Assessing the use of risk-based approaches in four major agencies – What is their impact on the approval of new medicines?

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DIA 2024 Global Annual Meeting | 16-20th June 2024 | San Diego, CA, USA



Introduction

- Over the last years, several regulatory agencies have developed risk-based approaches for the regulatory assessment of marketing authorisations of New Active Substances (NASs) as strategies to efficiently use limited resources and accelerate the availability of innovative therapies to their populations.
- Different risk-based approaches exist, such as:
  - **Unilateral reliance approaches.** Relying agencies take into account and give significant weight to the results of the assessments performed by another regulatory authority, trusted institution, or any other authoritative information in reaching its own decision
  - **Collaborative approaches.** All involved agencies review the complete dossier and discuss with each other their observations and conclusions. The responses derived from information requests are exchanged amongst participating agencies. An example of this type of approach is Project Orbis developed by FDA.
  - **Work-sharing approaches.** Each agency reviews a specific part of the dossier and shares its scientific review conclusions with the other participating agencies. An example of this type of approach is the Access Consortium, initially developed by Health Canada, HSA, Swissmedic and TGA and subsequently adopted by MHRA.
- Regulatory agencies retain sovereignty over their final decisions in all cases previously described.

Objectives

- Analyse the use of risk-based approaches (unilateral reliance, collaboration, and work-sharing) for the approval of New Active Substances (NASs) by four major agencies (FDA, Health Canada, Swissmedic and TGA).
- Evaluate the efficiency and impact of those approaches on the availability of NASs.

Methods

- **Data on approvals of New Active Substances (NASs) by FDA, Health Canada, Swissmedic, and TGA from 2018 to 2022 were gathered from public sources to answer the following questions.**
- **Part 1: What proportion of NASs have benefited from using risk-based approaches?**
  - Each approved NAS was categorised based on the utilised type of risk-based approach: *"Approved through unilateral reliance approaches"* (i.e. Art. 13 and 14 TPA for Swissmedic; COR-A and B for TGA); *"Approved through Project Orbis"* (for FDA, Health Canada, Swissmedic and TGA); and *"Approved through the Access Consortium"* (for Health Canada, Swissmedic and TGA)
- **Part 2: What impact did the utilisation of risk-based approaches have on the regulatory timelines, and by how much?**
  - Descriptive statistics were developed to analyse the median submission gap, approval time, rollout time and proportion in which expedited reviews have been utilised, broken down by type of risk-based approach.
- **Part 3: Regulatory case study – What additional proportion of NASs could have been submitted through the Access Consortium?**
  - An approach was developed to determine the number of NASs that could have been submitted and reviewed by the Access Consortium (i.e. NASs that were reviewed individually by each agency but at the same time as other Access Consortium members), which was limited to Health Canada, Swissmedic and TGA.

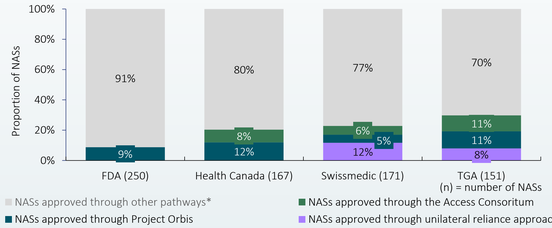
Definitions

- **Access Consortium** is a medium-sized coalition which was formed in 2007 by 'like-minded' regulatory agencies to promote greater collaboration and alignment of regulatory requirements. Its goal is to maximise international cooperation, reduce duplication, and increase each agency's capacity, ensuring timely access to high-quality, safe and effective medicines for patients.
- **Anti-cancer NASs** were defined as those that fall into therapeutic groups L and V (antineoplastic and immunomodulating agents and various, respectively) within the World Health Organisation Anatomical Therapeutic Chemical (ATC) Classification.
- **Approval time:** The time between the date of submission and the date of approval by the agency. This time includes agency and company time.
- **Expedited reviews** are categorised as 'Priority Review' by FDA, Health Canada, and TGA, and as 'Fast Track' by Swissmedic.
- **Project Orbis** is an initiative of the US FDA Oncology Center of Excellence that aims to give patients faster access to promising cancer treatments across the globe. Project Orbis partners work together on the review of submissions for cancer drugs. **Type A:** Applications submitted to the POP within 30 days of FDA submission. **Type B:** Applications submitted to the POP after 30 days of FDA submission. **Type C:** Applications submitted to the POP after FDA issues a positive opinion.
- **Submission gap*:** Time between the date of submission at the first regulatory agency to the date of regulatory submission to the target agency.
- **Rollout time:** The time between the date of submission at the first regulatory agency and the date of approval by the target agency.

Results

Part 1— What proportion of NASs have benefited from using risk-based approaches?

Figure 1. Percentage of NASs approved by four major agencies between 2018-2022 broken down by type of risk-based approach

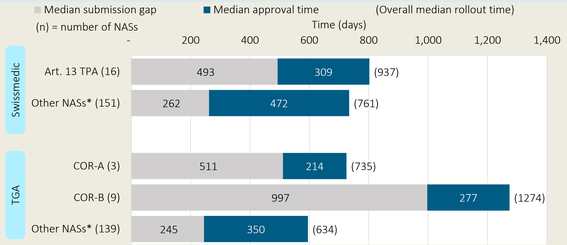


**: "Other pathways" refers to NASs approved through pathways other than Art. 13 and 14 TPA for Swissmedic, COR-A and B for TGA, Project Orbis and the Access Consortium.*

Between 2018 and 2022, the proportion of NASs that were approved through at least one risk-based approach (unilateral reliance, collaborative or work-sharing approaches) was 9% for FDA, 20% for Health Canada, 23% for Swissmedic, and 30% for TGA. It is worth noting that Project Orbis just stated in 2019.

Part 2— What impact did the utilisation of risk-based approaches have on the regulatory timelines, and by how much?

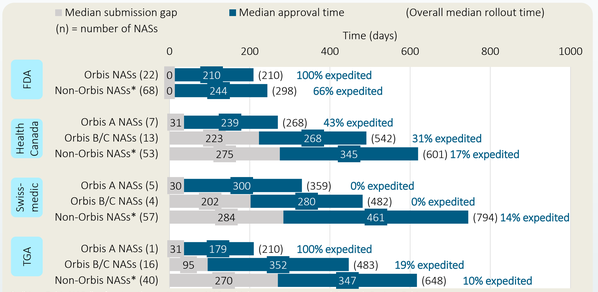
Figure 2. Median submission gap, approval and rollout time of NASs approved by Swissmedic and TGA between 2018-2022 (Unilateral reliance approaches vs. Others)



**: "Other NASs" refers to NASs approved through pathways other than Article 13 and 14 TPA. Four NASs approved through Art. 14 TPA were excluded from the analysis. For TGA, it refers to NASs approved through pathways other than COR-A and COR-B.*

- In general, NASs approved through unilateral reliance approaches have a shorter median approval time than other NASs.
- Median submission gaps are longer for unilateral reliance approaches than other NASs. This situation might be explained due to each agency's eligibility criteria for utilising unilateral reliance approaches (e.g. the need to wait to get reference agencies' assessment reports) and company strategy.

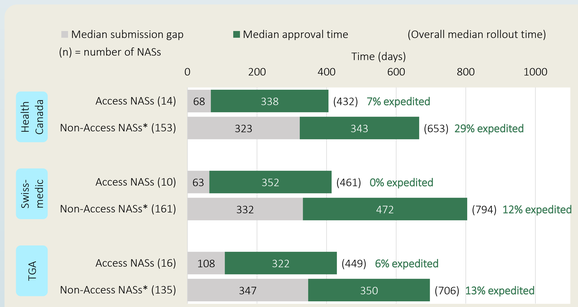
Figure 3. Median submission gap, approval and rollout time of NASs approved through Project Orbis compared to other anti-cancer NASs approved between 2019-2022



**: "Non-Orbis NASs" refers to other anti-cancer NASs which were not approved through Project Orbis.*

- The NASs approved through Project Orbis have shorter median approval times and submission gaps than non-Orbis NASs.
- The biggest observed impact was on the reduction of the median submission gap based on the factors studied for Project Orbis.
- In general, products approved via Project Orbis had a higher proportion of expedited reviews compared to Non-Orbis NASs, except for Swissmedic.

Figure 4. Median submission gap, approval and rollout time of NASs approved through the Access Consortium compared to Non-Access NASs approved between 2018-2022

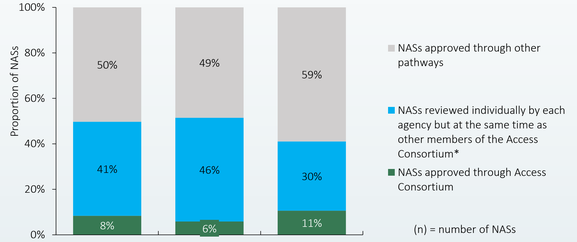


**: "Non-Access NASs" refers to NASs approved through pathways other than the Access Consortium.*

- The NASs approved through the Access Consortium have shorter median submission gaps and approval times than the non-Access NASs.
- The biggest observed impact was on the reduction of the median submission gap based on the factors studied for the Access Consortium.
- In general, products approved via the Access Consortium had a lower proportion of expedited reviews compared to Access NASs, except for Swissmedic.

Part 3— Regulatory case study – What additional proportion of NASs could have been submitted through the Access Consortium?

Figure 5. Percentage of NASs approved by three major agencies between 2018-2022 that were reviewed or could have been submitted through the Access Consortium.



**: Only NASs that could have been submitted through the Access Consortium and their submission gaps amongst Health Canada, Swissmedic and TGA were between 0 to 41 days (median submission gap amongst the three agencies for NASs approved through Access) were included in the analysis.*

Between 2018 and 2022, 46% of the NASs approved by Swissmedic were submitted by companies nearly simultaneously across Access Consortium agencies, followed by 41% in Health Canada and 30% in TGA.

Benefits of utilising collaborative and work-sharing risk-based approaches[1]

1. Enables timely access to high-quality, safe, and innovative therapies.
2. Promotes simultaneous submissions.
3. Improves effective and efficient use of agency resources.
4. Reduces duplicative efforts among agencies.
5. Increases agencies' predictability.
6. Improves harmonisation of marketing authorisation requirements.
7. Improves information sharing amongst regulators.

Conclusions

- The goal of the study was to evaluate of the efficiency and impact of utilising risk-based approaches in four major agencies from 2018 to 2022.
- The results of the study indicated that the usage of risk-based approaches lead to shorter regulatory timeline metrics, such as the submission gap and approval time for the marketing authorisation of NASs, which ultimately contribute to the timely availability of medicines.
- Assessing the impact of risk-based approaches through metrics is key to ensuring they are working efficiently and effectively[2].
- The utilisation of metrics can enable agencies to work towards more transparent, predictable, and harmonised regulatory processes, thus encouraging companies to submit through these approaches.

References

1. Centre for Innovation in Regulatory Science (2022) Workshop report – Collaborative models for regionalisation, work and information sharing: How do these fit into the regulatory toolkit?
2. Centre for Innovation in Regulatory Science (2024) CIRS R&D Briefing 91: Approaches to Implementing Regulatory Reliance – Considerations for Agencies. Centre for Innovation in Regulatory Science (CIRS), London, UK.

**: For the analysis of Project Orbis, four products were considered MLEs to the FDA and NASs to other agencies within the Project Orbis initiative. In these cases, the FDA submission date was used instead of the submission date at the first regulatory agency.*