

**LESSONS FROM THE
COVID-19 PANDEMIC**

**Modernizing Regulation
of Non-Prescription
Medicines Through
Increased Flexibility
and Digitalisation**



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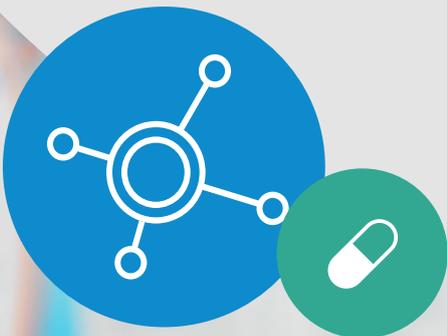
INTRODUCTION

Non-prescription medicines typically treat self-limiting conditions and prevent diseases—they are a critical component of an efficient and effective healthcare system. To ensure that non-prescription medicines continued to be available as an important option for consumers during the pandemic, regulatory authorities and the self-care industry took unprecedented actions, including increased collaboration and communication among regulatory authorities and between authorities and manufacturers. Many regulatory authorities also adopted policies, regulations, and processes to ensure continuity of critical medicines supplies.

For instance, some regulatory authorities reacted to the COVID-19 crisis by initiating risk-based approaches to simplify and streamline regulatory practices. This included postponement of certain pre-market

requirements and scheduled lifecycle management obligations or expedited risk-benefit reviews as well as digitalising agency practices and requirements. Among the simple solutions were the acceptance of digital instead of wet signatures by EMA, which started to issue electronic certificates for medicinal products (eCPPs). This ensured that EMA could provide certificates during the COVID-19 pandemic without any business disruption facilitating the regulatory compliance and timely access for medicines in importing countries.

The new policies, regulations, and processes were implemented without compromising the quality, safety, and efficacy of these medicines. However, in some instances, regulatory authorities were forced to prioritise their activities during the pandemic to ensure that the most important activities, such as those involving pharmacovigilance and the review of new anti-COVID therapies and vaccines, continued uninterrupted. Understandably, while regulators tried their best, service levels for some post-approval regulatory activities relevant to non-prescription medicines were impacted; for instance, variations and license renewals for self-care products were deprioritised, leading to delays and uncertainty in these processes. This may have exacerbated on-going product shortages. In the future, it will be important to look for alternative approaches to conduct these activities without compromising quality, safety, and efficacy.



MODERNIZING REGULATION OF NON-PRESCRIPTION MEDICINES THROUGH INCREASED FLEXIBILITY AND DIGITALISATION

BACKGROUND

Global Self-Care Federation (GSCF) believes that, as the world returns to a more normal environment, many of the innovative policies and regulation affecting non-prescription medicines should be assessed for potential adoption into standard practice. As regulatory bodies reflect on their actions during the pandemic, they might consider implementation of new best practices to modernize their approach to non-prescription medicines. Importantly, when considering new regulations, there should be more emphasis on “what” the required outcomes and standards necessary to protect public health should be rather than “how” to comply with good regulatory practices. Outcome-based regulation would help to meet the health and safety requirements through a modernised approach that is technology neutral, and allows for more flexibility to accommodate innovation and international supply chain complexity, while ensuring that the focus remains on what matters most, the outcomes of processes (quality of products).

Within the realm of modernizing regulatory oversight of non-prescription medicines, GSCF identified three key principles to help ensure greater sustainability and resilience:

- | **Digital technologies and increased international cooperation leveraged by regulatory authorities to streamline inspection practices.**
- | **Risk-based approaches to simplify and streamline regulatory practices instituted by governments and regulatory authorities for existing and new non-prescription medicine while keeping in place all effective provisions to ensure quality and authenticity.**
- | **Acceptance of real-world data (RWD) and resulting real-world evidence (RWE) by regulatory authorities to confirm safety and efficacy of established or potential new non-prescription medicines.**

LEVERAGING DIGITAL TECHNOLOGIES AND INCREASED INTERNATIONAL COOPERATION TO STREAMLINE INSPECTION PRACTICES

Regulatory authorities ensure that Good Manufacturing Practices (GMP) standards are met by all manufacturers for all approved products, including non-prescription medicines; they also oversee Good Clinical Practice (GCP) and Good Pharmacovigilance Practice (GVP) standards. These three sets of standards are collectively known as GxP. In addition, regulatory authorities have similar oversight of good distribution practices (GDP) which are the minimum standards that a wholesale distributor must meet to ensure that the quality and integrity of medicines is maintained throughout the supply chain.

As an example, regulatory oversight of GxP and GDP has historically been managed through on-site visits by health authorities. During the early stages of the COVID-19 pandemic, despite a preference by the regulatory authorities and the industry for on-site visits, virtual inspections had to be conducted. These virtual visits were shown to be as rigorous as on-site visits, where documents were submitted well in advance for inspectors to review, and included historical reports of previous inspections. They emerged as an innovative approach to maintaining high GxP and GDP standards, while optimizing agency resources. When documents and expectations regarding the virtual inspections are understood by the inspector and manufacturer beforehand, they offer several advantages for both parties. For the inspectors, time spent on every inspection is reduced considerably since there is no travel involved and the time can be invested in preparation and review of documents. This lack of travel further contributes to flexibility of schedules and reduction in the environmental footprint caused by the travel. Finally, it also enables industry experts across different locations to participate in the inspection. Although some regulatory authorities, such as the



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US FDA, have expressed a preference to return to on-site inspections once the COVID-19 pandemic subsides, **GSCF believes that there should be a greater willingness to use virtual inspections, where appropriate, going forward.**

Moreover, GSCF believes that **greater cross-agency collaboration, through the establishment of Mutual Recognition Agreements, can avoid unnecessary duplicative inspections to the same or similar standards.** This allows regulators to focus their limited resources on products and facilities in jurisdictions that potentially pose a higher risk. While we work towards mutual recognition,

the entire inspection process could be streamlined and harmonized through greater international cooperation, perhaps under the Pharmaceutical Inspection Co-operation Scheme (PIC/S).¹ GSCF believes that PIC/S, with its associated partner organisations and other organisations active in the field of GMP, could exercise good regulatory oversight of the entire product lifecycle. This would include the development of a general recommendation on risk-based approaches for virtual versus on-site inspections, clearly delineating situations in which digital technology can be leveraged. PIC/S can also continue to facilitate dialogue between PIC/S members and non-members

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on how to adopt reliance practices within national regulatory strategies. Lastly, GSCF welcomes training opportunities for inspectors on harmonised and standardised GMP practices through the PIC/S Inspectorates' Academy. Expansion of this practice, which was established before the pandemic, would help to establish common understanding that scientific and technical experts from the self-care sector are available to support.

Beyond remote inspections, GSCF believes **regulatory authorities could increase their use of digital technologies to streamline regulatory processes** in other ways. During the COVID-19 pandemic, many regulatory authorities were prepared to forego national requirements for original paper-based certificates and authentication, by means of wet signatures and/or by practices such as notarisation and embassy legalisation, in favour of electronic alternatives. In fact, these opportunities highlight a broader need for increased collaboration, building on the benefit of digital verification of regulatory documents.

A great example of this occurred in Canada,² where Health Canada established a pilot project to implement electronic issuance of Drug Establishment Licences (e-DELs). The pilot is expected to offer many benefits including: a) minimal disruption to the issuance of e-DELs during the COVID pandemic; b) a "greener" process for issuing e-DELs with the elimination of a paper-based process; and c) more efficient, streamlined, and cost-effective process that allows regulated parties to access their e-DELs in a more expeditious manner.

Regulatory authorities could increase their use of digital technologies to streamline regulatory processes.

RISK-BASED APPROACHES TO SIMPLIFY AND STREAMLINE REGULATORY PRACTICES

Beyond GxP, there are other opportunities to cement regulatory practices and best practices successfully undertaken during the COVID-19 pandemic by various regulatory authorities. For instance, “skip testing”, a process employed to reduce the analytical testing burden associated with frequency batch production, can easily be streamlined. Rather than test all batches within a given interval, the number of batches tested should be commensurate with risk. If potential risks have been identified and well understood, such that testing is expected to be consistent batch to batch, it may

be appropriate to test pre-selected batches, while ‘skipping’ the remaining ones. This reduction is justified by a visibly low risk of any batches failing specification.

This is particularly true for non-prescription medicines, which are generally well-characterised due to their long history of use. GSCF believes that **regulatory authorities should work with manufacturers to develop a framework which defines when and how to implement risk-based skip testing** for finished product batches. This would improve the reactivity of the supply chain, releasing batches quicker, especially for products at risk for shortages.

Current post-approval changes and renewal systems present many challenges as national and regional regulatory authorities take vastly different approaches. This has, at times, resulted in fragmented local regulatory requirements,

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inconsistent approval timelines, divergent regulatory authority decisions, and other issues that can lead to disproportionately lengthy times for approvals, diverted resources and budgets for regulatory authorities (and manufacturers), and several versions of products approved globally with little added benefit to the consumer. To help ensure cross-border regulations serve the needs of a global sector and its consumers, opportunities such as **global convergence of regulatory requirements, mutual reliance, or recognition of prior applicable decisions by other regulatory authorities, together with other cooperation initiatives** would provide a more efficient environment for the management of post-approval changes and renewals.

GSCF welcomes the WHO-ICMRA report on regulatory flexibilities/agilities as implemented by National Regulatory Authorities during Covid-19 pandemic³ as the first step. COVID-19 led to regulatory pragmatism in some markets regarding the life-cycle management activities for self-care products. This, in turn, demonstrates that regulation of non-prescription medicines can be adjusted to the risk levels without a reduction in quality or consumer safety. Post-approval regulation of non-prescription medicines, including **simplified approvals of variations, is also an area for possible modification** since risk management measures for these well characterized products are generally understood. From a global perspective, where possible, post-approval changes should follow a common international system, which is evidence- and risk-based, and which establishes unified data requirements across regulatory authorities. Minor quality variations and other modifications requiring purely administrative changes should not require regulatory approval prior to implementation. Agencies could either be notified in a periodic report or such changes should be maintained within the manufacturer’s quality system and reviewed during inspections. For example, under the “do and tell” model in the EU, for a minor variation that has no or only a minimal impact on the quality, safety or efficacy of the medicinal product, the manufacturer must simply notify the regulatory authority within 12 months of the variation.





Variations of a moderate and major nature in terms of impact on quality and safety should still be reviewed within set and predictable timelines before their implementation. In

Europe, with regards to the evaluation within national phase procedures, health authorities could commit to a 30-day timeline to approve a single variation for simultaneous implementation everywhere. In

the USA, Japan, and Australia, there is no regulatory licence renewal process for non-prescription medicines while in the EU and UK, renewals for non-prescription medicines are normally not required beyond five years after first marketing authorisation. Considering good pharmacovigilance practices worldwide and their well-established safety profile, the review of the safety of non-prescription products does not need to be done through a formal renewal. And, since quality aspects are continuously re-evaluated and updated through post-approval life-cycle management, the need for the licence renewal process should be deemed to be unnecessary.

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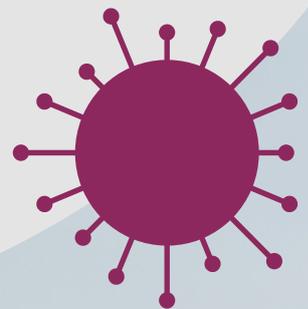
REGULATORY AUTHORITIES COULD MAKE INCREASED USE OF REAL-WORLD DATA (RWD) AND RESULTING REAL-WORLD EVIDENCE (RWE)

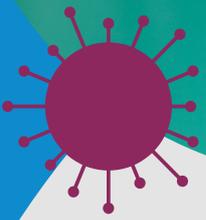
A recent peer-reviewed article suggested a variety of regulatory applications specific to non-prescription medicines.⁵

The article identified three areas for the use of RWD and RWE to inform regulatory processes specific to non-prescription medicines:

- a) Enhancing re-classification from prescription-only to non-prescription status (Rx-to-OTC switch).
- b) Investigating real-world effectiveness to complement available clinical evidence and benefit-risk balance for a non-prescription medicine application.
- c) Addressing potential post-marketing safety concerns.

GSCF agrees with the authors and encourages regulatory authorities to collaborate with manufacturers to increase acceptability, application, and use of RWD and RWE in support of non-prescription medicines.





CONCLUSION

During the COVID-19 pandemic, consumers across the globe turned increasingly toward self-care, not only to manage mild to moderate symptoms of COVID-19, but also to diagnose and treat other self-limiting conditions as well as maintain general wellness. To ensure that non-prescription medicines continued to be available as an important option for consumers during the pandemic, regulators and the self-care industry took unprecedented actions, including increased collaboration and communication between and among regulators and manufacturers. Many governments and regulators also adopted policies, regulations, and processes to ensure continuity and quality of critical supplies. These new measures were implemented without compromising the quality, safety, and efficacy of non-prescription medicines.

As the world slowly returns to “pre-pandemic” state, many of the innovative policies and regulations effecting non-prescription medicines should be assessed for potential adoption into normal practice. In addition, as regulatory bodies reflect on their actions during the pandemic, whether successful or not, they might consider implementation of new best practices to modernize their approach to non-prescription medicines. This should include increased use of digital technologies and enhanced international cooperation to streamline and harmonize inspection practices. There is also an opportunity to simplify and streamline regulatory practice for non-prescription medicines more broadly, without negatively impacting safety. The use of RWD remains an untapped, but promising opportunity to support the safety and efficacy of new and prospective non-prescription medicines.



REFERENCES

- 1 The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) It seeks to lead the international development, implementation, and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products.
- 2 Health Canada Memorandum: DEL Bulletin LEPP No. 81 Electronic Issuance of Drug Establishment Licenses. 2 Apr 2020. A copy can be obtained by emailing hc.del.questions-lepp.sc@canada.ca.
- 3 WHO-ICMRA report on the review of regulatory flexibilities/agilities as implemented by National Regulatory Authorities during Covid-19 pandemic –December 2020. Available at: https://www.icmra.info/drupal/sites/default/files/2021-12/Regulatory_Flexibilities_during_COVID-19_Report.pdf.
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- 5 Csoke E, Francis MJ, Ma L, Pohlhaus DT, Landes S, Anquez-Traxler C. How can real-world evidence aid decision making during the life cycle of non-prescription medicines? *Clin Transl Sci*. 2021 Aug 18.



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GSCF is dedicated to a world where self-care provides individuals, families, and communities with the ability to manage their health and prevent diseases with or without the support of a health-care provider. Successful self-care provides individuals with greater choice of healthcare options and more accessible entries to care—e.g., through pharmacies; greater value for care when treating ailments and chronic conditions; and can lead to long-term better health outcomes. It also can decrease the burden on healthcare systems and professional medical personnel; increase freedom for innovation in healthcare; and make progress toward universal health coverage.