Health Policy Initiative

International cooperation for registration of medicines

Opportunities for India

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Introduction

International cooperation – Why?

Globally interconnected medicine supply chains warrants rigorous medicine regulation - International cooperation initiatives also promote ease of doing business for an increasingly global pharmaceutical industry and enhance the attractiveness of initiatives like 'Make in India'

Limited Resources with National Medicines Regulatory Authorities (NMRAs) - Regulators can no longer promote public health by means of an inward-looking attitude – they need to connect and cooperate with counterparts in other countries and make best use of their limited resources

Learning opportunity for maturing jurisdictions - Contrary to the apprehension that participation in international cooperation would compromise national sovereignty, international cooperation initiatives could be learning platforms for maturing regulatory authorities

Benefits to public health - International cooperation can be seen as a tool to foster faster accessibility and availability of quality medicines

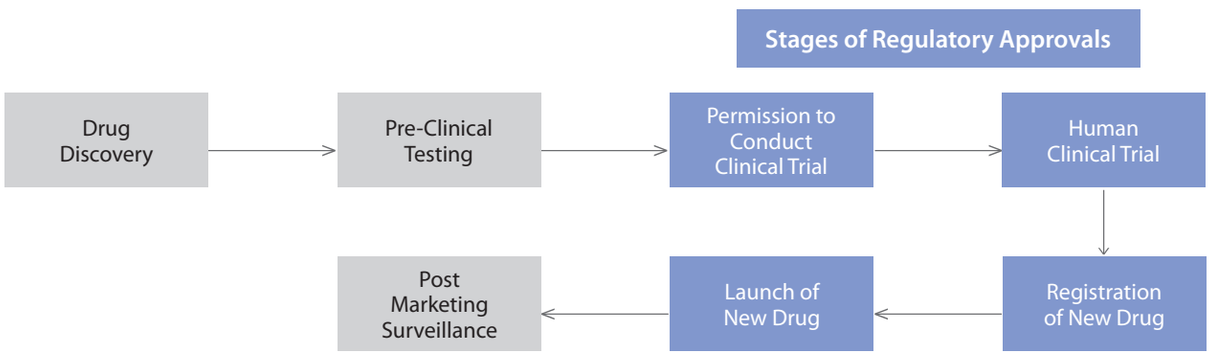
Why focus on medicine registration?

Drug registration is a critical step for the introduction of a medicine in a country (refer to figure 1 below for the steps involved in drug development and the stages requiring regulatory approvals).The process starts with the submission of a dossier by a company to the regulator and culminates in approval / rejection and subsequent registration of the final product on the basis of an assessment of safety, quality and efficacy parameters of the drug (refer to figure 2 for India's current drug registration process).

Given 'unnecessary differences' in local regulatory procedures for drug registration combined with differential local regulatory capacities, the cross border movement—and universal availability—of medicines is not as seamless as one would hope, to say the least.

Improved and more efficient drug registration processes are critical not only in the backdrop of the changing dynamics of the Indian pharmaceutical industry and its efforts towards drug discovery, but more importantly in the wake of the rapidly changing burden of disease and demand for newer and better treatment options.

Figure 1: Stages of Regulatory Approvals in the Process of Drug Development



Source: Developed by Authors

Countries have explored various pathways for international cooperation

Convergence –
Asia Pacific Economic Cooperation (APEC), International Generic Drug Regulators' Programme (IGDRP)

Harmonisation –
European Union, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), African Medicines Regulatory Harmonisation (AMRH), Pharmaceutical Inspection Co-operation Scheme (PIC/S), Pan American Network for Drug Regulatory Harmonization (PANDRH)

Collaborations –
Mutual recognition agreements, bi-lateral and multi-lateral agreements, regional cooperation - Association of South-east Asian Nations (ASEAN)

International cooperation – Opportunities for India

Indian drug regulators have largely stayed away from ongoing initiatives of international cooperation, despite India being a signatory to the international health goals—earlier under the Millennium Development Goals (MDG), and now the Sustainable Development Goals (SDG), framework of the United Nations—as well as growing international participation and stature of the country generally.

International cooperation can result in

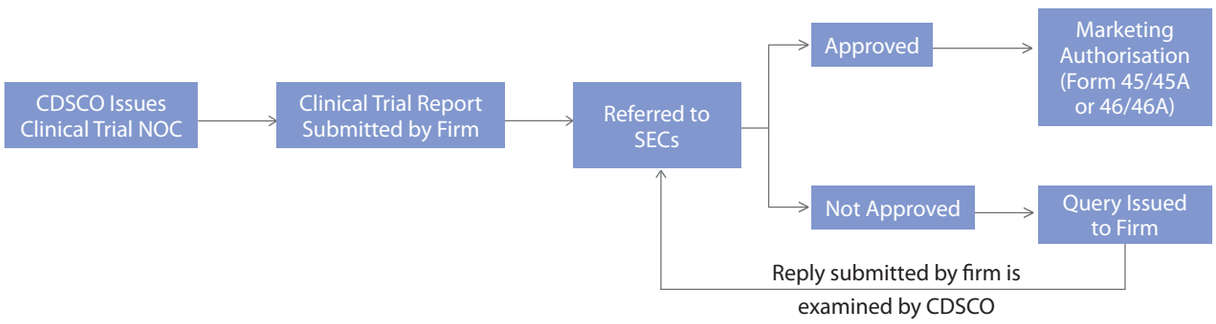
- Possibilities for participating in systemized/facilitated routes of medicine registration,
- Enhanced access to markets resulting in more legitimate business that brings in more registered medicines and weeds out fake or substandard ones in the domestic market,
- Efficient utilization of regulatory resources by reduction of duplicative processes.

An obvious positive spillover of the process would be increased confidence in the health system, both domestically and globally.

The purpose of this brief is to outline some of these opportunities for India in the form of policy recommendations. In the pages that follow, policy recommendations are presented thematically. Each recommendation is supported by a rationale and corresponding challenges that the regulator may face in the process of implementing them. These recommendations are aimed at short/medium/long term goals. For a detailed analysis of these themes, please refer to our Report.

Implementation Horizon: Short-term goal Medium-term goal Long-term goal

Figure 2: New Drug Registration Process at Central Drugs Standard Control Organization (CDSCO)



Source: Developed by Authors

RECOMMENDATION 1

Periodic assessment of new drug approvals – to identify areas of unmet medical needs, which the regulator can address through various international cooperation initiatives

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- By carrying out periodic assessments of drug approvals (on an annual basis), the regulator can identify areas of under-served medical needs
- Subsequently, incentives can be provided to the companies (including expedited review pathways) for such disease categories, thus paving the way for newer treatment options

Potential challenges in operationalisation

- In order to ensure that expedited reviews are treated as an exception and not the norm, the regulator would have to spell out the meaning of 'rare disease' & unmet medical needs, which would be challenging given the lack of adequate variables and data to define it (see the box below)

Unpacking Unmet Medical Needs

For expediting the review of certain essential drugs – the Apex Committee has recommended that for the drugs already approved outside India, waiver of clinical trial in Indian population may be considered only in cases such as,

- national emergency,
- extreme urgency,
- epidemic,
- orphan drugs for rare diseases and
- drugs indicated for conditions/diseases for which there is no therapy.

Additionally, the Apex Committee considers grant of CT waivers on the recommendation of SEC and Technical Committee, on a case by case basis, reflections of which are published in the minutes of the meeting of the various committees. These developments are indicative of the regulatory thinking, however, substantive regulatory guidance is required insofar as the exact definition and requirements to be presented for unmet medical needs are concerned.

RECOMMENDATION 2

India should seek learning opportunities at global forums such as ICH and IGDRP

Target Agency - CDSCO, Ministry of Health & Family Welfare and Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers

Rationale

- Participation in the meetings of global forums will benefit India – learning from the experience of the developed countries and contributing to the discussions
- Instead of reinventing the wheel, India can consider the merits of adopting established scientific guidelines discussed at these forums
- Opportunities on the lines of observership at global forums, such as that of ICH and IGDRP, will facilitate a meaningful dialogue, wherein the Indian regulator can voice their views/insights/concerns on critical areas

Potential challenges in operationalisation

- Proactive participation in the international fora depends upon the political will and urgency of the issue at hand
- Successful implementation and enforcement of best practices encoded in the national legislation and guidance documents, is an iterative process and therefore resource intensive

RECOMMENDATION 3

Potential cooperation initiatives – regional cooperation initiatives (likes of ZAZI-BONA, EU) – could be explored for India

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- Regional group formed of the basis on similar disease pattern can generate collective demand for medicines which can work as an incentive to innovate for such a potentially large market
- It can further create opportunities to address the issue pertaining to the lack of technical expertise with the regulator –
  - joint assessments with the experts of mature jurisdictions,
  - joint review collaboration with neighbouring countries (could be explored in BIMSTEC) or countries with similar disease burden or pharmerging economies (like BRICS),
  - participation in Facilitated Review Pathways (FRPs) through international cooperation programs, eg: President's Emergency Plan for AIDS Relief (PEPFAR) of the US FDA and Article 58 of the EMA

Potential challenges in operationalisation

- Regional initiatives face challenges due to varied local characteristics of its member countries – different backgrounds, local industry conditions, levels of economic development, regulatory requirements and capacities, political relations, trust, etc.
- It would be an elaborative exercise to identify areas of neglected diseases

RECOMMENDATION 1

Pre-filing consultations for an efficient registration process

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

CDSCO offers an administrative pre-screening check of dossiers. However, at present, there is no provision for a thorough pre-submission consultation between the applicant and the regulator, that can ensure compliance with the regulatory requirements

- Such consultation greatly reduces the potential for delays in the approval process that may stem from incomplete documentation
- Submission of a dossier of improved quality obviates the need for many queries raised during the approval cycle

Potential challenges in operationalisation

- Given the numerous responsibilities that they are entrusted with, the CDSCO would certainly need more hands to start pre-submission consultations
- There would be a need to carefully evaluate if pre-filing consultations are required for every category of a new drug application and whether such advice would be binding on the regulator and paid for by the applicant

RECOMMENDATION 2

Extensive guidance documents explaining the process, timelines and requirements for a marketing authorization application for greater procedural clarity

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- Such guidances can be linked to the SUGAM information portal in order to ensure real time dissemination of information
- Could lead to significant saving of resources – both regulatory and industry – as in many cases availability of relevant guidance on e-platforms could reduce the time taken to contact nodal regulatory official

Potential challenges in operationalisation

- The said recommendation will require dedicated personnel for maintaining and updating the SUGAM information portal on a day-to-day basis

RECOMMENDATION 3

Bridging the gap between SUGAM and the internationally followed eCTD to provide a lifecycle approach to the dossier format and submission process

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- While SUGAM is being seen as a game changer, firms operating on a global scale are already reaping the benefits of electronic Common Technical Document (eCTD) as a submission gateway
- Most regulatory jurisdictions have found it useful to adopt a common platform like eCTD
- India could also consider bridging the gap between the presently existing SUGAM, which is only a submission platform, to the eCTD format which has a dual gateway

Potential challenges in operationalisation

- As of now, only CDCSO staff has access to the SUGAM software, and reforming SUGAM on the lines of eCTD may result in additional hurdles because then every reviewer's system will have to be fitted with the new software. This implies further training costs with additional technical difficulties, which will require a phased implementation

RECOMMENDATION 4

Building a team of in-house reviewers towards creating institutional memory

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- Having an in-house review team, instead of the current system of reliance on external reviewers, would be more efficient in terms of both time and cost
- Creating a team of experts who are solely dedicated to this task will enable strengthening of institutional memory
- Such specialists could be directly recruited into the regulatory system making dossier review their primary responsibility

Potential challenges in operationalisation

- Building an in-house review team is a time and resource intensive process. The regulator would be required to plan the composition of the review team, required budget, and targeted timeline to implement this
- Additionally, these reviewers would require regular training to keep them abreast with latest regulatory science and best practices

RECOMMENDATION 5

To ensure timeliness in the review process, project managers should work in tandem with review experts

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- Project managers, in addition to in-house reviewers, would help CDSCO in ensuring a time bound and transparent review process
- The project managers would also act as a nodal point for smooth interface between the regulator and the applicant

Potential challenges in operationalisation

- There would be a need to clearly specify the nature of their work, which would in turn be based on the budgetary flexibilities of the regulatory authority

RECOMMENDATION 1

Collate a dataset – may be through SUGAM - which can be used to conduct impact assessments of policy changes to understand which regulatory shocks have desired effects and which do not

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- CDCSO would have to further widen the ambit of SUGAM and use it to compile a dataset with details on applications and approvals by type of drug, time to approval, etc.
- A rich dataset that is publically accessible, would enable researchers to carry out an effective analysis of various regulatory policies of the government
- This would help in designing of better policies by addressing gaps in previous policies, as well as ensuring better implementation of existing policies

Potential challenges in operationalisation

- There are significant costs – both in terms of time and funds – to be incurred by the regulator in building this dataset
- This will necessitate appointment of some personnel on full-time basis to monitor the databank and update it on real-time basis

RECOMMENDATION 2

India must focus on internal harmonisation within the country and provide initial support to small scale industry in the process of upward integration

Target Agency - CDSCO, Ministry of Health & Family Welfare

Rationale

- There is need for mechanisms that aim at streamlining the regulatory environment such as those that bring about internal harmonisation and enable uniform implementation of existing rules and laws across the country
- This process will help weed out manufacturers of fake medicines i.e. those that contain no or an incorrect active ingredient, and help in providing the much-needed credibility of quality

Potential challenges in operationalisation

- Technical costs to the government/regulator will be that of administering new protocols, through increasing the regulatory bandwidth in terms of human, financial and technological resources
- The costs are likely to be significant for medium and small players who have a limited scale of production and/or might export to countries with relatively less stringent requirements and protocols

The way forward

Improved and more efficient drug registration processes are critical not only in the backdrop of the changing dynamics of the Indian pharmaceutical industry and its efforts towards drug discovery, but more importantly in the wake of the rapidly changing burden of disease and demand for newer and better treatment options. Nevertheless, Indian drug regulators have largely stayed away from ongoing initiatives of international cooperation, despite India being a signatory to the international health goals – earlier under the MDG, and now the SDG, framework of the United Nations – as well as growing international participation and stature of the country generally. Indian regulatory framework cannot operate in isolation from the general aspiration and approach of the Government of India as far as external affairs and international participation are concerned, not to talk of India's critical need to tackle its health challenges, particularly the massive burden of premature mortality.

For developing countries such as India, international cooperation initiatives can serve as learning opportunities as well, where mature and less mature regulatory agencies collectively address issues common to all regulatory partners. India's public health demands should drive its interest and the nature of participation in international cooperation. Areas of benefit include providing expedited review pathways through international agreements in under-served disease categories, joint assessments through collaboration among regulators of countries with similar disease burdens, and the like. Although a number of harmonisation and cooperation initiatives such as the creation of single market of EU, ICH and ASEAN were initially driven by a vision to enhance trade between participating countries, the regulators' mandate to protect and promote public health makes it important to account for the public health imperative on a priority basis.

In one of the recent developments, India has joined the ranks of observers at the ICH. This is a welcome step – but India's drug regulators need to be adequately empowered within the existing administrative framework, and likewise be expected to participate proactively in international forums, learn from them as well as contribute to the shaping of international processes wherever needed and possible, for their own as well as global public health.

India has arrived at the world stage – the nation's drug regulators should too!

A snapshot of cross country comparison

India	USA	Europe
Medicine Regulatory Agency		
Central Drug Standards Control Organisation	US Food and Drug Administration	European Medical Agency; Competent authorities of member states
Medicine Legislation		
Drugs and Cosmetics Act, 1940 Drugs and Cosmetics Rules 1945	Federal Food, Drug and Cosmetic Act , 1938	Directive 2001/83/EC Regulation (EC) No 726/2004
Medicine Registration Process		
Pre-Submission of Application		
Administrative pre-screening check, but no pre-submission meeting	Pre-submission meeting to discuss the format and content of the anticipated application	Pre-submission meeting with the EMA/ relevant competent authority (as applicable) is recommended to better plan the application
Submission of Application		
CTD is recommended	CTD/eCTD is used widely	CTD/eCTD is used widely
Review of Application		
External review committees	In-house experts alongside external committees	In-house experts and committees within the EMA and competent authorities of Member States
Average Approval Time		
New Drug Application –180 days Subsequent New drug Application – 120 days	Priority review – 8 months Standard review – 10 months	210 regulatory days
Ongoing international Cooperation Initiatives		
ICH – observer MOUs with MHRA	ICH – founding member IGDRP, APEC, PANDRH MOUs	ICH – founding member IGDRP

South Africa	Singapore	Indonesia
Medicine Regulatory Agency		
Medical Control Council	Health Sciences Authority	National Agency for Drug and Food Control
Medicine Legislation		
Medicines and Related Substances Control Act (Act 101 of 1965)	Health Products Act, 2007	Decree of the Head of National Agency of Drug and Food Control, 1950
Medicine Registration Process		
Pre-Submission of Application		
Pre-submission meeting with MCC to address issues related to the development of biological medicines in the planning phase of such products	Pre-submission consultation (an enquiry or a meeting) takes place with the HSA – helps in choosing the evaluation route	Pre-registration meeting is conducted to decide the evaluation path and the NADFC has to come out with its decision within 40 days
Submission of Application		
CTD used for all applications and eCTD is mandatory for New Chemical Entities	ICH CTD & ASEAN CTD (ACTD) both are used for application submission. All applications must be made on-line via the PRISM portal	Only ACTD is used for application submission
Review of Application		
External review committees	Panel of internal and external reviewers	Panel of internal and external reviewers
Average Approval Time		
No statutory timeline	**Full Review:-** NDA Application – 270 days **Abridged Review:-** NDA Application – 180 days; GDA Application – 240 days **Verification Review:-** NDA Application – 60 days; GDA Application – 120 days	Orphan drugs/drugs for life threatening diseases – 100 days New drugs already approved in certain other countries – 150 days Others that do not qualify in the above two categories – 300 days
Ongoing International Cooperation Initiatives		
AMRH (SADC, ZAZIBONA), IGDRP, MOU with Swissmedic	ASEAN ICH – Observer ICMRA, PIC/s, APEC and IGDRP MOUs with a number of countries such as Australia, Canada, Switzerland, USA, UK etc	ASEAN, APEC

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