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Review Article **Open Access**

Index of application status transparency and availability of public information for Project Orbis agencies

Sso H. Lee[*,a], Lauren T. Hotaki[b], Kukhwa Oh[c], Jessica Samuel[d], Krystal de Villiers[e], Kirubel Eshetie[f], Yee H. Looi[g], Eiman Atiek[h], Fanny Cudré-Mauroux[h], Ulrich-Peter Rohr[h], Graham Searle[i], Lenardo N. Santos[j], Silmara C. da. S. Andreoli[j], Yoko Aoi[k], Masakazu Hirata[l], Caroline Voltz-Girolt[m], Carlos Aicardo[m], Callan Cain[n], Tal Naggan[o], Anat Boehm-Cagan[o], Michal Hirsch-Vexberg[o], Osnat Luxenburg[o], Nabbiya Ahmed[p], Laura Johnson[p], Melissa Hunt[p], Duc Vu[p], Marc R. Theoret[b], Dianne Spillman[b], R. Angelo de Claro[b,q]

[a] *U.S. Food and Drug Administration, Division of Regulatory Operations for Oncologic Diseases, Silver Spring, MD, USA*
[b] *U.S. Food and Drug Administration, Oncology Center for Excellence, Silver Spring, MD, USA*
[c] *U.S. Food and Drug Administration, Global Policy and Strategy, Silver Spring, MD, USA*
[d] *University of Rhode Island College of Pharmacy, Kingston, RI, USA*
[e] *University of Florida College of Pharmacy, Gainesville, FL, USA*
[f] *Chicago State University College of Pharmacy, Chicago, IL, USA*
[g] *Health Sciences Authority, Singapore, Singapore*
[h] *Swissmedic, Swiss Agency for Therapeutic Products, Bern, Switzerland*
[i] *Medicines and Healthcare Products Regulatory Agency, London, United Kingdom*
[j] *Brazilian National Health Surveillance Agency, Brasília, Brazil*
[k] *Pharmaceuticals and Medical Devices Agency, Office of New Drug V, Tokyo, Japan*
[l] *Pharmaceuticals and Medical Devices Agency, Division of Consultation, Kansai Branch, Osaka, Japan*
[m] *European Medicines Agency, Amsterdam, The Netherlands*
[n] *Therapeutic Goods Administration, Canberra, ACT, Australia*
[o] *The Medical Technology, Health Information, Innovation and Research Directorate, Ministry of Health, Jerusalem, Israel*
[p] *Health Canada, Government of Canada, Ottawa, Canada*
[q] *U.S. Food and Drug Administration,, Office of Oncologic Diseases, Silver Spring, MD, USA*

Abstract

The purpose of this paper is to provide a guideline for understanding and comparing the regulatory framework of Project Orbis Partners (POPs) and Project Orbis observers, with a focus on their approaches to drug approvals, rejections, and withdrawals. While each agency has its own regulatory framework and guidance, there are some similarities and differences between the language used to describe drug approvals, rejections, withdrawals, and the public availability of these decisions. Project Orbis is an international partnership of regulatory agency, led by the U.S. Food and Drug Administration (FDA), aimed at streamlining the submission and review processes to expedite the global availability of oncology medications for patients. Since its inception, Australia's Therapeutic Goods Administration (TGA), Brazil's National Health Surveillance Agency (ANVISA), Canada's Health Canada (HC), Israel's Ministry of Health (IMoH) Medical Technologies, Health Information, Innovation and Research (MTIIR) Directorate, Singapore's Health Sciences Authority (HSA), Switzerland's Swissmedic (SMC), and United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) have joined and become POPs. Other international agencies such as, the European Medicines Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) are currently observing Project Orbis, as of late 2023. They are not full Project Orbis partners but work closely with the FDA to facilitate oncology drug approval through international collaboration.

Running Title: An Index of the FDA and international regulators involved in Project Orbis looking at the similarities and differences between approval, rejection, and withdrawal characteristics of applications and public transparency of actions.

Keywords: Global; Transparency, Approvals, Complete Response, Rejection, Withdrawal, Project Orbis Partners (POPs), AusPAR

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*Corresponding author

1. Introduction

The FDA's Oncology Center of Excellence (OCE) has collaborated with multiple international agencies through Project Orbis in various capacities beginning in May 2019. Currently, those international agencies are TGA, ANVISA, HC, MTIIR, HSA, SMC, and MHRA. As of late 2023, EMA and PMDA have participated as Project Orbis observers, not traditional partners. Although the FDA, POPs and Project Orbis observers collaborate to facilitate concurrent submission and review of oncology products, there are distinctions among the public transparency of each agency's regulatory decisions. The purpose of this review is to index the regulatory language used to describe the filing, preliminary decision, approval, rejection, withdrawal, publication status, timeline of each agency and to provide a comprehensive review of where and if information can be found in the public domain. By documenting these differences, this review serves as a crucial reference for understanding how regulatory transparency varies and impacts public access to information. (1)

2. Regulatory Agency Information Pertaining to Action Transparency

2.1 Australia TGA

In Australia, the TGA uses the term *failed to pass preliminary assessment* or *not accepted for evaluation* for refused to file applications (applications that cannot move into the review phase due to missing information) and these decisions are not disclosed to the public. Applications for new active substances or new indications that have passed preliminary assessment and are currently under review are publicly available. The TGA's Decision Delegate (reviewer) provides their intention to approve or reject an application following the evaluation phase. This critical document, termed the *Delegate's Overview* summaries the data presented by the applicant after the evaluation phase, and forms the basis to seek advice from the expert Advisory Committee on Medicines (ACM)/Advisory Committee on Vaccines (ACV). The Delegate's Overview is made available to the applicant for feedback, and the applicant's response is considered at the expert advisory committee. The TGA delineates submissions into three categories: *approved*, *rejected*, and *withdrawn submissions*. When appropriate, these classifications are generally made publicly available through the Australian Public Assessment Report (AusPAR). The AusPAR provides comprehensive insights into the stage of the submission process leading up to the approval, rejection, and withdrawal of new active substances and most new indications. The AusPAR is published shortly after a regulatory decision is made, or after withdrawal of the application following the provision of a response to delegates overview. The publication timeline depends on public health needs. Further emphasizing transparency, the TGA updates monthly a list of new prescription medicine registrations. A Decision Summary of new active substances is normally published within 10 calendar days of registration. If an application is rejected, it is publicly posted in an AusPAR. Following the TGA's decision, applicants have a 90-day window to lodge a "section 60 review". If the applicant does not lodge an appeal within 90 calendar days, an AusPAR will be published. If the applicant does lodge an appeal, TGA will publish an AusPAR once the review is completed, and a summary of the review and its outcome will be posted in the AusPAR. Withdrawals are announced in an AusPAR if the submission is withdrawn after submitting a response to the Delegate's overview within 14 calendar days response period. If the submission is withdrawn before submitting a response within the 14 calendar days period to the Delegate's Overview, then no AusPAR is released to the public, and no information is released regarding the submission withdrawal. (2-6)

2.2 Brazil ANVISA

In Brazil, once a product is submitted to ANVISA, the existence of an application prior to decision becomes public on their website. However, the information is limited. They do not disclose the name of the product and active pharmaceutical ingredient (API), instead they display the product by codes until the product is approved or rejected. Although the product codes are public information, this is mostly for applicants to be able to follow their products' status and allow them to track how many products are in front of them to be assessed. If any information is missing during the review of the dossier, the applicant will receive a clarification request from the agency. If mandatory documentation is not provided, a rejection letter may be issued. Each clarification request(s) must be addressed within 120 calendar days. Once a decision has been made, it is published in the Official Gazette for both, *approvals* and *rejections*. A summary of approval decisions is available to the public. If the decision is unfavorable, applicants can appeal within 30 calendar days. The appeal office will review the submitted documents, and in case the rejection is upheld, the final rejection status is published in the Official Gazette. If the conclusion calls for a reconsideration of the decision, the team will make a final decision considering the information submitted in the appeal file. This decision whether it is a final approval or rejection, will be published in two weeks (calendar dates). When a definitive decision is made, a detailed report is available on ANVISA's website. This comprehensive report provides overall information about the quality, safety, and efficacy of the product as well as reasons for any rejection. *Withdrawals* are possible at any step of the review process. The status of withdrawal is published, but the details of the decision are not made public and it simply becomes an internal administrative update of the status of the dossier to "withdrawn upon applicant's request". (7-10)

2.3 Canada HC

In Canada, initial feedback during the submission screening phase may be provided through a Screening Deficiency Notice (SDN). If not addressed within 45 calendar days, it can lead to a *Screening Rejection Letter* (SRL). HC does not provide a formal mechanism for sharing PD with the applicant or the public. The applicant may informally request a submission status update from the appropriate HC review team. Eligible submissions that are successfully screened and under review are listed

in the "Submissions Under Review" (SUR) lists until the submission concludes. Once concluded, the submissions and their outcomes are publicly available in a list of completed submissions. HC primarily categorizes submissions as *authorized/approved/positive decision*, *negative decision*, or *canceled/withdrawn*. Authorized decisions result in a Notice of Compliance (NOC) which is issued following a satisfactory scientific review of the submission and signifies compliance with the Food and Drug Regulations in Canada. During review a Notice of Deficiency (NOD) can be issued when a submission is found to be deficient and/or contains significant omissions that preclude continuing scientific review. The applicant must address the deficiencies/omissions and submit a response to the NOD within 45 or 90 calendar days. A Notice of Deficiency-Withdrawal (NOD-W) is issued if the applicant fails to submit an appropriate response to a NOD. A Notice of Non-Compliance (NON) is issued when a submission review has been completed and is found to be incomplete or non-compliant with regulatory requirements during the scientific review. The applicant must address the issues and submit a response to the NON within 45 or 90 calendar days. A Notice of Non-Compliance-Withdrawal (NON-W) is issued if the applicant fails to submit an appropriate response to a NON. Both NODs and NONs are interim actions and are not publicly available, while NOD-Ws and NON-Ws are final negative decisions. The rationale for the decision may be published in a Regulatory Decision Summary for applicable submissions. An applicant-initiated withdrawal is termed a *cancellation*. A Cancellation Acknowledgement Letter is issued when a submission is voluntarily withdrawn by the applicant during the scientific review, but prior to issuance of a HC positive or negative decision. Following a cancellation, the applicant may resubmit at any time. A Summary of Cancellation (SC) is published for eligible submissions. The rationale for eligible HC positive and negative decisions is available publicly as Summary Basis of Decision (SBD) and/or Regulatory Decision Summary (RDS) on the Drug and Health Product Portal (DHPP), either 84 calendar days or 21 to 35 calendar days after the date of the final decision, respectively. (11-18)

2.4 Europe EMA

In Europe, a PD called *opinion* made by the Committee for Medicinal Products for Human Use (CHMP) at 210 calendar days of submission is made available to the public on Friday following the CHMP plenary meeting. This PD is published on the EMA website and covers a summary of opinion for approval, opinion for refusal and questions/answers, and information on the withdrawal of the marketing authorization applications. Prior to a final decision, EMA publishes an updated list of medicines for human use currently under evaluation on their website each month. EMA sends the CHMP opinion to the applicant and to the European Commission. Once the European Commission (EC) officially reviews the CHMP opinion and issues a final decision, outcomes such as approval or non-approval will be published in the Public Health - Union Register of medicinal products and the Official Journal of the European Union. The outcomes are termed *authorized or refused*, respectively. After removing commercially confidential information and personal data, the EMA's publishes the European Public Assessment Report (EPAR) as an information resource containing several documents including a public assessment report on the authorized, refused, or *withdrawn* application submission. If the medicine is authorized, EMA will publish on its website the EPAR – including medicine overview (lay language), the Risk Management Plan (RMP) summary, the product information, the product details, the authorization details, and the public assessment report. The EPAR for authorized and refused applications will be published within two weeks (calendar days) of the EC's decision. EPARs for withdrawn applications will be published on the EMA website within three months (calendar days) of receipt of the withdrawal letter from the applicant. (19-23)

2.5 Israel MTIIR

In Israel, MTIIR conducts a preliminary screening process of the marketing authorization application to evaluate its completeness and adherence to Israeli registration guidelines. If the application is deemed incomplete, it will be rejected within the preliminary evaluation process and termed as *rejection*. The reasons will be communicated to the applicant and will not be disclosed to the public. After a comprehensive review, PD is conveyed through *in-principle authorization* letters. These letters, akin to positive opinion decisions, detail the indication and any post-marketing requirements (PMR). Although these letters are shared with the applicant, their content, including the existence of an application, remains confidential and is not disclosed to the public. The terminology used for approval is *authorized*, and the approval is made public and updated once a month during the month following the approval. An application that is not authorized is termed as *rejected*. Reasons for rejection are communicated to the applicant and are not made public. If an applicant decides to withdraw their application, it is termed as *withdrawn*, and this is also not made public. All approvals are published in the Israeli Drug Registry once a month, specifically in the month (calendar day) subsequent to the approval. (24-28)

2.6 Japan PMDA

In Japan, the PMDA provides a preliminary *review report* to the applicant as non-public information before finalizing its decision. The PDMA does not publish a review status of applications. The PMDA's term for an approval decision is *marketing approval or approval* and is made public. If an application fails to meet the criteria defined by the Pharmaceuticals and Medical Devices Act (PMD Act), the *approval will not be granted*, which equates to a non-approval. At any point before the final decision, the applicant has the option to *withdraw* its application and these withdrawals will not be publicized. PMDA's finalized review report is reviewed by the Ministry of Health, Labour and Welfare (MHLW) and its standing committee, the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), before they decide whether to grant approval. The PMDA regularly publishes all the review reports for new molecular entities and partial changes to existing approved products such as new

indications or dosages. The PMDA List of Approved Products publishes with all approvals, including additional indication expansions and dosages, within one to two business days following approval. (29-32)

2.7 Singapore HSA

In Singapore, the HSA screens applications within 50 business days upon receipt of the application. During this time, the HSA reviews the dossier for completeness and determines whether the application will be accepted or not. If the application is refused to file, it is called *not accepted for evaluation*. HSA do not disclose the existence of application. Regarding regulatory decisions, applicants are informed of one of the following outcomes: *approval/approvable* or *non-approvable/rejection.* For an approvable application, the application becomes approved once the applicant adequately responds to minor deficiencies. An application may be termed non-approvable if it contains major deficiencies. A rejection is issued if the response fails to address the major deficiencies in the HSA's non-approvable decision. This decision is final and is not in the public domain. The *withdrawal* process happens if an applicant fails to reply within the given timeframe after an approvable or a non-approvable decision. Once withdrawn, the application is officially closed, and this is not publicly disclosed. Upon approval, the product is simultaneously added to the public on the Register of Therapeutic Product. The HSA publishes summary reports of benefit-risk assessments for newly approved drugs. Furthermore, the list of new drugs and indication approvals are published on a Listing of Approvals and Post-registration Actions website monthly (business day). (33-36)

2.8 Switzerland SMC

In Switzerland, SMC offers a private PD to the applicant, prior to an official decision. There is no other terminology for PD. SMC also publishes the submitted applications within 30 calendar days of the formal control (filing period), which is in the next issue of the Swissmedic Journal. Until the official decision is determined, no further publication is made concerning the status of the applications. Upon review, if the application is refused to file it is termed *formal objection*. The approval process is termed market *authorisation*. A non-approval at SMC is termed *rejected*. The decision to approve or reject a marketing authorisation application (MAA) is made public through the Swiss Public Assessment Report (SwissPAR) and the Swissmedic Journal. The SwissPAR is a summary evaluation report for all human medicinal products with a new active substance, including transplant products. There are additional supplementary reports for approved or rejected applications that relate to indications extensions. Additionally, SMC publishes a condensed version of the SwissPAR, known as the Public Summary SwissPAR. The Public Summary SwissPAR is intended to make SMC's authorisation decisions transparent to the wider public and announces relevant information on medicinal products. If an applicant has *withdrawn* that application, it will be published in the Swissmedic Journal including limited information. An important caveat to note is that most of the time an applicant chooses to withdraw an application after a negative PD, which will then not result in a public rejection since the application is withdrawn. If no appeal against the official decision on authorisation or rejection has been filed within the permitted time limit of 30 calendar days, the publication timeline from regulatory decision to publication in the SwissPAR is 60 calendar days. SMC publishes the Public Summary SwissPAR no later than 60 calendar days after publication of the SwissPAR on its website. (37-39)

2.9 United Kingdom MHRA

In the United Kingdom, MHRA can invalidate an incomplete application before any assessment has started and this is not made public, which is called *invalidation*. MHRA does not disclose the existence of an application under evaluation. During assessment of the application, MHRA share their PD via the Request for Information (RFI) action, but this is also not made public. There are multiple terminologies for an approval which are *marketing authorisation (MA) granted, granted with conditions, exceptional grant (MA under exceptional circumstance), conditionally granted (conditional MA)*, or *variations granted*. Once the decision is made, it is published in the Public Assessment Report (PAR). There is no statutory timeline, but MHRA aims to publish within 60 calendar days after approval. For new active substances Mas, a public announcement is made on the day of grant and the PAR is published within 30 calendar days. MHRA may also publish a Safety Public Assessment Report following the assessment of a significant safety issue. An application that is a non-approval is termed as *refused* and the withdrawal is termed as *withdrawn*. Both decisions are not made public. (40-47)

2.10 United States FDA

In the United States, the FDA conducts a filing review to assess the completeness of an application within 60 calendar days of submission. If an application is deemed incomplete, a *refuse-to-file* (RTF) letter is issued to the applicant which is not publicly available. The *approval* and *withdrawal* terminology are the same, but non-approval is termed a *complete response* and a letter will be provided to the applicant if the FDA determines that the application is not approved. Although approval is made public, the FDA will not publicly disclose the existence of an application or abbreviated application prior to an approval letter or tentative approval letter is sent to the applicant, unless the FDA decides to bring a marketing application to an Advisory Committee. Both complete response and withdrawal are not made public. In general, the FDA publishes new approvals through Drugs@FDA within two business days of approval, which includes information about drugs approved for human use in the United States. The database does not include information about FDA-approved products regulated by the Center for Biologics Evaluation and Research (CBER), which may include vaccines, cellular and gene therapy products or blood products. Products regulated under CBER are posted in the Purple Book database and CBER biological approvals website. (48-55)

Table 1 (a). Summary of Each Agency Information

Parameters	TGA		ANVISA		HC		EMA		MTIIR	
	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology
Refuse to File	No	Fail to pass preliminary assessment /not accepted for evaluation	N/A	N/A	No	SDN; SRL	N/A	N/A	No	Rejection
Preliminary Decision	N/A	N/A	N/A	N/A	N/A	N/A	Yes	Opinion made by the CHMP: Approval - Summary of Opinion; Negative Opinion - Refusal Q&A	No	In-principle authorizatio n letter
Approvals	Yes	Approved submission	Yes	Approval	Yes	Authorized, Approved, Positive Decision, Notice of Compliance	Yes	Authorized	Yes	Authorized
Non-Approvals	Yes	Rejected submission	Yes	Rejection	Yes	Negative Decision, Notice of Non-Compliance	Yes	Refused	No	Rejected
Withdrawals	Yes	Withdrawn submission	Yes	Withdrawal	Yes	Cancellation	Yes	Withdrawn	No	Withdrawn
Disclose the status of an application prior to decision	Yes		Yes		Yes		Yes		No	

Parameters	TGA		ANVISA		HC		EMA		MTIIR	
	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology
Publication	AusPAR; Decision Summary; Prescription medicines registration webpage, TGA guidance and resources webpage		Official Gazette – Regulation of products; Official Gazette - Queries		Drug and health product SUR; SBD; RDS; DHPP		Public Health – Union Register of medicinal products and the Official Journal of the European Union; EPAR		Israeli Drug Registry	
Publication Timeline from decision	Approvals: Depends Rejections: Sponsor is allowed 90 cd to appeal the decision. If no appeal is made, the AusPAR will be published. If an appeal is made, the outcome of the appeal will be included in the AusPAR WD: Depends. An AusPAR is only published if the submission is withdrawn after the due date for the sponsor's response to the Delegate's Overview		2 weeks (cd)		84 cd or 21 to 35 cd after the date of the final decision and/or cancellation		CHMP: Withdrawal, positive or negative opinion of Application: Friday following next CHMP plenary EPAR: Approvals and Refusals: 2 weeks (cd) after the EC decision Withdrawn EPAR: Within three months (cd) of receipt of withdrawal letter		Updated once a month (cd) during the month following the approval	

Table 1 (b). Summary of Each Agency Information

Parameters	PMDA		HSA		SMC		MHRA		FDA	
	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology
Refuse to File	N/A	N/A	No	Not accepted for evaluation	No	Formal objection	No	Invalidation	No	Refuse to File
Preliminary Decision	No	Review report	N/A	N/A	No	Preliminary Decision	No	Request for Information	N/A	N/A

Parameters	PMDA		HSA		SMC		MHRA		FDA	
	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology	Public	Terminology
Approvals	Yes	Marketing Approval (Approval)	Yes	Approval/ Approvable	Yes	Market Authorisation	Yes, for Marketing Authorisation	Marketing Authorisation/ Granted, Granted with conditions, Exceptional Grant, Conditionally Granted; Variations Granted	Yes	Approval
Non-Approvals	Yes	Approval not granted	No	Non-approvable/ Rejection	Yes	Rejected	No	Refused	No	Complete Response
Withdrawals	No	Withdraw	No	Withdrawal	Yes	Withdrawn	No	Withdrawn	No	Withdraw
Disclose the status of an application prior to decision	No		No		Yes		No		No	
Publication	Review report (with MHLW's decision on approval); PMDA List of Approved Products		Register of Therapeutic Product; Listing of Approvals and Post-Registration Actions; Summary Report of Benefit-Risk Assessment		SwissPAR Summary SwissPAR Swissmedic Journal		Public Assessment Reports		Drugs@FDA Purple Book	
Publication Timeline from decision	1-2 bd after the approval		Upon an "approval" regulatory decision the product will be simultaneously listed on the Register of Therapeutic Product A list of products approval and new approved indication will be published monthly (bd)		SwissPAR: 60 cd Summary SwissPAR: 120 cd (60 cd after publication of the SwissPAR) Swissmedic Journal: the following month (Journal issued every month) and in the corresponding list (updated every month)		No statutory timeline, aim to publish with 60 cd; Within 30 cd for a new active substance marketing authorisation		2 bd	

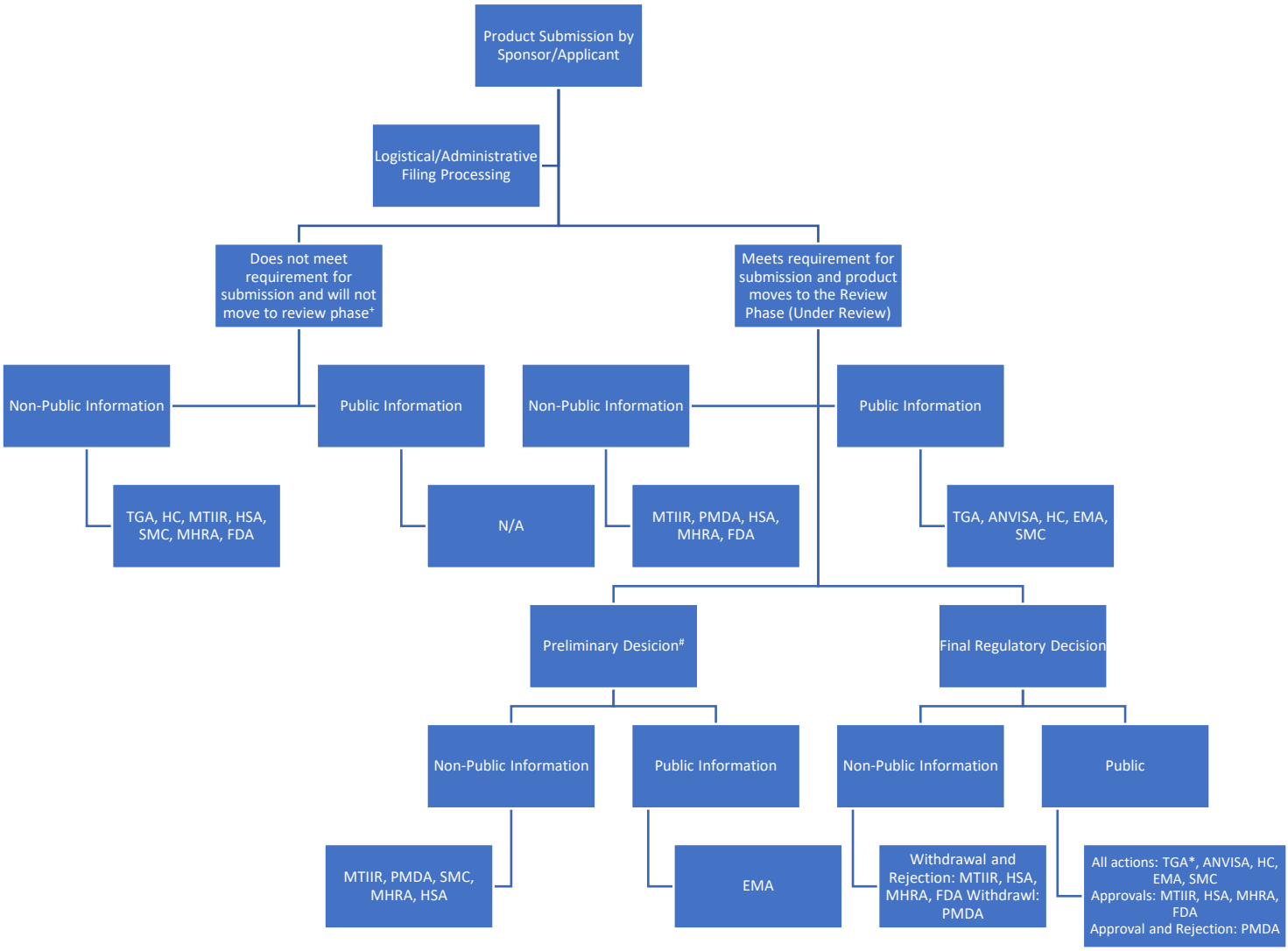

Figure 1. Hierarch of Terms

+ These agencies do not have formal refuse to file pathways: ANVISA, EMA, PMDA
# Not applicable to TGA, ANVISA or FDA. These agencies do not offer a preliminary decision to the sponsor/applicant.
* TGA: If the submission is withdrawn within the 14-day period to the Delegate's Overview, the details are not disclosed to the public

3. Discussion:

The focus of this paper is to deliver the information from the different agencies into one concise location to use as a reference. Transparency decisions vary throughout all international regulatory agencies, and those have their own positive and negative potentials. Increased transparency has been found to gain more trust amongst applicants and regulatory agencies. However, this increase could also lead to confusion and misinterpretation. Therefore, the difference in transparency between each international regulatory agency has been expected. (56-60)

TGA, HC, MTIIR, HSA, SMC, MHRA and FDA have an initial refuse to file mechanism for incomplete submissions which all are not disclosed to the public. TGA, EMA, MTIIR, PMDA, SMC, and MHRA have preliminary decisions that are issued to the applicant before official action is taken on an application to give the applicant a chance to respond to the agency's planned action. Only EMA publishes the CHMP preliminary decision(s) to the public. All approvals at each agency are publicly posted but have different terminologies, such as EMA and MTIIR's authorized, HC's positive decision/authorized/approved, TGA's approved submission, and MHRA's and SMC's marketing authorisation. TGA, ANVISA, HC, EMA and SMC disclose the existence of an application under review, but MTIIR, PMDA, HSA, MHRA, and FDA keep the status of an ongoing review confidential. Most agencies' non-approval term is rejected submission or rejection; whereas HC uses the term "negative decision", PMDA uses "approval not granted" and FDA uses the unique term "complete response" which refers to the complete response letter sent to the applicant informing them of their non-approval. All rejections are publicly available for TGA, ANVISA, HC, EMA, PMDA, and SMC. The agencies that do not disclose rejections publicly are MTIIR, HSA, MHRA and FDA. All agencies use the term withdrawn or withdrawal, except for HC which uses the term cancellation for applications that the sponsor decides to rescind from submission. The agencies that disclose

withdrawn applications during the drug review publicly are TGA, ANVISA, HC, EMA, and SMC. The agencies that do not disclose applicant withdrawn applications publicly are MTIIR, PMDA, HSA, MHRA and FDA. Each agency has a place where they publish certain information publicly at given timelines after regulatory action has been decided. Overall, the agencies differ in having their own sets of published reports, websites, and publication timelines after regulatory action. The common denominator for all agencies is that all approvals are publicly posted.

4. Conclusion

The FDA, POPs and Project Orbis observers collaborate to facilitate concurrent submission and review; however, there are distinctions among the public transparency of each agency's regulatory decisions. Therefore, the purpose of this paper has been to describe the different regulatory decisions and terminologies associated with each international agency to serve as a crucial reference for applicants and regulatory agencies' understanding. An aim was to examine the nomenclature and public availability of the different actions that a regulatory agency can take and guide to impact public access where those actions could be found in the public domain.

Author Contributions

All authors contributed to the concept, content, and interpretation of the work and agree to be accountable for all aspects of the work including the accuracy or integrity of any part of the work.

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Declarations

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

Conflict of Interest

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List of Abbreviations:

ANVISA – Agencia Nacional de Vigilancia Sanitaria
AusPAR – Australian Public Assessment Reports
Bd = Business days
Cd= Calendar days
DHPP = Drug and Health Product Portal
EC = European Commission
EMA – European Medicines Agency
EPAR = European Public Assessments Report
FDA – Food and Drug Administration
HC – Health Canada
HSA – Health Sciences Authority
MHRA – United Kingdom Medicines and Healthcare Products Regulatory Agency
MTIIR – Medical Technology, Health Information, Innovation and Research
NOC: Notice of Compliance
PMDA – Pharmaceuticals and Medical Devices Agency

References

1. FDA. Project Orbis [Internet]. United States: FDA; Aug 2024 [cited 2023 Jul 05]. Available from: https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis
2. Australian Government Department of Health Therapeutic Goods Administration. Australian Public Assessment Report (AusPAR) Guidance [Internet]. Australia: TGA; 2010 [cited 2023 Aug 29]. Available from: https://www.tga.gov.au/resources/resource/guidance/australian-public-assessment-report-auspar-guidance
3. Australian Government Department of Health Therapeutic Goods Administration. Provisional approval pathway: prescription medicines [Internet]. Australia: TGA [cited 2023 Aug 29]. Available from: https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines
4. Australian Government Department of Health Therapeutic Goods Administration. Australian Register of Therapeutic Goods (ARTG) [Internet]. Australia: TGA; 2018 Mar 20 [cited 2023 Aug 29]. Available from: https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg
5. Australian Government Department of Health and Aged Care. Therapeutic Goods Administration. Phase 7: Decision [Internet]. Australia: TGA; 2021 Aug 12 [cited 2023 Aug 29]. Available from: https://www.tga.gov.au/how-we-regulate/supply-therapeutic-good/supply-prescription-medicine/application-process/prescription-medicines-registration-process/phase-7-decision
6. Australian Government Department of Health Therapeutic Goods Administration. Prescription medicines under evaluation [Internet]. Australia: TGA [cited 2023 Aug 29]. Available from: https://www.tga.gov.au/resources/prescription-medicines-under-evaluation
7. Global Regulatory Partners. How are Health Products regulated with Brazil's ANVISA? [Internet]. Brazil: ANVISA; 2023 Jul 11 [cited 2023 Aug 29]. Available from: https://globalregulatorypartners.com/how-does-product-regulation-work-at-anvisa/
8. Global Regulatory Partners. Synthetic Drug Registration Requirement. Main Reasons for Registration rejection from ANIVSA [Internet]. Brazil: ANVISA; 2020 Oct 3 [cited 2023 Aug 29]. Available from: https://globalregulatorypartners.com/brazils-anvisa-outlines-reasons-for-the-approval-and-rejection-of-registration-of-synthetic-drugs/
9. Government of Brazil. Queries – ANVISA National Health Surveillance Agency [Internet]. Brazil: ANVISA [cited 2023 Aug 29]. Available from: https://consultas.anvisa.gov.br/#/documentos/tecnicos/
10. Gov.br Ministry of Health. Regulation of Products Drugs [Internet]. Brazil: ANVISA; 2020 Oct 29 [cited 2023 Aug 29]. Available from: https://www.gov.br/anvisa/pt-br/english/regulation-of-products/drugs

11. Government of Canada. Notice of Compliance Database [Internet]. Canada: HC; 2023 [cited 2023 Aug 29]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/database.html
12. Government of Canada. Notice: Phase III of Pre-Market Transparency Initiatives for Prescription Drugs [Internet]. Canada: HC; 2018 Aug 21 [cited 2023 Aug 29]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/premarket-transparency-initiatives-notice.html
13. Government of Canada. Advisories, Warnings and Recalls – Drugs and health products [Internet]. Canada: HC; 2023 Mar 07 [cited 2023 Aug 29]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/advisories-warnings-recalls.html
14. Government of Canada. How Drugs Are Reviewed in Canada [Internet]. Canada: HC; 2015 Feb 12 [cited 2023 Aug 29]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html
15. Government of Canada. Regulatory Decision Summary [Internet]. Canada: HC; 2024 Mar 26 [cited 2024 Aug 02]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/regulatory-decision-summary.html
16. Government of Canada. Guidance Document: Management of Drug Submissions & Applications [Internet]. Canada: HC; 2022 Aug 02 [cited 2023 Aug 29]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry/document.html
17. Government of Canada. Drug and Health Product Submissions Under Review [Internet]. Canada: HC; 2023 [cited 2023 Aug 29]. Available from: https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/submissions-under-review.html
18. Government of Canada. Summary Basis Decision [Internet]. Canada: HC [cited 2023 Aug 29]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/summary-basis-decision.html
19. European Medicines Agency. What we publish and when [Internet]. Europe: EMA; 2022 May 25 [cited 2023 Sep 5]. Available from: https://www.ema.europa.eu/en/medicines/what-we-publish-medicines-when
20. European Medicines Agency. Authorisation of Medicines [Internet]. Europe: EMA; 2019 Mar 04 [cited 2023 Sep 5]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines
21. European Medicines Agency. From lab to patient: The journey of a medicine assessed by EMA [Internet]. Europe: EMA; 2019 Mar 04 [cited 2023 Sep 5]. Available from: https://www.ema.europa.eu/en/from-lab-to-patient-timeline#:~:text=The%20role%20of%20EMA%20is,of%20receipt%20of%20EMA%27s%20recommendation.
22. European Medicines Agency. How EMA evaluates medicines for human use [Internet]. EMA; 2019 Mar 04 [cited 2023 Sep 5]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/how-ema-evaluates-medicines#assessment-process-section
23. European Medicines Agency [Internet]. Europe: EMA; 2023 [cited 2023 Sep 5]. Available from: https://www.ema.europa.eu/en/medicines/medicines-human-use-under-evaluation
24. Ministry of Health Israel. Israeli Drug Registry [Internet]. Israel: MTIIR; 2023 [cited 2023 Sep 28]. Available from: https://israeldrugs.health.gov.il/
25. Ministry of Health Israel. Drug application procedure [Internet]. Israel: MTIIR; 2012 [cited 2023 Sep 28]. Available from: https://www.health.gov.il/hozer/Reg08_2012.pdf
26. Ministry of Health Israel [Internet]. Israel: MTIIR [cited 2023 Sep 28]. Available from: https://www.health.gov.il/English/MinistryUnits/HealthDivision/MedicalTechnologies/Drugs/Registration/Pages/default.aspx
27. Ministry of Health Israel. Rejection of registration application [Internet]. Israel: MTIIR; 2009 Nov [cited 2023 Sep 28]. Available from: http://www.health.gov.il/hozer/DR_15.pdf
28. Ministry of Health Israel. Appeal to the Director's decision to reject an application for registration of a drug or a new indication or to impose restrictions on a drug as part of its registration [Internet]. Israel: MTIIR; 2009 Nov [cited 2023 Sep 28]. Available from: https://www.health.gov.il/hozer/DR_73.pdf
29. Pharmaceuticals and Medical Devices Agency (PMDA) [Internet]. Japan: PMDA [cited 2023 Sep 5]. Available from: https://www.pmda.go.jp/english/reviews-services/reviews/0001.html
30. Pharmaceuticals and Medical Devices Agency. List of Approved Products [Internet]. Japan: PMDA [cited 2023 Sep 5]. Available from: https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0003.html
31. Pharmaceuticals and Medical Devices Agency. Points to be considered by the review staff involved in the evaluation process of new drug [Internet]. Japan: PMDA; 2008 [cited 2023 Sep 5]. Available from: https://www.pmda.go.jp/files/000153830.pdf
32. Pharmaceuticals and Medical Devices Agency. Annual Report [Internet]. Japan: PMDA [cited 2023 Sep 5]. Available from: https://www.pmda.go.jp/english/about-pmda/annual-reports/0001.html
33. Singapore Government Agency Website HSA. Registration Overview of Therapeutic Goods [Internet]. Singapore: HAS; 2018 Dec 18 [cited 2023 Sep 6]. Available from: https://www.hsa.gov.sg/therapeutic-products/register/overview/screening-evaluation
34. Singapore Government Agency Website HSA. Guidance on the Therapeutic Products [Internet]. Singapore: HSA;2023 [cited 2023 Sep 6]. Available from: https://www.hsa.gov.sg/therapeutic-products/guidance-documents
35. Singapore Government Agency Website HSA. Guidance on the therapeutic products – Target Processing Timeline: Appendix 5 [Internet]. Singapore: HSA;2024 Aug [cited 2024 Aug 06]. Available from: https://www.hsa.gov.sg/docs/default-source/hprg-tpb/guidances/appendix-5_target-processing-timeline.pdf?sfvrsn=2a3259a5_2
36. Singapore Government Agency Website HSA. Therapeutic Products – Listing of Approvals and Post-Registration Actions [Internet]. Singapore: HSA [cited 2023 Sep 6]. Available from:

https://www.hsa.gov.sg/therapeutic-products/approvals-and-post-reg-actions
37. Swissmedic. Swiss Public Assessment Report (SwissPAR) [Internet]. Switzerland: SMC [cited 2023 Sep 6]. Available from: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/swisspar.html
38. Swissmedic. Swiss Publication Assessment Report (SwissPAR) Questions and Answers [Internet]. Switzerland: SMC; 2019 [cited 2023 Sep 6]. Available from: https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl_hmv_iv/faq-swisspar.pdf.download.pdf
39. Swissmedic. Authorisations of human medicine [Internet]. Switzerland: SMC [cited 2023 Sep 6]. Available from: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations.html
40. GOV.UK. Guidance Medicines: apply for a variation to your marketing authorization [Internet]. United Kingdom: MHRA; 2014 [cited 2023 Sep 6]. Available from: https://www.gov.uk/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation
41. GOV.UK. Guidance Apply for a license to market a medicine in the UK [Internet]. United Kingdom: MHRA; 2014 [cited 2023 Sep 6]. Available from: https://www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk#rejection.
42. GOV.UK European Commission (EC) decision Reliance procedure [Internet]. United Kingdom: MHRA; 2021 [cited 2023 Sep 6]. Available from: https://www.gov.uk/guidance/european-commission-ec-decision-reliance-procedure
43. GOV.UK. Guidance Renewing marketing authorisations for medicines [Internet]. United Kingdom: MHRA; 2020 [cited 2023 Sep 6]. Available from: https://www.gov.uk/guidance/renew-marketing-authorisation-for-a-human-medicine
44. GOV.UK. Guidance 150-day assessment for national applications for medicines [Internet]. United Kingdom: MHRA; 2020 [cited 2023 Sep 6]. Available from: https://www.gov.uk/guidance/guidance-on-150-day-assessment-for-national-applications-for-medicines#eligibility
45. GOV.UK. Guidance Find product information about medicines [Internet]. United Kingdom: MHRA; 2019 [cited 2023 Sep 6]. Available from: https://www.gov.uk/guidance/find-product-information-about-medicines
46. GOV.UK. MHRA. Products About This Service [Internet]. United Kingdom: MHRA [cited 2023 Sep 6]. Available from: https://products.mhra.gov.uk/about
47. GOV.UK. Guidance. Safety Public Assessment Reports [Internet]. United Kingdom: MHRA; 2019 [cited 2023 Sep 6]. Available from: https://www.gov.uk/guidance/safety-public-assessment-reports
48. JAMA Internal Medicine. Contents of US Food and Drug Administration Refuse-to-File Letters for New Drug Applications and Efficacy Supplements and their Public Disclosure by Applicants [Internet]. United States: FDA; 2021 [cited 2023 Sep 6]. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2775955#:~:text=Within%2060%20days%20of%20application,the%20reasons%20preventing%20full%20reviews.
49. FDA. Center for Drug Evaluation and Research (CDER). Manual of Policies and Procedures [Internet]. United States: FDA; 2007 [cited 2023 Sep 6]. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwizh8z5ps2AAxUiElkFHYXJCRcQFnoECBMQAQ&url=https%3A%2F%2Fwww.fda.gov%2Fmedia%2F72756%2Fdownload&usg=AOvVaw2mUNUdUs36UumbgEJ_rY0d&opi=89978449
50. FDA. Pre-market approvals are published in the Official Gazette, enabling marketing authorisation. The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective [Internet]. United States: FDA; 2017 Nov 24 [cited 2023 Sep 6]. Available from: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective
51. FDA. Code of Federal Regulations: FDA Action on Applications and Abbreviated Applications. Title 21, Volume 5 [Internet]. United States: FDA; 2023 [cited 2023 Sep 6]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.4
52. FDA. Code of Federal Regulations: Complete Response Letter to the Applicant - Title 21, Volume 5, Part 314, Subpart D [Internet]. United States: FDA [cited 2023 Sep 6]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.110
53. FDA. Purple Book – Database of Licensed Biological Products [Internet]. United States: FDA [cited 2023 Sep 6]. Available from: https://purplebooksearch.fda.gov/#:~:text=The%20Purple%20Book%20database%20contains,products%2C%20and%20their%20reference%20products
54. FDA. Drugs@FDA Frequently Asked Questions [Internet]. United States: FDA [cited 2023 Sep 6]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=faq.page
55. FDA. Biological Approvals by Year [Internet]. United States: FDA [cited 2023 Sep 6]. Available from: https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year
56. Löfstedt R, Way D, Bouder F, Evensen D. Transparency of medicines data and safety issues–a European/US study of doctors' opinions: what does the evidence show? Journal of Risk Research [Internet]. 2016 Jan 14 [cited 2024 Jun 25]; 19(9):1172-1184. Available from: https://www.research.ed.ac.uk/en/publications/transparency-of-medicines-data-and-safety-issues-a-europeanus-stu
57. Grimmelikhuijsen S, Herkes F, Leistikow I, Verkroost J, Vries F, Zijlstra WG. Can decision transparency increase citizen trust in regulatory agencies? Evidence from a representative survey experiment. Regulation & Governance [Internet]. 2019 Sep 30 [cited 2024 Jun 25];15(1):17-31. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/rego.12278
58. Hunter, Phillip. More transparency for clinical trial data, the decision by the European Medicines Agency to make clinical trial reports publicly available could provide a boon for biomedical research. EMBO reports [Internet]. 2014 Dec 4 [cited 2024 Jun 25];16: 21-23. Available from: https://www.embopress.org/doi/full/10.15252/embr.201439894
59. Peter Papathanasiou, Laurent Brassart, Paul Blake, Anna Hart, Lel Whitbread, Richard Pembrey, Jill Kieffer, Transparency in drug regulation: public assessment reports in Europe and Australia. Drug Discovery Today [Internet]. 2016 [cited 2024 Jun 25]; volume 21(11):1806-1813. Available from: https://www.sciencedirect.com/science/article/pii/S1359644616302434?via%3Dihub
60. Wieseler B, McGauran N. Secrecy or transparency? The future of regulatory trial data. CMAJ [Internet]. 2017 Feb 6 [cited 2024 Jun 25]; 189(5):E185-E186. Available from: https://www.cmaj.ca/content/189/5/E185