPC's performance. For instance, it isn't clear why the drug liposomal amphotericin, which is included by the National List of Essential Medicines and the WHO Model List of Essential Medicines, and was widely used in India even before the Covid pandemic, is not included in IP 2022.

   For the sake of transparency, and in order to allow external assessments, the IPC must publish both the framework and how well IP 2022 performs against it.

4. The entire burden of upgrading quality specifications of Indian drugs does not lie on IPC alone, which is merely a standards-setting body, not a regulatory body. Both CDSCO and state drug regulators have the last word when it comes to quality specifications, given that they can impose more stringent specifications than the IPC mandates.

   Further, IPC has no power to take regulatory action against manufacturers when they fail to comply with specifications; only CDSCO and state regulators do.

   Yet, the CDSCO and state drug regulators aren't pulling their weight when it comes to ensuring drug quality. In the case of itraconazole, for instance, it is unclear how CDSCO and state regulators allowed manufacturers to get away with using sub-par dissolution methods while setting specifications.

   Further, the CDSCO and state drug regulators often create problems which the IPC cannot solve. For instance, the responsibility of approving an unsustainably large number of FDCs in India lies squarely on state regulators. Even after the Kokate committee's intervention, though, the CDSCO has failed to provide the IPC with a clear list of FDCs approved in India.

   This means that if the IPC has to work to its full capacity, the CDSCO must be compelled to work more closely with the IPC.

5. The IPC's vision and its objectives give undue weightage to the capabilities of Indian manufacturers. As per the organisation's annual reports, its vision is to "promote the highest standards for drugs for use in humans and animals within practical limits of the technologies available for manufacture and analysis".

   This vision statement imposes unnecessary caveats on the IPC's responsibility to protect patient health. New threats to drug safety and efficacy are identified every day, and tackling these threats necessarily requires manufacturers to upgrade their technologies. To refuse to upgrade quality standards, because manufacturers currently don't have the technology, is to place the cart before the horse. Yet, this is what the IPC is doing by repeatedly using the lack of technology and skills as an excuse to delay improvements.

   The IPC must rethink its objectives in a way that puts patients first and the pharmaceutical industry later. The pharmaceutical industry exists to serve patients, and not vice versa.

6. If the IPC is unable to upgrade specifications because of the concern that this may lead to supply shortages, one answer is for the Indian government to invest more in bolstering the small- and mid-sized industry. The Department of Pharmaceuticals can consider expanding its Production Linked Incentive schemes to help manufacturers with common testing facilities. This will help manufacturers to comply with difficult specifications, like nitrosamine limits.

A Review of

“A STUDY ON THE INDIAN PHARMACOPOEIA AND HOW IT IMPACTS DRUG QUALITY”

Authored by PRIYANKA PULLA”

Reviewed by: Shirish Kulkarni, Ph.D.

About - Dr. Shirish Kulkarni

"Dr. Shirish Kulkarni is an independent pharmaceutical consultant providing services to Pharmaceutical Companies since Jan. 2019. He has over 30 years of experience in Pharmaceutical Product development. Prior to moving to USA, he was at Sun Pharmaceutical Industries Ltd., India as a Senior Vice President of R&D and he was responsible for the development of generic as well as value added generic products. Before that, he was heading Advanced Drug Delivery Systems at Lupin Research Park, Pune, India with a primary focus on developing innovative and novel dosage form. Just prior to moving to India, he worked as an Associate Director of Pharmaceutical Development with GPC Biotech Inc., Princeton, NJ, USA; as a Senior Scientist with Upsher-Smith Laboratories, and as a Formulation Scientist with Monsanto Co., which is now part of Pfizer Inc. He has also worked in India as a Drug Inspector with Maharashtra State FDA; as a Development Pharmacist with E. Merck (India) Ltd.; and as a Research Associate with Rallis India Ltd. He holds B. Pharm. and M. Pharm. degrees from India, MS degree from Dalhousie University, Canada, and a Ph.D. degree from Auburn University, USA. He has been honorary member of Sigma Xi and Phi Kappa Phi scientific organizations. During his career span over 30 years, he has worked on formulations of novel medicines and many generic drugs including several first to file Para IV ANDAs. He has visited and/or audited several companies, which specialized in novel drug delivery, formulation development, manufacturing, packaging and clinical supply operations in the USA, Canada, Europe, South America and India. He has over 55 patents, 35 scientific publications and presentations in various international journals and conferences.

The Review

A. General Comments and Observations

I have reviewed "A study on the Indian Pharmacopoeia and how it impacts Drug Quality" (the report) for various aspects such as, the presented scientific and regulatory content, its relevance to the topic of discussion, references cited, hyperlinks to those references (if the link opens or not) and if those references are appropriate and relevant with respect to the comments/statements made in the report.

The scientific and regulatory content presented in the report is certainly relevant to the topic and includes historical and current understanding of the international and Indian quality requirements and their differences. I did not find any glaring factual scientific errors, omissions, or misinterpretations of the quality requirements. I have asked for a few clarifications in the form of notes which are attached to the relevant and specific parts of the report.

The scientific and regulatory content presented in the report is adequately supported by the relevant references. Hyperlinks to these references do open the correct websites, excepts for a couple of links, which did not open the referred site when I tried. I have marked such hyperlinks in the report. Please check and fix, if needed. The references cited are correct, relevant, and provide appropriate support to the comments/statements made in the report.

I have made a few, minor editorial corrections which are highlighted in "track changes".

I have had a few but very interesting and candid discussions with my former colleagues from the state FDA (I worked as a Drug Inspector in early 90's for a couple of years) and from the Indian pharma industries on Nitrosamine, cost of medicines, implications of mandatory compliance with ICH guidelines on the availability of medicines etc. I have summarized those points in the subsequent sections.

Discussions and recommendations presented in the report are with good intentions, well thought, and reasonable. However, at present, there is a significant reluctance in adopting ICH guidelines due to various obvious and non-obvious reasons, which will make it nearly impossible to accept some of those recommendations. Therefore, I have proposed a somewhat different, stepwise and timebound approach to avoid such all or none type of situations, which I have discussed in the subsequent sections of this review. This approach is based on my

understanding of the impact of compliance with the ICH guidelines on the manufacturing and testing of medicines, ensuring continuous supply of medicines, time needed for building capabilities, and at the same time, improving patient safety concerns.

B. Dual Quality Standards in India

It is true that the Indian pharma regulators and manufacturers feel skeptical about real intentions of ICH guidelines due to less transparency and restricted membership during its formative years. At the same time, Indian pharma companies experienced evergreening of patents and bullying by large multinational companies by forcing Indian companies to face expensive patent litigations and bringing them to settlement table. Very few Indian companies have that kind of financial muscle power to fight against a battery of attorneys employed by large MNCs. And there are no options but to settle such litigations. However, this skepticism has now grown into protectionism of local pharma industries mainly due to the potential for higher profits, as they can lobby within India for the status quo with respect to quality standards. Outside India, this choice is not there. Even then, no one should forget that this (relaxed quality standard) situation is potentially dangerous and harmful to Indian patients. Profit margins do increase when there are relaxed or no requirements for certain quality tests, as it automatically reduces the batch failure rate. Obviously, with stringent quality requirements there is a higher probability of batch failure. Additionally, the company must bear added testing cost, manufacturing and destruction costs and batch failure root cause analysis and investigation cost. Also, a failed batch triggers a tedious paperwork which is questioned by almost every regulatory/quality related person, within and outside the company. There are no incentives to uphold quality, but there can be serious repercussions if one points out systemic or batch specific failures.

I had long discussions regarding Nitrosamine impurities with a few people knowledgeable in this area. There is a strong resistance to implement Nitrosamine related guidelines in India. One of the major objections is, even though these are known carcinogens, there is a big ambiguity about what dose and duration of intake would have potential to cause cancer in human. Although, one can detect and quantify impurities at nanogram level, it doesn't justify setting stringent limits. FDA has proposed a limit up to 96 ng/day which is based on a daily exposure to these impurities that approximates a 1:100,000 cancer risk after 70 years of exposure. Practically speaking this is a very stringent limit when compared to many processed food items which contain higher amounts of nitrosamine impurities. For example, salami contains as much as 80 ng/g of these impurities, and typical serving of salami is 3.5 ounces (99.22 g). In Japan, average

intake of these impurities is about 500 ng/day mainly due to their diet containing fish and other seafoods. Despite such high contents of impurities there are no limits and mandatory testing requirements for such food items. I had no arguments to counter this logic other than "Two wrongs don't make one right" and "Medicines are taken by sick people whose immunity is already compromised and food is taken by healthy people".

C. Impact of adopting ICH guidelines on the cost and availability of medicines

First, let us agree that quality comes at a cost and the cost of medicine is a sensitive issue in a developing country, like India. Although Indian economy is the 5th largest in the world, about 83 million people in India live below the poverty line. India's per capita income in 2021 was about $1835 (which is about $6390 in terms of purchasing power parity). Therefore, cost of anything and everything is an important issue. As the report has pointed out, there are over 8000 pharmaceutical manufacturers in India creating a fierce competition in this area and helping to keep medicine prices low. All reasons for non-affordability of medicines, albeit many true, are used to keep ICH guidelines at arm's length. But the devil lies in the deeper details.

Please refer to the table below showing the wholesale and retail prices of a few medicines sold in India. Also, I have added retail price of similar medicines sold in the USA.

Product	**Brand Name**	**Quantity**	**Wholesale Price*^ (WP) in INR**	**High WP/ Low WP**	**Retail Price^ (MRP) in INR**	**MRP/ WP**
Rosuvastatin 10mg Tablet	Crestor®	30 Tablets	127	235%	624	491%
	Altstatin	30 Tablets	54		237	439%
Crestor® Sold in USA**	Crestor®USA	30 Tablets	N/A	N/A	27,527	N/A

Fenofibrate 145mg Tablet	Fenolip	10 Tablets	79	527%	124	157%
	Fenabrate	10 Tablets	15		106	710%
Generic of Lofibra 135mg Sold in USA**	Generic Lofibra ®USA	10 Tablets	N/A	N/A	1,819	N/A

Source Indiamart.com, **Source: GeniusRx.com, ^Exchange Rate 1 USD to INR= 81.2 in Sept 2022.

Price differences among medicines sold in India

Typically, a manufacturer sells medicinal products to a wholesaler with at least 30% profit margin. And the wholesaler sells these products to retail pharmacies with at least another 30% mark up. Sometimes there are several wholesaler or distributors before medicine reaches to retail pharmacy. Therefore, it is reasonable to assume that the manufacturer's selling price is at least 25% below the wholesaler's price, by backward calculation. If the wholesaler's price for Crestor tablets is INR 127, the manufacturer's selling price can't be more than INR 95. Even then the customer pays, INR 624, which is whopping 6.8 times than the manufacturer's selling price!!!! And this, by all means, is a very conservative estimate.

Since Crestor is a brand product, the manufacturer's selling price would include all promotional costs as well. If you compare that to a local brand which is not actively promoted, the manufacturer's selling price goes down even further to about INR 40.

The main reason for this exercise is to show that a retail customer is already paying a very high price for the medicines due to mark up by various middlemen. There is enough room to accommodate any increase in the manufacturing and testing cost due to ICH compliance, without increasing the retail price. Just to continue with Crestor example, the manufacturer's selling price would not go beyond INR 100 due to ICH compliance, as per my rough estimate. Since Crestor is a MNC's brand, aren't they supposed to comply with the ICH guidelines, no matter where they manufacture, test and sell? If they are, there shouldn't be any increase in price at all. If the retail price is not increased due to this compliance, the only negative impact would be on the profit margins of retail pharmacies which would be marginal. Therefore, I don't agree that the ICH compliance would increase retail price of medicines. Yes, the batch failure rate would increase, and

other investigational costs would also increase, if a manufacturer is not complying with the GMP standards, and that is the main crux of the issue. Therefore, every manufacturer or marketing company will use this as an excuse to increase the retail price to compensate for losses arising due to increase in batch failure rate, if the ICH compliance becomes mandatory.

Any abrupt change in the regulatory requirements for manufacturing and testing (e.g., ICH compliance) would definitely have an impact on the availability of medicines, since majority of the 8000 and odd manufacturers are small to medium scale and they are not equipped to handle such changes. Many small companies will simply shut down. There will be a lot of political pressure to maintain status quo with respect to current regulatory requirements to ensure that there are no significant job losses and companies are not going bankrupt. Just a few years back, pioglitazone was suddenly banned due to its potential for bladder cancer. Many manufacturers, wholesalers, and retailers in fact made higher profits by selling it in grey market, which was even more dangerous to patients. Neither patients nor their doctors were worried about the bladder cancer potential. Now, pioglitazone is again available in the market with a bladder cancer warning on its label.

Therefore, in the upcoming section I have proposed a stepwise and timebound change in regulatory requirements to ensure that there are no shock waves in the pharma market.

D. Impact of adopting ICH guidelines on the patients in India

There is no doubt that the medicine safety and efficacy would improve when ICH guidelines are adopted in India. In fact, it is high time that India should take concrete steps towards aligning IP and CDSCO quality standards to ICH guidelines.

Indian health care system is highly fragmented, and pharmacovigilance is still in its nascent stage. Other than major/ serious /severe side effects are observed, there is not much reporting of adverse events, and their compilation as well as evaluation. Therefore, it is very difficult to assess undesirable impact of current relaxed requirements of IP and CDSCO. Thanks to the silver lining of Covid 19, adverse events reporting, and data compilation have shown some improvements recently.

Although, I have already shown that the retail price of medicines should not increase due to ICH compliance, manufacturers and marketing companies will use this as an excuse to increase the retail price, which will be a direct hit to a patient's wallet.

E. Suggestions and Recommendations

Some suggestions which can be implemented as soon as possible:

1. IPC should improve general monograph for dosage form of IP as close as possible to ICH guidelines.
2. IPC should target to include 90% or more monographs for all marketed medicines into IP in every revision.
3. As a priority, IP should include monographs for all NLEM products.

As mentioned previously, any abrupt change in compliance requirements, would create a chaotic situation in Indian pharma market. Also, many companies do not have necessary infrastructure to analyse products as per ICH guidelines. State govt. as well as private labs are also in the same situation. They will need funds to procure equipment needed and train their staff to operate these equipment and understand documentary requirements in case of failures. However, unless forced by the Govt. agencies, the local pharma industry will not take necessary steps to comply with the ICH guidelines.

Therefore, a carrot and stick approach is needed. The following is a broad outline of suggestions for the stepwise and time bound transition from current quality standards to compliance with the ICH guidelines.

Category I (Product specific)

Which Products/Tests: All new products (containing single active or FDC, and modified release product) where same type of product has not been previously approved. Here "same type" includes same active/s, same unit dose, same dosage form, and same route of administration, and in case of modified release, similar modified release pattern requiring no clinical studies.

Time for Compliance: All new products should comply with the ICH guidelines within two years of initiation of change in requirements. CDSCO should not approve any new product without ICH compliance after 2 years of change initiation. Product approval can be revoked if an approved new product doesn't meet compliance requirement after 2 years of initiation of change.

Rationale: Most of the new products are developed and launched by big pharma companies who are well equipped to comply with the ICH requirements.

Category II (Specific Critical test requirement):

Which Products/Tests: Already approved drug products which are known to contain mutagenic, carcinogenic, teratogenic or any other highly toxic impurities. Additionally, all sterile products where sterility and endotoxin tests are required.

Time for Compliance: All these products should comply with the ICH guidelines with respect to these critical tests (only) within two years of initiation of change in requirements. After 2 years of initiation of change, CDSCO should not approve any such product without ICH compliance with respect to these tests.

Rationale: This is a serious safety concern and needs to be addressed immediately. Since this requirement is for critical tests only, drug shortage is expected to be minimum.

Category III (Product Specific):

Which Products/Tests: All drug products which are meant for long term treatment, typically for more than 30 days.

Time for Compliance: These drug products should comply with the ICH guidelines within 4 years of change initiation.

Rationale: During the long-term treatment, patient's exposure to harmful impurities is cumulative.

Category IV (Product and Tests):

Which Products/Tests: All remaining drug products and all quality tests.

Time for Compliance: All drug products should comply with all requirements of ICH within 6 years of initiation of change.

Rationale: Six years is a sufficient time to update infrastructure and comply with the ICH guidelines, without creating drug shortage.

In order to facilitate smooth transition, the Govt. (Ministry of Health) needs to ensure adequate funding is provided to govt. laboratories as well as private laboratories to develop necessary infrastructure. Similarly, Govt. may provide subsidized analytical testing facilities to small/medium scale pharma companies based on their annual turnover limits. Also, the Govt. can further incentivise pharma companies by allowing to mention "ICH Compliant" on their product label (a marketing advantage). This will help to speed up the process.

Quality consciousness is a mindset for doing right things even when no one is looking or checking, and changing current mindset is going to be an uphill task, if not impossible.