CIRS Centre for Innovation in Regulatory Science

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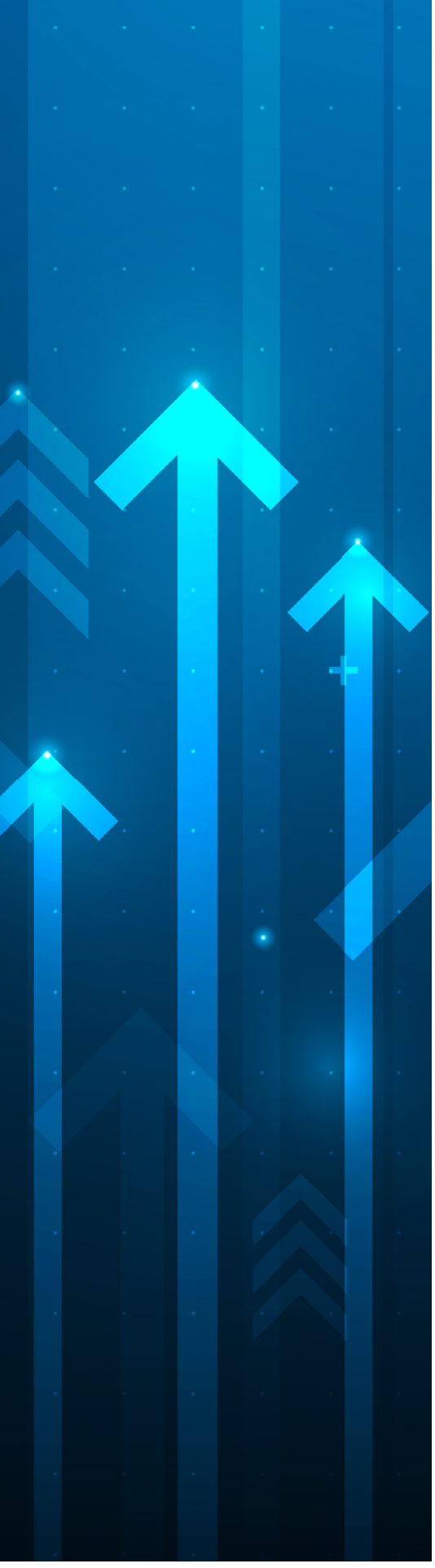
CIRS R&D Briefing 92

# Appraisal of public assessment reports (PARs) as tools to guide reliance decision making by regulatory agencies



CIRS Centre for Innovation in Regulatory Science

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# Infographic summary

The World Health Organisation recommends that regulatory agencies should use public assessment reports (PARs) as the primary information source for risk-based assessments, however, relying agencies are often challenged by the availability and completeness of PARs.

CIRS undertook a study to assess whether the information needed for reliance is included in the PARs of reference agencies (US, EU, Canada, Switzerland, Australia and Brazil).

As every agency has different reliance requirements, CIRS consolidated a generic list of information that could be of value to risk-based reviews. This list, which was subdivided into five sections based on PAR topics (e.g. clinical), was used to assess the inclusion of reliance-relevant information within the PARs.

The 33 assessed PARs contained the majority of the reliance-relevant information identified. The degree of inclusion of reliance-relevant information in the PARs varied across agencies and by PAR section, but no single PAR contained all the reliance-relevant information based on the generic list utilised in this study.

Clinical, Benefit-Risk Assessment and Regulatory Background sections within the PARs contained the largest amount of reliance-relevant information, whereas CMC and non-clinical sections contained the least. However, it should be noted that this information may be included in other documents such as the dossier and non-public assessment reports.

**Recommendations from this study:**

- Ensure clear communication between agencies and companies during a reliance review.
- Raise awareness of the importance of PARs for implementing reliance.
- Improve the availability, completeness and usability of PARs.
- Advocate for a harmonised standard PAR template which can be used by current and emerging reference agencies.

# Executive summary

Regulatory reliance facilitates regulatory approvals, allows the use of resources more efficiently, and ultimately serves patients by accelerating access to quality-assured, safe, and effective medicines. The World Health Organisation (WHO) recommends that national regulatory agencies should use public assessment reports (PARs) as the primary sources of information for risk-based assessments. However, relying agencies are often challenged by the redacted nature of PARs regarding safety, quality or efficacy.

CIRS undertook a study to assess whether the information needed for reliance is included in PARs of reference agencies. Six new active substances (NASs) from seven reference agencies were assessed, namely, the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada, Swissmedic, Therapeutic Goods Administration (TGA), Brazilian Health Regulatory Agency (ANVISA), and Medicines and Healthcare products Regulatory Agency (MHRA). Since each agency has different reliance requirements, CIRS consolidated a generic, non-agency-specific list of information that could be of value to undertaking risk-based reviews. This list was used to assess the inclusion of reliance-relevant information within the PARs.

Based on the 33 PARs assessed in this study, it was found that publicly available reference agency documentation contains the majority of the information that relying agencies may require for risk-based reviews. However, none of the agency PARs contained all the identified reliance-relevant information. The Clinical, Benefit-Risk Assessment and Regulatory Background sections of the PARs often contained the greatest amount of reliance-relevant information. In contrast, the Chemistry, Manufacturing and Controls (CMC) and Non-Clinical sections had the least amount of reliance-relevant information.

A comparison of the agencies revealed that PARs developed by EMA and FDA contained more detailed reliance-relevant information than those PARs developed by TGA, ANVISA, Health Canada and Swissmedic. However, it should be noted that a relatively small cohort of PARs was identified for assessment.

In conclusion, no single PAR contained all the reliance-relevant information based on the generic list utilised in this study. However, the PARs contained helpful information that can be used to inform regulatory decisions and their usability for reliance purposes will depend on the relying agencies' guidelines and requirements. Finally, it should be noted that in addition to PARs, other documents are important to support reliance decision making, such as the marketing authorisation application (MAA) dossier provided by the applicant, the Certificate of Pharmaceutical Product (CPP), and/or the non-public assessment report from the reference agency. The relying agency can refer to such additional documentation for any clarifications, to understand further the information that the reference agency considered, and to understand the reference agency's decision-making process.

Recommendations for the future should focus on ensuring clear communication between agencies and companies during a reliance review; raising awareness of the importance of PARs for implementing reliance; improving the availability, completeness and usability of PARs; and advocating for a harmonised standard PAR template or comparable relevant elements within a PAR, which can be used by current and emerging reference agencies.

# Introduction

Around the world, regulatory agencies seek to protect public health and improve patient access to quality-assured, effective, safe and innovative medicines. Nonetheless, agencies have been challenged in terms of available resources and the capacity to respond promptly to the demands of new technological developments and innovative therapies. As a result, agencies have started focusing on addressing these demands by implementing risk-based approaches, such as utilising reliance through the lifecycle of medicinal products.

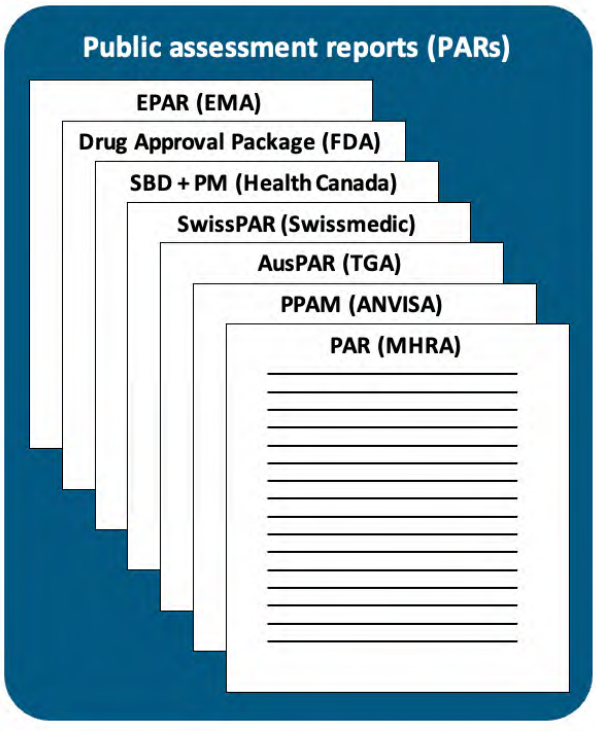
Reliance is defined by WHO as "the act whereby the regulatory authority in one jurisdiction (relying agency) takes into account and gives significant weight to assessments performed by another regulatory authority (reference agency), trusted institution or any other authoritative information, to reach its own decision while remaining independent, responsible and accountable for the decision taken, even when it relies on the decisions, assessments and information of others".

However, companies and agencies are challenged when implementing such models, particularly regarding the availability of successful case studies, clear guidelines, tools and templates to enable information sharing. The availability of assessment reports (both public and non-public) has been highlighted as a particular challenge (CIRS, 2022 Workshop).

# What are public assessment reports (PARs), and what are they used for?

PARs are public resources of information produced by regulatory agencies that provide knowledge about the results of the evaluation process of an MAA for a new drug or additional indication of a medicinal product. PARs comprise a core set of regulatory documents and outline how the agency assessed the dossier. PARs are mainly used to transparently communicate the basis for the decision to patients, healthcare professionals and industry representatives.

In addition, certain information may be removed (redacted) before the reports are published. The PAR redaction, and consequently what is considered confidential, is regulated by the regulatory agency's legal framework, which often differs in each jurisdiction. For instance, PARs are often redacted to remove confidential information, including commercially confidential information and personal protected data e.g. reviewers' names.



# Problem statement

In Annex 10, "Good reliance practices in the regulation of medical products: high level principles and considerations", WHO recommends that national regulatory agencies that seek to act as reference agencies are encouraged to issue PARs in a common language to document their regulatory decisions whereas relying agencies should use such reports as the primary source of information for assessments.

Even though the WHO provided these recommendations, reference and relying agencies still face challenges in creating and utilising PARs respectively. This may be a result of the fact that PARs were not created initially for the purpose of supporting reliance decision making. For instance, relying agencies are challenged to understand the decision making of the reference agency and may also be challenged by the redacted nature of PARs. Another challenge that may be faced by relying agencies is multiple documents, formats, structures, contents and granularity of the information described in PARs developed by reference agencies. Indeed, currently there is no common harmonised format for the structure and content of PARs.

To further evaluate the utility of PARs to support risk-based reviews, CIRS undertook a study to assess what reliance-relevant information can be found in PARs, how agencies' PARs compare to each other and to document whether the information described in PARs can be used to support the reliance decision-making process. The current report describes the results of such analysis.

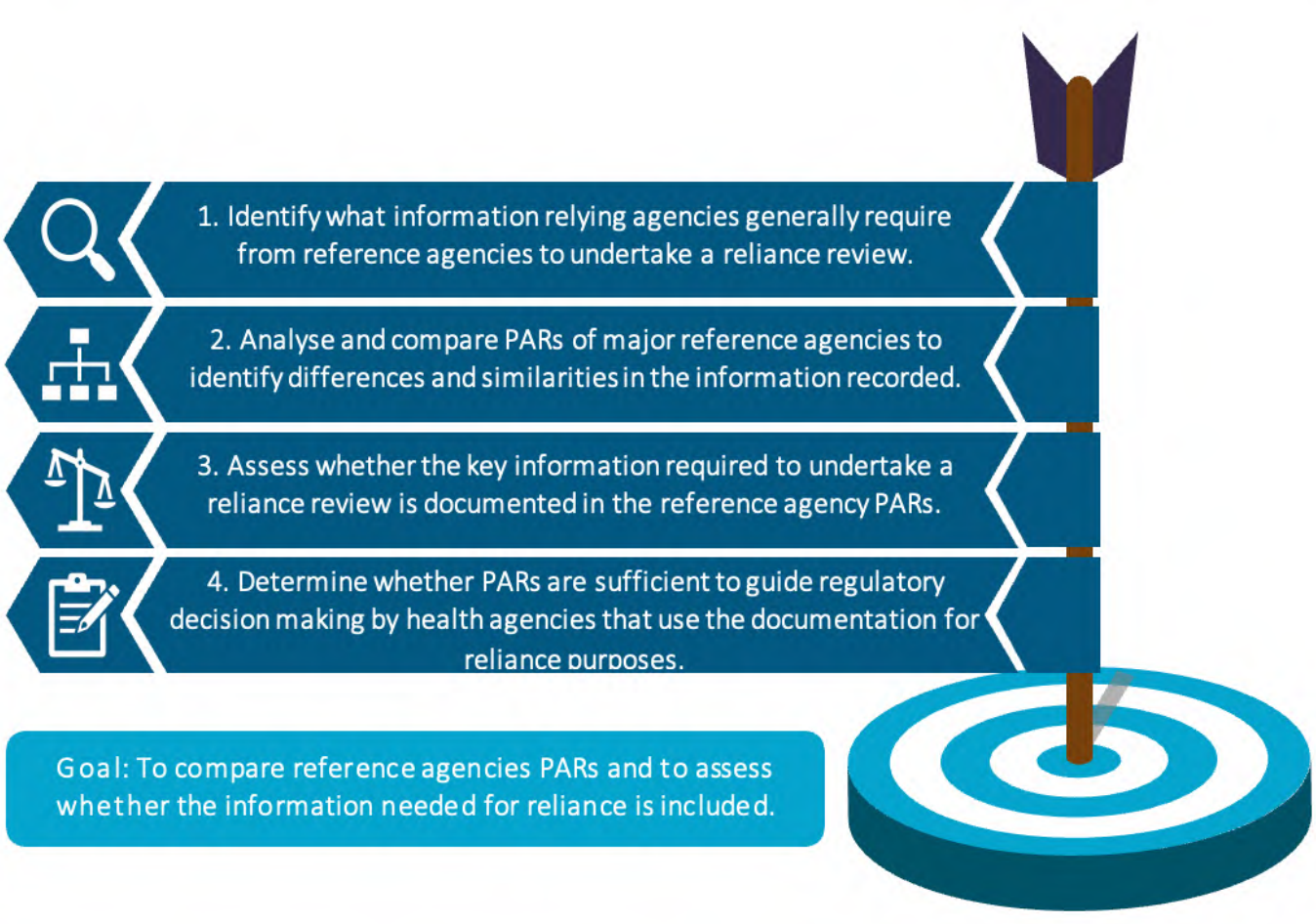
Finally, it should be noted that in addition to PARs, other documents are important to support reliance decision making, such as the MAA dossier provided by the applicant, the CPP, and/or the non-public assessment reports from the reference agency. This additional documentation can be utilised by the relying agency to seek any clarifications and further understand the information that was considered by the reference agency. Overall, the review of the dossier together with the assessment report enables a way to compare the information submitted and how this information was considered by the reference agency. Nevertheless, the focus of this work was on PARs only.

# Goal and objectives

The goal (light blue) and objectives (dark blue) of the study are described in Figure 1. The overall goal was to compare reference agency PARs and assess whether they contain information that is needed by agencies undertaking a reliance review. Since each agency has different reliance requirements, CIRS firstly consolidated a generic, non-agency-specific list of information required by relying agencies to enable a reliance decision.

Secondly, CIRS analysed the PARs from reference agencies against the list of information generally required by agencies for reliance. This ultimately enabled an evaluation of the utility of PARs for reliance.

*Figure 1. Main goal and specific objectives.*



# Method

The study was undertaken by evaluating PARs from reference agencies for selected products. 33 PARs for six new active substances (NASs) approved by seven reference agencies were assessed.

The assessment was done by comparing the information described in each PAR against a generic and non-agency-specific list of key information that relying agencies generally require to implement risk-based/reliance reviews in the authorisation processes of medicines. The development of this list and the PAR assessment process are described on pages 10 to 12.

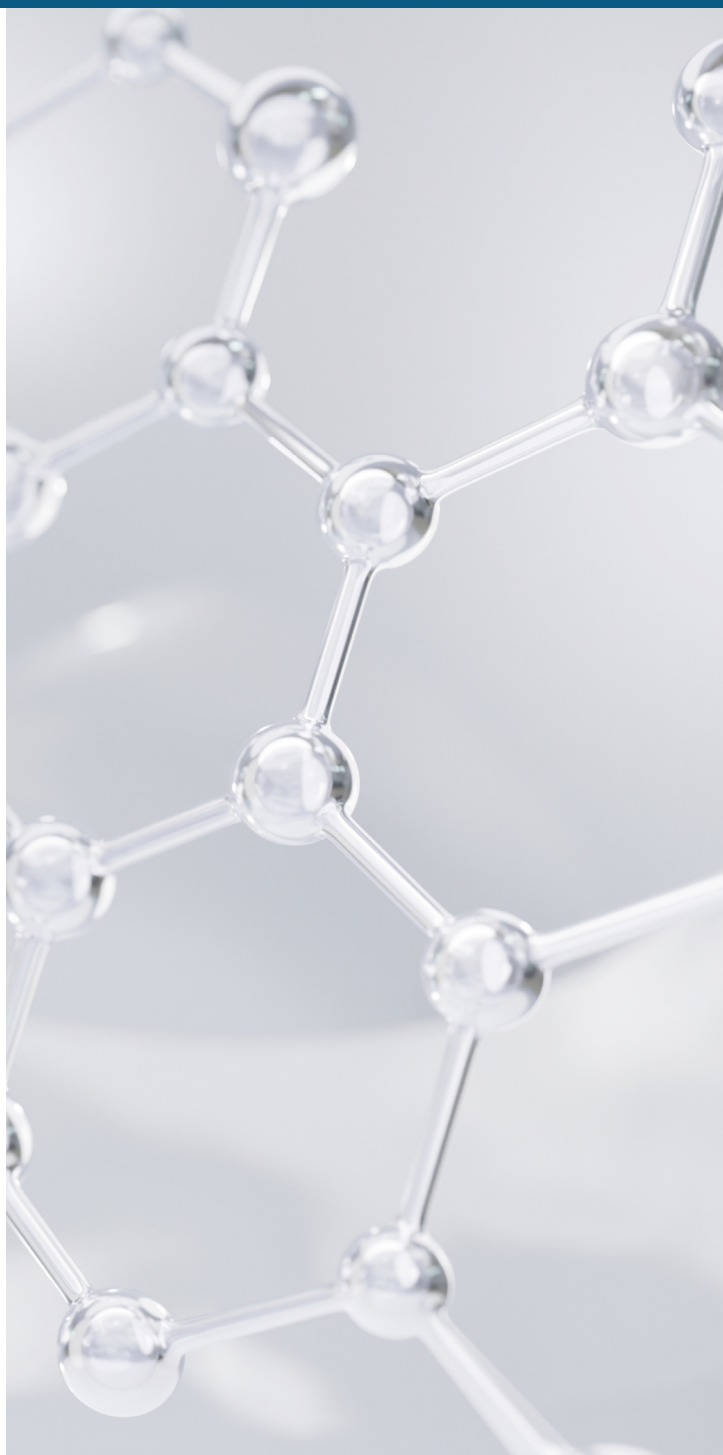
## Inclusion criteria

To ensure a representative cohort of products, the following criteria were applied to select products for this study from CIRS proprietary Regulatory Review Times Database:

1. Products that have been approved between 2018 and 2021.
2. Products from different Anatomical Therapeutic Chemical (ATC) groups were selected to ensure representativeness of therapy areas.
3. Different product types were selected:
    a. Up to three biological products where one was considered an advanced therapy medicinal product (ATMP).
    b. Up to three small molecules.
4. Products with special designations/pathways were selected e.g. orphan drugs, and products utilising different facilitated regulatory pathways (FRPs).

FDA, EMA, Health Canada, Swissmedic, TGA, ANVISA, and MHRA were selected as they produce PARs and are utilised as reference agencies for the purpose of reliance. It should be noted that all agencies produced PARs in English, except for ANVISA, where the documents were translated from Portuguese to English.

Data sources and websites from which the PARs were retrieved are listed in the Appendix.



# Summary of the NAS characteristics

After applying the inclusion criteria Table 1 outlines the NASs selected for the assessment.

| | | | | | Reference agencies | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ✓: PAR assessed in this study | | | | | Orphan designation | |
| **Brand name** | **Generic name** | **ATC group** | **Type of drug** | **ATMP** | **FDA** | **EMA** | **Health Canada** | **Swissmedic** | **TGA** | **ANVISA** | **MHRA** |
| **Enhertu** | **trastuzumab deruxtecan** | **L** | **Biological product** | **-** | ✓*»†‡ | ✓*» | ✓»‡ | ✓»‡ | ✓»‡ | ✓* | **PAR not found** |
| **Cablivi** | **caplacizumab** | **B** | **Biological product** | **-** | ✓*† | ✓ | ✓* | ✓R | ✓R | **PAR not found** | **N/A**** |
| **Zolgensma** | **onasemnogene abeparvovec** | **M** | **Biological product** | **ATMP** | ✓*† | ✓» | ✓* | **PAR not found** | ✓ | **PAR not found** | **N/A**** |
| **Evrysdi** | **risdiplam** | **M** | **Small molecule** | **-** | ✓*† | ✓*† | ✓* | ✓* | ✓* | ✓ | ✓R |
| **Nubeqa** | **darolutamide** | **L** | **Small molecule** | **-** | ✓*† | ✓ | ✓Ws | ✓ | ✓Ws | ✓ | **N/A**** |
| **Xofluza** | **baloxavir marboxil** | **J** | **Small molecule** | **-** | ✓* | ✓ | ✓Ws | ✓Ws | ✓Ws | **Not approved** | **PAR not found** |

*Table 1. Summary of the characteristics of the 33 PARs assessed in this study.*

**Types of facilitated regulatory pathways (FRPs) used within the scientific assessment (see "Definitions" for more detail).**

***:** **Expedited review.**

**†:** **Earlier/ Intensive dialogue review.**

**‡:** **Collaborative review (Project Orbis).**

**»:** **Accelerated/ Conditional/ Provisional approval.**

**Ws:** **Work-sharing review (Access Consortium).**

**R:** **Reliance.**

****: Not applicable as the NAS was not approved nationally by MHRA but approved in the UK through the EMA centralised procedure.**

**NOTE:** due to the limited number of compounds approved nationally by MHRA, the results of this agency were excluded from this report. In addition, although the focus of this study was on initial marketing authorisations (NASs), an analysis of the availability of PARs for major post-approval changes such as new indications—also know as major line extensions (MLEs)— or dosage forms was also undertaken. However, it was not possible to retrieve full PARs for the MLEs from these products across the majority of the agencies considered, therefore MLE PARs were not included in the analysis.

# Main stages of the study

The study was developed in three main stages which are described in Figure 2.

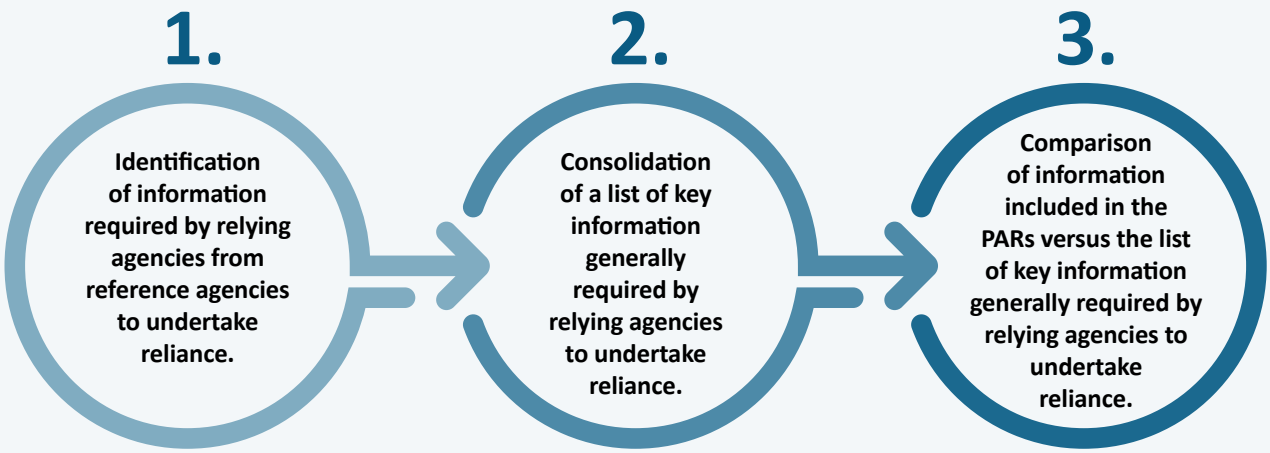



*Figure 2. Main stages of the study.*

**Stage 1:**

Since each agency has different reliance requirements, CIRS firstly consolidated a generic, non-agency-specific list of information required by relying agencies to enable a risk-based decision. The first stage therefore was focused on identifying and collecting the relevant information from the list of references described below:

- **Singapore:** https://www.hsa.gov.sg/therapeutic-products/register/guides/new-drug/abridged-evaluation.
- **Australia:** https://www.tga.gov.au/resources/resource/guidance/comparable-overseas-regulators-cors-prescription-medicines.
- **Brazil (Biologics):** Orientação de Serviço nº 45, de 16 de fevereiro de 2018 — Agência Nacional de Vigilância Sanitária- Anvisa (www.gov.br).
- **Brazil (Chemicals):** Orientação de Serviço nº 70 de 2019- GESEF.pdf — Agência Nacional de Vigilância Sanitária- Anvisa (www.gov.br).
- **Saudi Arabia:** Registration According to Verification and Abridged | Saudi Food and Drug Authority (www.sfda.gov.sa).
- **Malaysia:** Facilitated-Registration-Pathway-Guideline_Final.pdf (www.npra.gov.my).
- **World Health Organisation (WHO).** Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations (https://www.who.int/publications/m/item/annex-10-trs-1033).
- **CIRS workshop reports** (https://cirsci.org/reports/).
- **CIRS interactions with agencies.**

## Main stages of the study

**Stage 2:** Subsequently, for the second stage, the information collected was reviewed and consolidated into a single list of key information – a non-agency specific list of information that agencies generally require for the purpose of reliance. Such list was divided into five sections and subdivided into topics and subtopics to ensure a consistent and efficient assessment across all PARs. The main sections and topics are described in Table 2.

*Table 2. Main sections and topics of the list of key information that relying agencies generally require to implement risk-based/reliance reviews in the authorisation processes of medicines.*

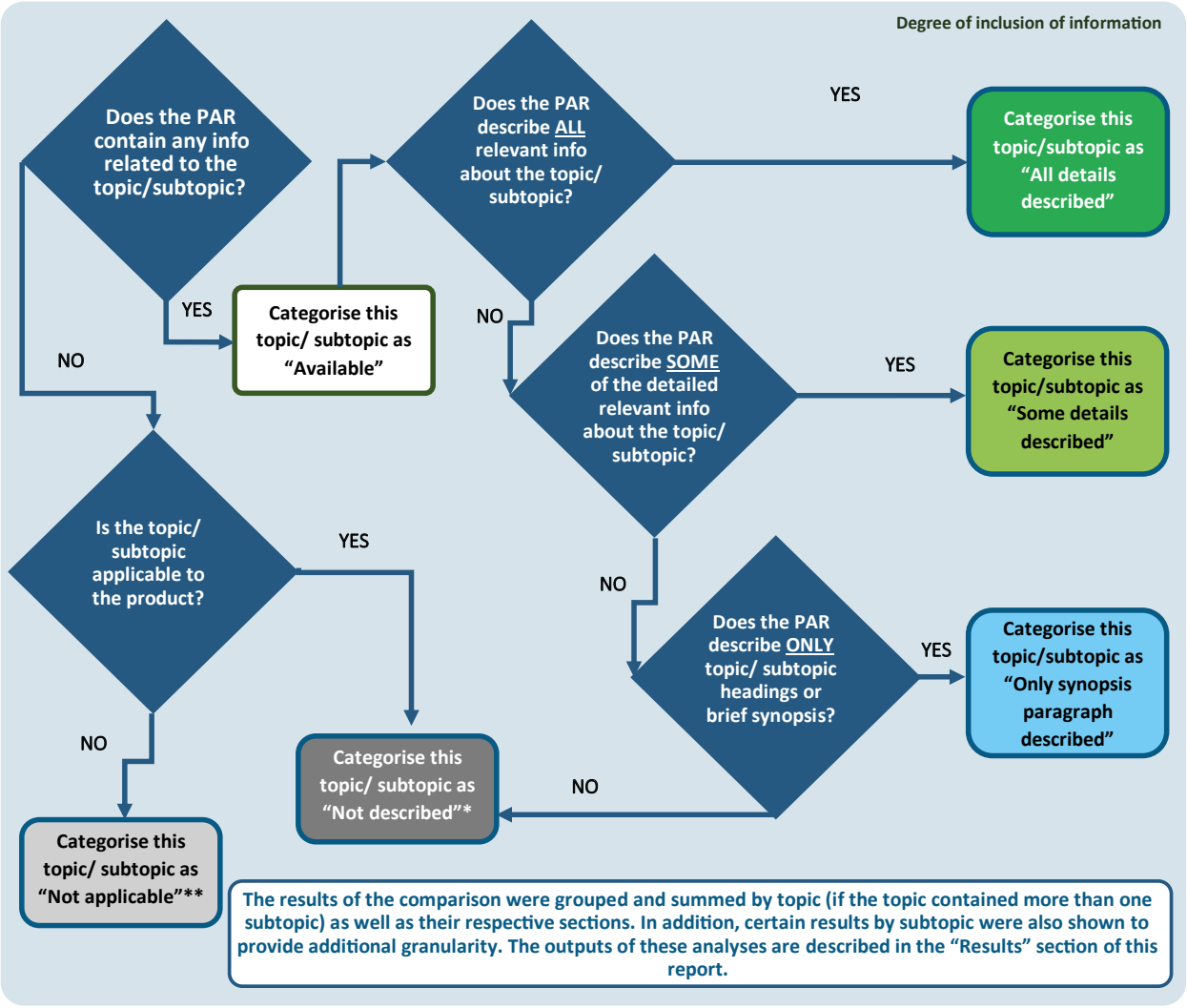
| Section | Topic |
|---|---|
| 1. Regulatory Background | 1. List of steps taken in the regulatory process of the product within the individual agency. |
| | 2. List of countries in which the product has been approved, withdrawn, or rejected. |
| | 3. Questions and answers raised during the scientific assessment. |
| | 4. Summaries of meetings (e.g., within the agency, with companies). |
| | 5. Discussion of a divergent decision within the agency. |
| | 6. Labelling (e.g., Package insert and leaflet). |
| | 7. Final decision of the agency. |
| | 8. Rationale for orphan designation. |
| | 9. Rationale for using FRPs by the agency |
| 2. CMC | 1. Certification of the manufacturing facilities. |
| | 2. Raw materials (e.g., manufacture, quality and stability of the API, excipients). |
| | 3. Finished pharmaceutical product (e.g., manufacture, quality and stability of the finished dosage form). |
| | 4. Transportation and storage conditions. |
| 3. Non-clinical | 1. Non-clinical studies. |
| 4. Clinical | 1. Therapeutic indication and dose. |
| | 2. Clinical studies (e.g., pivotal and supplemental). |
| | 3. Effects and precautionary actions in diverse populations. |
| 5. Benefit-Risk Assessment | 1. Benefit-Risk Assessment. |
| | 2. Assessment of the ethnic factors. |
| | 3. Other obligations to complete after the recommendation/approval. |

The above-mentioned list of key information does not aim to establish what information should be included in a PAR, but what information agencies may generally look for to undertake reliance-based marketing authorisation processes. Additional information on topics and subtopics is described in the Appendix.

## Main stages of the study

**Stage 3:** Lastly, a comparison was made by comparing the inclusion of information of the 33 PARs using each topic and subtopic described in the "list of key information that relying agencies generally require to implement risk-based/reliance reviews in the authorisation processes of medicines" in Table 2. The assessment process is summarised in Figure 3.

*Figure 3. Flow chart of the assessment carried out on the 33 PARs*




**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*
***: Some subtopics may not be applicable due to the intrinsic features of the product or the agency (e.g., orphan designation for Health Canada as the agency does not currently have an orphan policy).*

Finally, it should also be noted that in addition to PARs, relying agencies may use other sources of information to undertake reliance-based decisions (e.g., the MAA dossier provided by the applicant, CPPs, and/or non-public assessment reports etc). However, this was not in scope for the analysis undertaken. Therefore it would also be useful to assess those documents to determine their utility for enabling a reliance review. As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.

# Results

The results of this report are grouped into three sections:

- "Overall summary" – summarises overall results broken down by agency.
- "Summary of sections" – results broken down by agency and PAR section.
- "Detailed results by section" – results broken for each agency and outlining results within each PAR section.

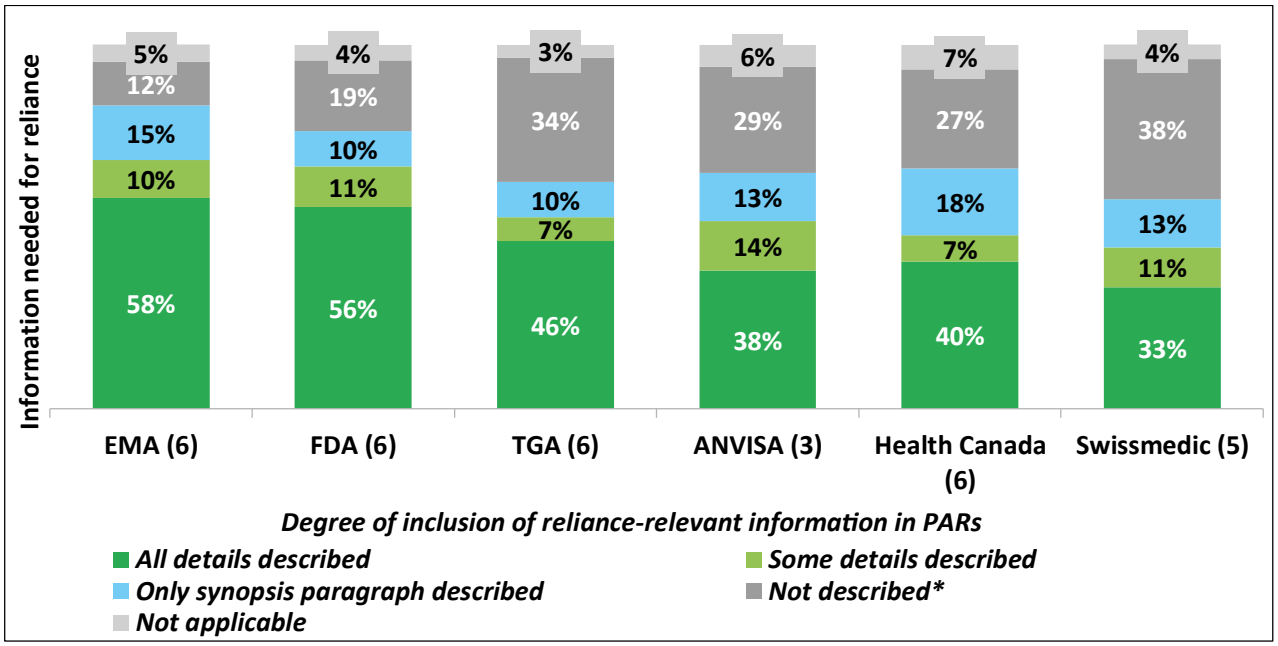
**NOTE:** The percentages described in the 'Key messages' of each Results section are the total sum of "all details described" and "some details described" categories (unless specified otherwise). Due to the limited number of compounds approved nationally by MHRA, the results of this agency were excluded from this report.

## Overall summary

Each PAR was assessed against the reliance-relevant topics and subtopics described in the Method section. The results for all PARs were consolidated and broken down by agency.

Figure 4 summarises the inclusion of reliance-relevant information across all NAS PARs assessed for each reference agency.

*Figure 4. Inclusion of reliance-relevant information in PARs, by agency*




*(n): Number of public assessment reports (PARs)*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

### *Key messages:*

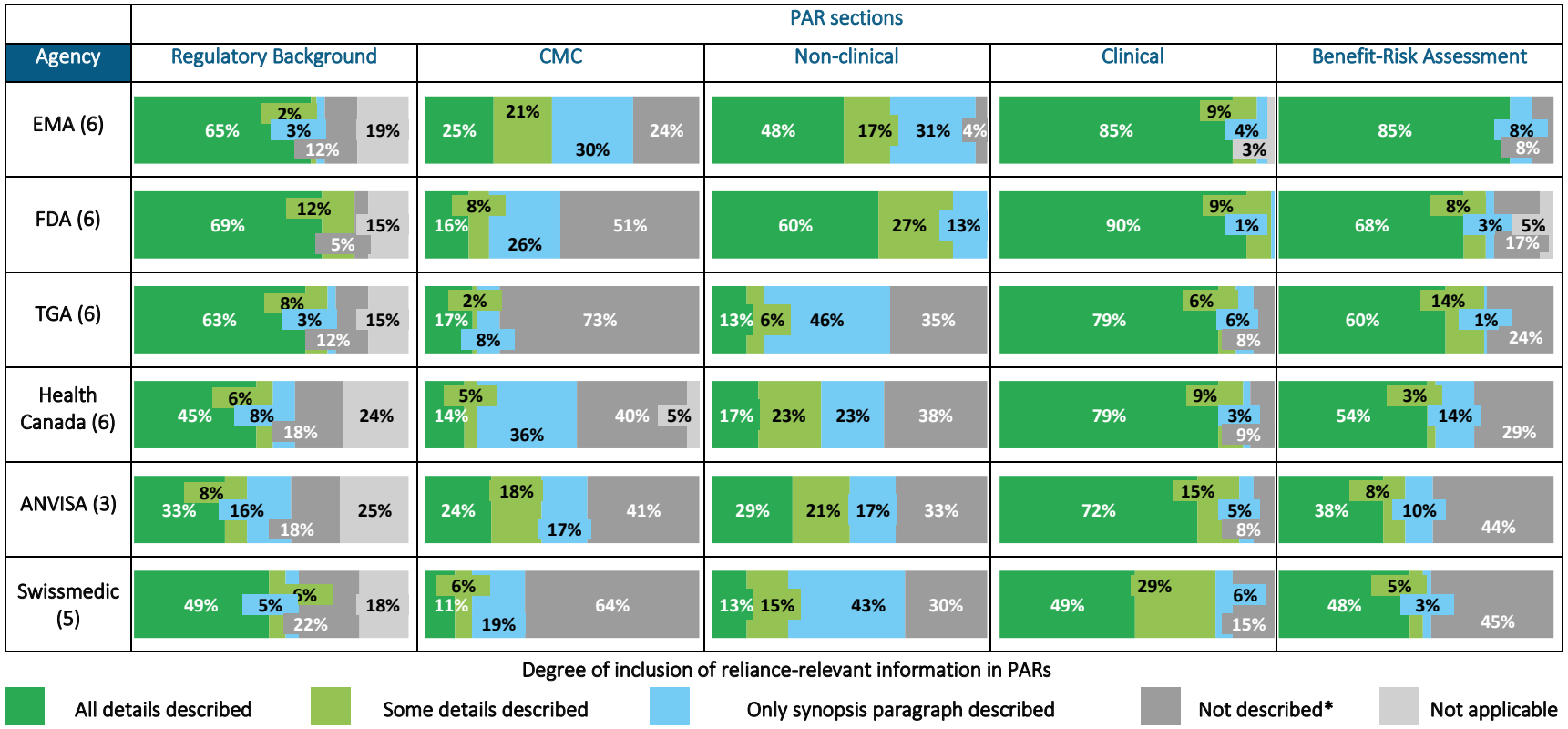
- In general, PARs appear to contain the majority of information that relying agencies may require for reliance – the degree of inclusion of reliance-relevant information varied from 68% to 44% across the six agencies.
- For PARs developed by EMA, 68% of the information needed for reliance was included ("all details described" and "some details described") compared to 67% for FDA, 53% for TGA, 52% for ANVISA, 47% for Health Canada, and Swissmedic with 44%.
- 38% of reliance-relevant information was not included in Swissmedic's PARs, followed by TGA with 34%, 29% for ANVISA, 27% for Health Canada, 19% for FDA and 12% for EMA.

# Summary of sections

Each PAR was assessed against the reliance-relevant topics and subtopics as described in the Method section. The results for all PARs were consolidated and broken down by agency and by section (e.g., Regulatory Background, CMC, Non-clinical, etc.).

Figure 5 summarises the inclusion of reliance-relevant information across all PARs assessed for each reference agency, broken down by each PAR section.

*Figure 5. Inclusion of reliance-relevant information in PARs, by agency and by PAR section.*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

***Key messages:***

- In general, the PARs sections ranked as follows in terms of degree of inclusion of reliance-relevant information: 1st. Clinical, 2nd. Benefit-Risk Assessment, 3rd. Regulatory Background, 4rd. CMC and 5th. Non-clinical.
- For the Clinical section, FDA's PARs included the highest percentage (99%) of reliance-relevant information, whereas Swissmedic's PARs described the lowest proportion (78%).
- For the Benefit-Risk Assessment section, EMA's PARs contained the highest percentage (85%) of reliance-relevant information. In contrast, ANVISA's PARs described the lowest proportion (46%).
- For the Regulatory Background section, FDA's PARs described the highest percentage (81%) of reliance-relevant information, while ANVISA's PARs described the lowest proportion (41%).
- For the Non-clinical section, FDA's PARs described the highest percentage (87%) of reliance-relevant information. In contrast, TGA's PARs described the lowest proportion (19%).
- For the CMC section, EMA's PARs described the highest percentage (46%) of reliance-relevant information, whereas Swissmedic's PARs described the lowest proportion (17%).

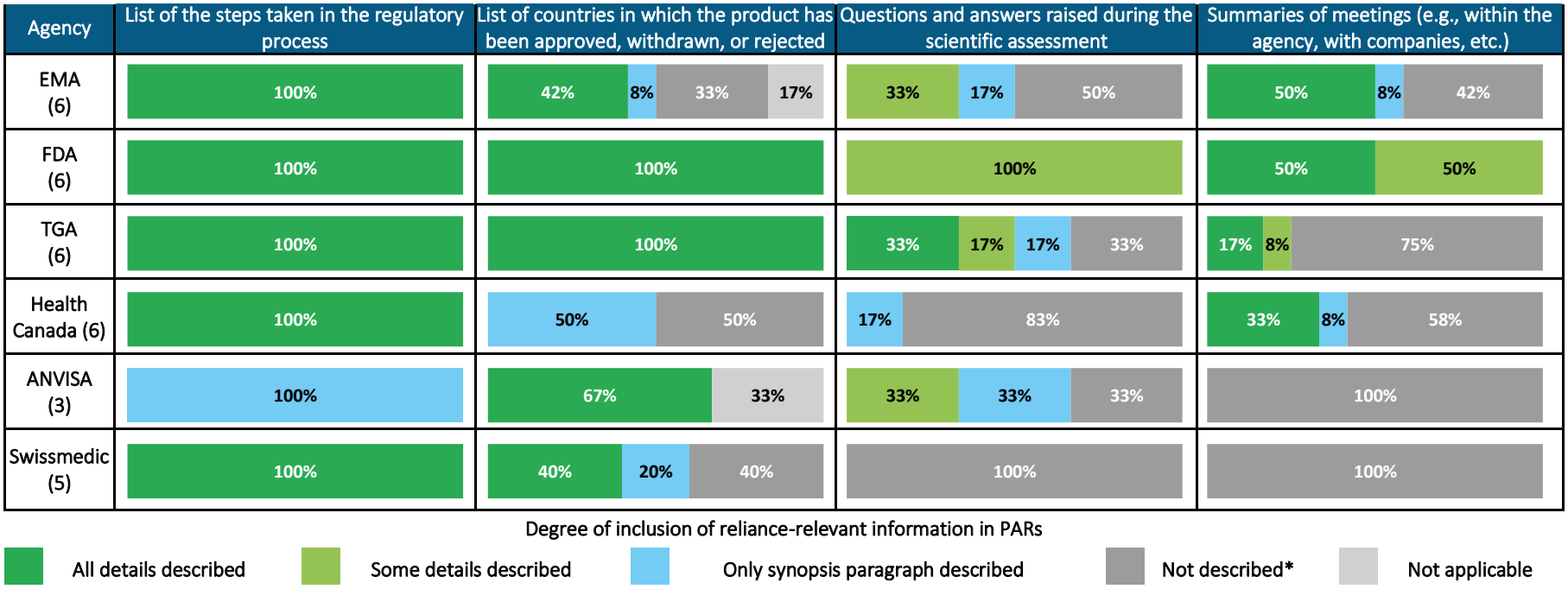
# Detailed analysis by section

A further granularisation by topic and subtopic (when applicable) of the Regulatory Background, CMC, Non-clinical, Clinical and Benefit-Risk Assessment sections was undertaken to analyse in detail the inclusion of reliance-relevant information within the appraised PAR sections.

## Regulatory Background section

Each PAR was assessed against the reliance-relevant topics and subtopics as described in the Method section. The results for all PARs were consolidated and broken down by agency and by topic (e.g., list of steps taken in the regulatory process) within the Regulatory Background section.
Figures 6 and 7 summarise the inclusion of reliance-relevant information across all PARs assessed for each reference agency, broken down by each topic for the Regulatory Background section.

*Figure 6. Inclusion of reliance-relevant information in PARs, by agency and by topic for the Regulatory Background section.*

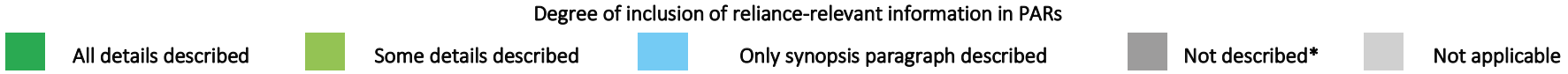



*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

*Figure 7. Inclusion of reliance-relevant information in PARs, by agency and by topic for the Regulatory Background section (cont.)*

| Agency | Topics | | | | |
|---|---|---|---|---|---|
| | Discussion of divergent decision within the agency | Labelling (e.g., Package insert and leaflet) | Final decision of the agency | Rationale for orphan designation | Rationale for using FRPs by the agency |
| EMA (6) | 100% | 100% | 100% | 50% 50% | 67% 33% |
| FDA (6) | 100% | 89% 11% | 100% | 33% 17% 50% | 100% |
| TGA (6) | 17% 83% | 67% 33% | 100% | 33% 11% 6% 50% | 83% 17% |
| Health Canada (6) | 100% | 67% 33% | 100% | 100% | 100% |
| ANVISA (3) | 100% | 67% 33% | 100% | 11% 22% 67% | 33% 67% |
| Swissmedic (5) | 100% | 67% 33% | 100% | 27% 13% 60% | 80% 20% |




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

### *Key messages:*

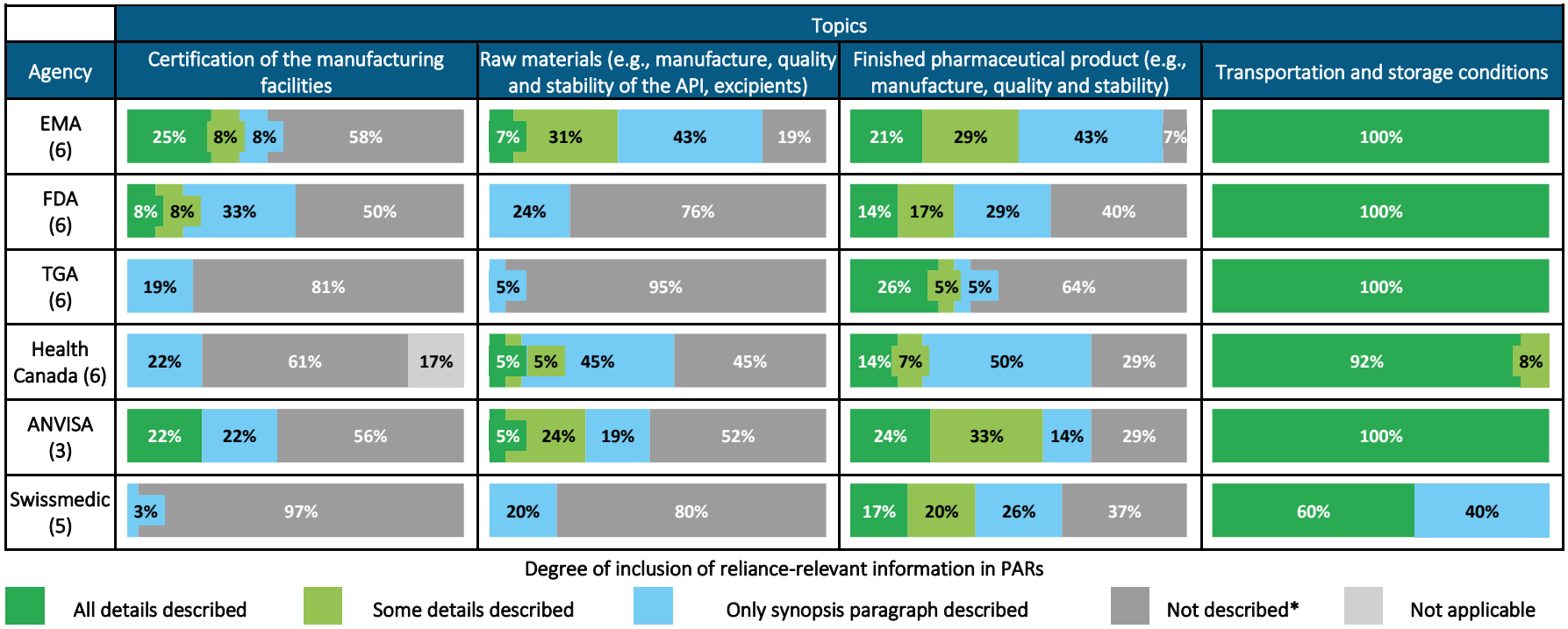
- In general, the Regulatory Background section ranked 2nd in terms of degree of inclusion of reliance-relevant information compared to the other five PAR sections.
- Across the agencies, the PARs from FDA contained the highest proportion of reliance-relevant information for the Regulatory Background section, followed by TGA, EMA, Health Canada, Swissmedic and ANVISA.
- Regarding specific topics:
    - The PARs from EMA, FDA, TGA, Health Canada and Swissmedic assessed in this study contained 100% of the information relating to the ***"list of steps taken in the regulatory process"***.
    - All PARs assessed in this study contained 100% of the reliance-relevant information regarding the ***"final decision of the agency"***.
    - For the topic of ***"labelling"***, FDA's PARs contained 89% of reliance-relevant information since the information relating to the subtopic ***"descriptions of what must be shown on the label"*** was not found for two products (results not shown).
    - The reliance-relevant information regarding the rationale for using facilitated regulatory pathways (FRPs) was described by all agencies where applicable.
    - All applicable PARs developed by EMA described all ***"rationale for orphan designation"*** subtopics. In contrast, the ***"descriptions of the reasons why the orphan drug status was granted"*** was the subtopic least described among the other applicable PARs (results not shown).

## CMC section

Each PAR was assessed against the reliance-relevant topics and subtopics as described in the Method section. The results for all PARs were consolidated and broken down by agency and by topic (e.g., certification of the manufacturing facilities) within the CMC section.

Figure 8 summarises the inclusion of reliance-relevant information across all PARs assessed for each reference agency, broken down by each topic for the CMC section.

*Figure 8. Inclusion of reliance-relevant information in PARs, by agency and by topic for the CMC section.*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

### *Key messages:*

- In general, the CMC section ranked 4th in terms of degree of inclusion regarding reliance-relevant information compared to the other five PAR sections.
- Across the agencies, the PARs from EMA contained the highest proportion of reliance-relevant information, followed by FDA, Health Canada, TGA, ANVISA and Swissmedic.
- Regarding specific topics:
    - ***"Transportation and storage conditions"*** topic was described in all PARs assessed in this study.
    - ***"Certification of the manufacturing facilities"*** and ***"raw materials (e.g., manufacture, quality and stability of the API, excipients)"*** were the least described topics in the agency PARs. For the former, only 33% of the reliance-relevant information was found in EMA's PARs, followed by ANVISA with 22% and FDA with 16%. For the latter, only 38% of the reliance-relevant information was found among EMA's PARs, followed by ANVISA with 29% and Health Canada with 10%.
    - For the ***"finished pharmaceutical product"*** topic, 57% of reliance-relevant information was described in ANVISA's PARs, followed by 50% for EMA, 37% for Swissmedic, 31% for both TGA and FDA and 21% for Health Canada.
    - In addition to the ***"finished pharmaceutical product"*** topic, the most frequently detailed subtopics were the ***"description of the container closure system"*** and the ***"qualitative list of raw materials",*** whereas the ***"list of reference materials"*** and the ***"description of the manufacturing process"*** were the least described subtopics (results not shown). However, this information should be available in the dossier, for the reviewer to refer to.

## Non-clinical section

Each PAR was assessed against the reliance-relevant topics and subtopics as described in the Method section. The results for all PARs were consolidated and broken down by agency, topic (e.g., non-clinical studies), and subtopic (e.g., list of studies performed) within the Non-clinical section to provide further granularity.

Figures 9 and 10 summarise the inclusion of reliance-relevant information across all PARs assessed for each reference agency, broken down by each topic and subtopic for the Non-clinical section.

*Figure 9. Inclusion of reliance-relevant information in PARs by agency, topic and subtopic for the Non-clinical (NC) section.*

| | Topic | Subtopics | | | |
|---|---|---|---|---|---|
| Agency | Non-clinical (NC) studies | List of studies performed (NC) | Description of the purpose of each study (NC) | Description of the study setup (NC) | Description of the models used (NC) |
| EMA (6) | 48% 17% 31% 4% | 67% 33% | 83% 17% | 17% 50% 33% | 50% 17% 33% |
| FDA (6) | 60% 27% 13% | 83% 17% | 100% | 67% 33% | 67% 33% |
| TGA (6) | 13% 6% 46% 35% | 100% | 17% 83% | 33% 67% | 33% 67% |
| Health Canada (6) | 17% 23% 23% 38% | 100% | 33% 33% 33% | 33% 33% 33% | 50% 50% |
| ANVISA (3) | 29% 21% 17% 33% | 33% 33% 33% | 67% 33% | 33% 33% 33% | 33% 33% 33% |
| Swissmedic (5) | 13% 15% 43% 30% | 40% 60% | 20% 80% | 40% 20% 40% | 40% 60% |

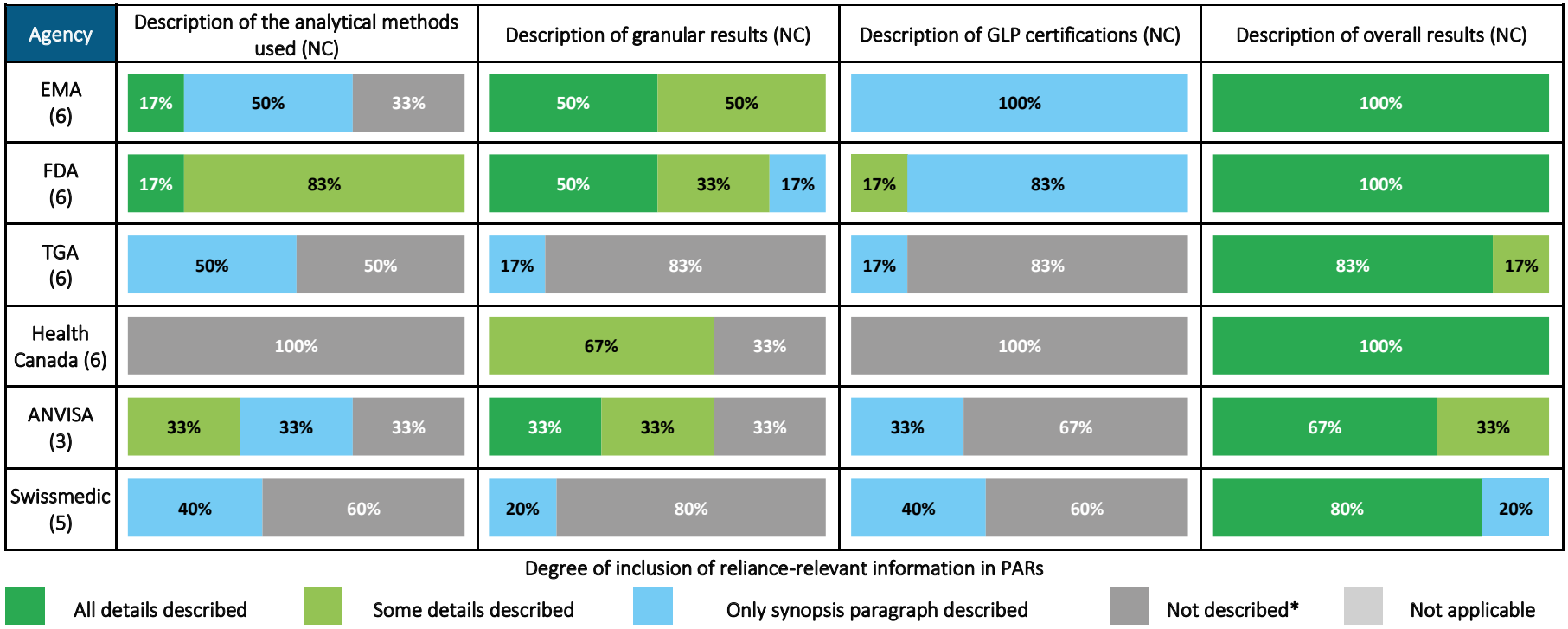
Degree of inclusion of reliance-relevant information in PARs

All details described | Some details described | Only synopsis paragraph described | Not described* | Not applicable

*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

*Figure 10. Inclusion of reliance-relevant information in PARs, by agency, topic and subtopic for the Non-clinical (NC) section (cont.)*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

### *Key messages:*

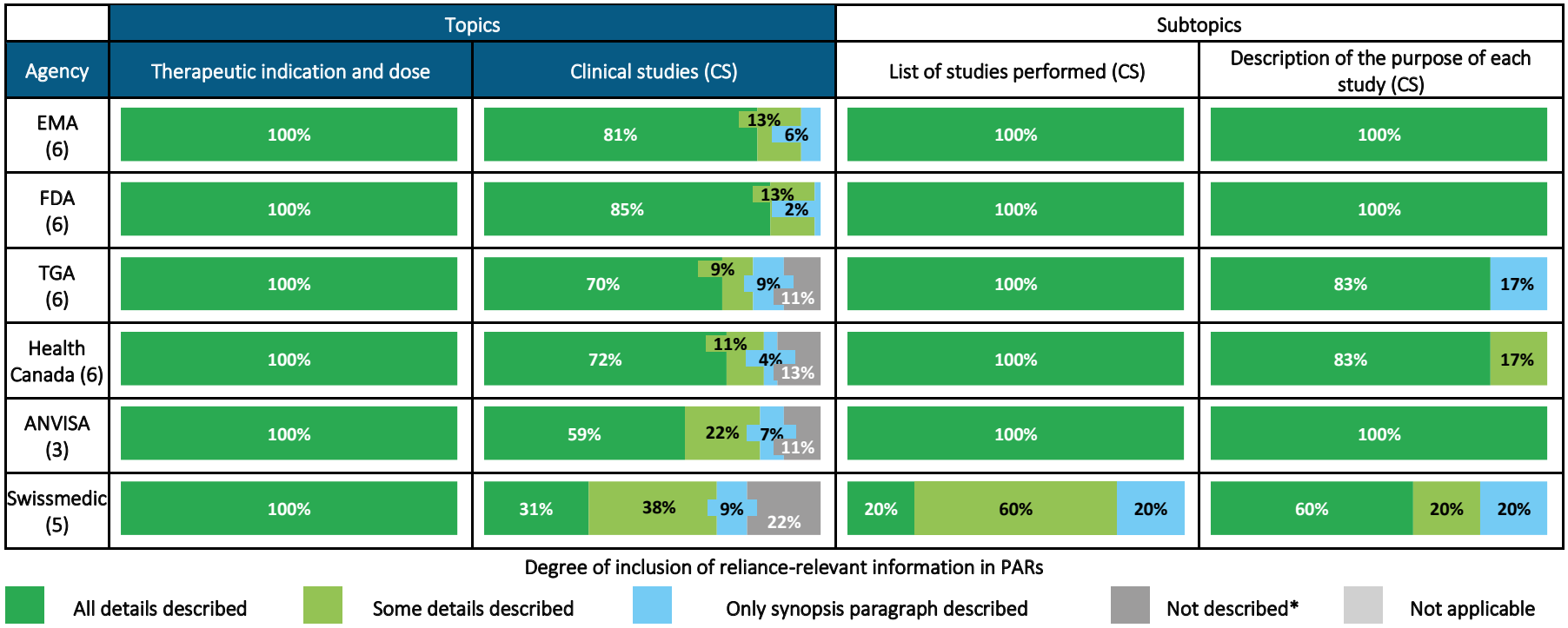
- In general, the Non-clinical section ranked 5th in terms of degree of inclusion regarding reliance-relevant information compared to the other five PAR sections.
- Across the agencies, the PARs from FDA contained the highest proportion of reliance-relevant information, followed by EMA, Health Canada, TGA, Swissmedic and ANVISA.
- Regarding specific topics and subtopics:
    - All agencies generally included in their PARs some level of detail regarding the studies conducted, including their purpose and setup.
    - The *"description of the models used"* was disclosed by all agencies in most PARs, but only FDA and EMA described all details.
    - The *"description of overall results"* was the most detailed subtopic in the Non-clinical section since all PARs from all agencies contained at least 80% of the reliance-relevant information.
    - In contrast, the *"description of granular results"* subtopic was less well described, particularly by TGA and Swissmedic, followed by the *"description of the analytical methods used "*subtopic and the *"description of GLP certifications"* subtopic, where only a limited description or no information was described. However, this information should be available in the dossier, for the reviewer to refer to.

## Clinical section

Each PAR was assessed against the reliance-relevant topics and subtopics as described in the Method section. The results for all PARs were consolidated and broken down by agency, topic (e.g., therapeutic indication and dose), and subtopic (e.g., list of studies performed) within the Clinical section to provide further granularity.

Figures 11, 12, and 13 summarise the inclusion of reliance-relevant information across all PARs assessed for each reference agency, broken down by each topic and subtopic for the Clinical section.

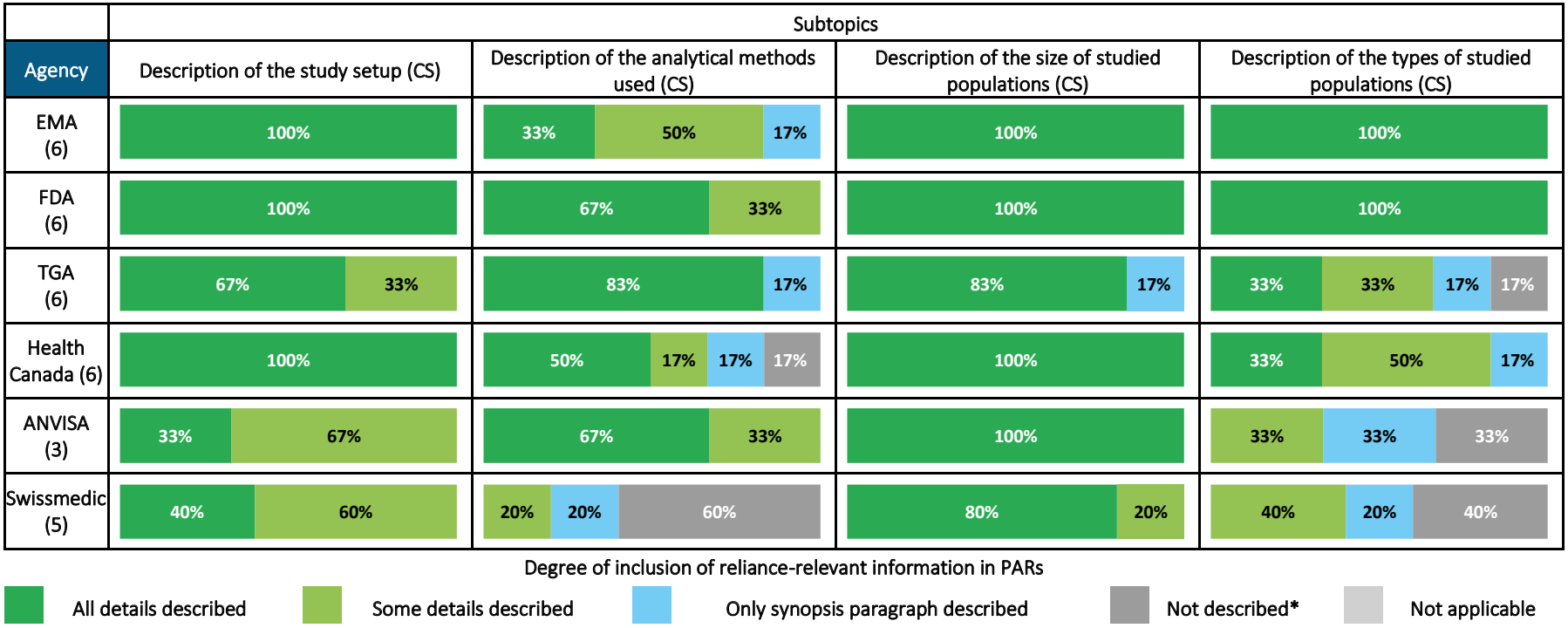
*Figure 11. Inclusion of reliance-relevant information in PARs, by agency, topic and subtopic for the Clinical section.*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

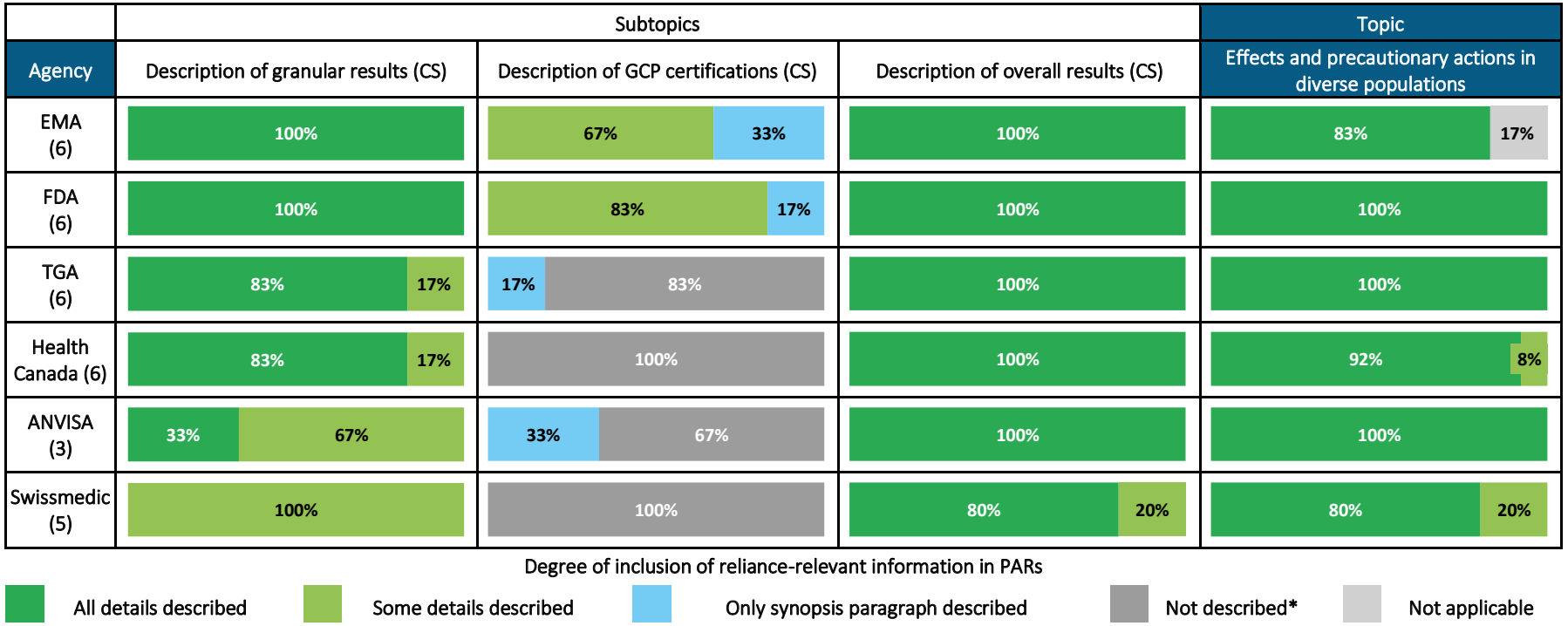
*Figure 12. Inclusion of reliance-relevant information in PARs, by agency, topic and subtopic for the Clinical section (cont.)*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

*Figure 13. Inclusion of reliance-relevant information in PARs, by agency, topic and subtopic for the Clinical section (cont.)*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

### *Key messages:*

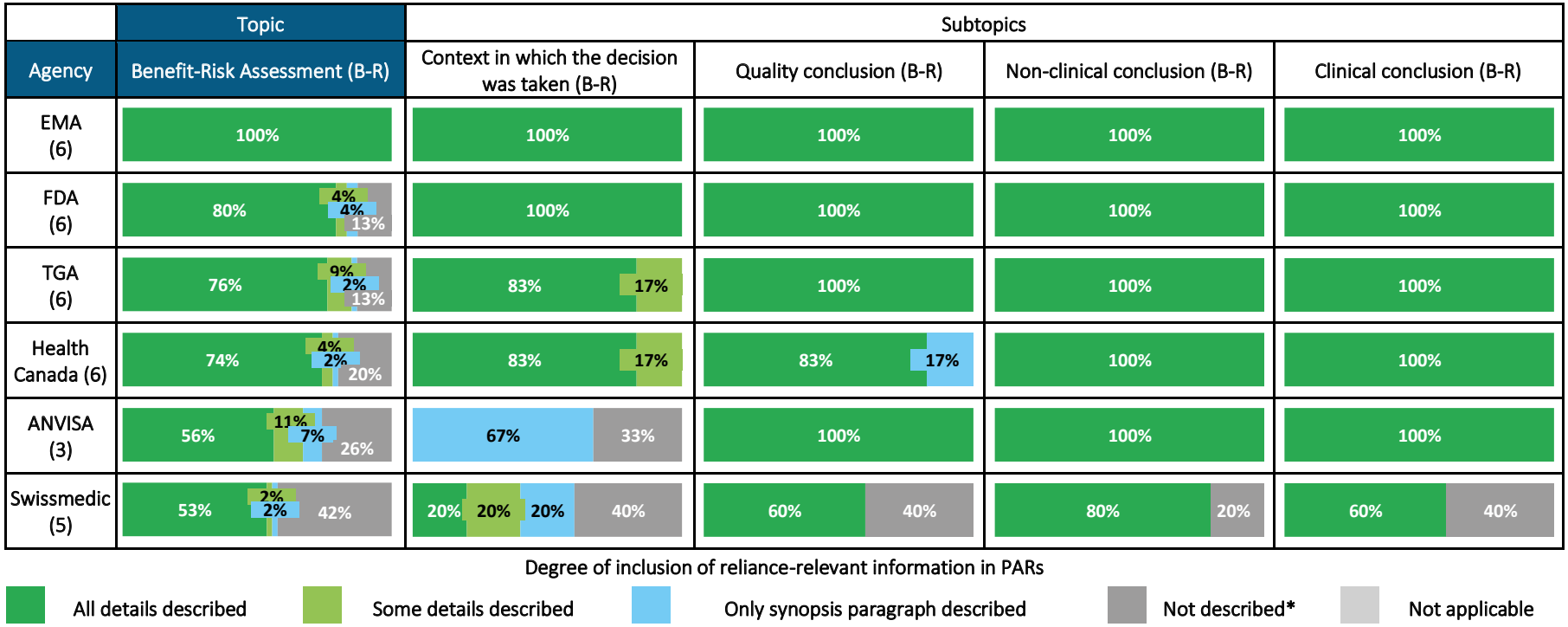
- In general, the Clinical section ranked 1st in terms of degree of inclusion regarding reliance-relevant information compared to the other five PAR sections.
- Across the agencies, the PARs from FDA contained the highest proportion of reliance-relevant information, followed by EMA, Health Canada, TGA, Swissmedic and ANVISA.
- Regarding specific topics and subtopics:
    - All PARs assessed in this study contained 100% of the reliance-relevant information regarding the topic ***"therapeutic indication and dose"***.
    - The results for the ***"clinical studies"*** topic were also displayed by subtopic to provide additional granularity. The subtopics, such as the ***"list of studies performed"*** and ***"description of the purpose of each study"***, were detailed in all PARs developed by EMA, FDA and ANVISA, and in the majority of PARs from TGA and Swissmedic (around 80%).
    - Subtopics such as the ***"description of the analytical methods used"*** and the ***"description of the types of studied populations"*** were less well described.
    - For instance, three Swissmedic PARs and one Health Canada PAR did not contain information for the ***"description of the analytical methods used"***, while for the ***"description of the types of studied populations"***, reliance-relevant information was not described in one of TGA's PARs, one of ANVISA's PARs and two of Swissmedic's PARs.
    - The information related to the ***"description of overall results"*** subtopic was described either as ***"fully"*** or in ***"some detail"*** within all agency PARs assessed in this study.
    - In contrast, the ***"description of GCP certifications"*** was the least described subtopic, where 83% of FDA's PARs and 67% of EMA's PARs contained this information.
    - Lastly, all PARs, where applicable, contained all reliance-relevant information related to the ***"effects and precautionary actions in diverse populations"*** topic.

## Benefit-Risk Assessment section

Each PAR was assessed against the reliance-relevant topics and subtopics as described in the Method section. The results for all PARs were consolidated and broken down by agency, topic (e.g., Benefit-Risk Assessment), and subtopic (e.g., context in which the decision was taken) within the Benefit-Risk Assessment section to provide further granularity.

Figures 14, 15 and 16 summarise the inclusion of reliance-relevant information across all PARs assessed for each reference agency, broken down by each topic and subtopic for the Benefit-risk Assessment section.

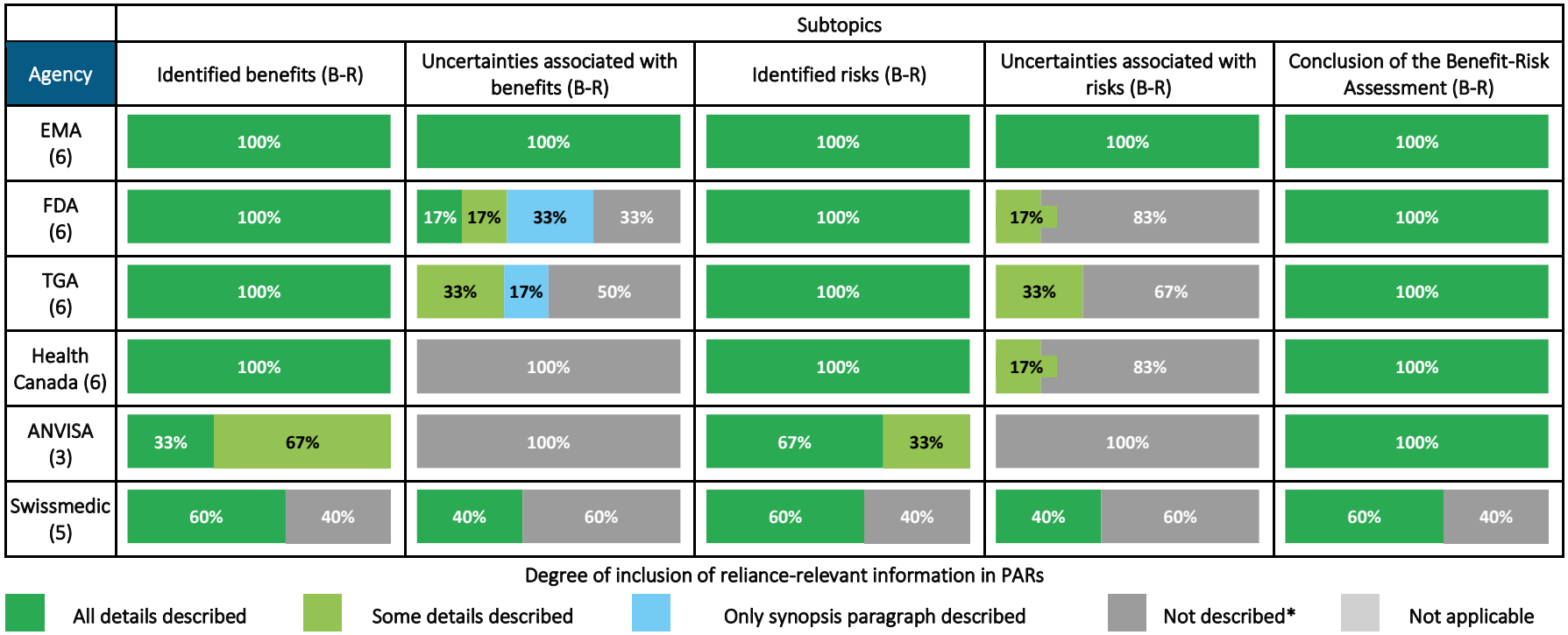
*Figure 14. Inclusion of reliance-relevant information in PARs, by agency, topic and subtopic for the Benefit-Risk Assessment(B-R) section.*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

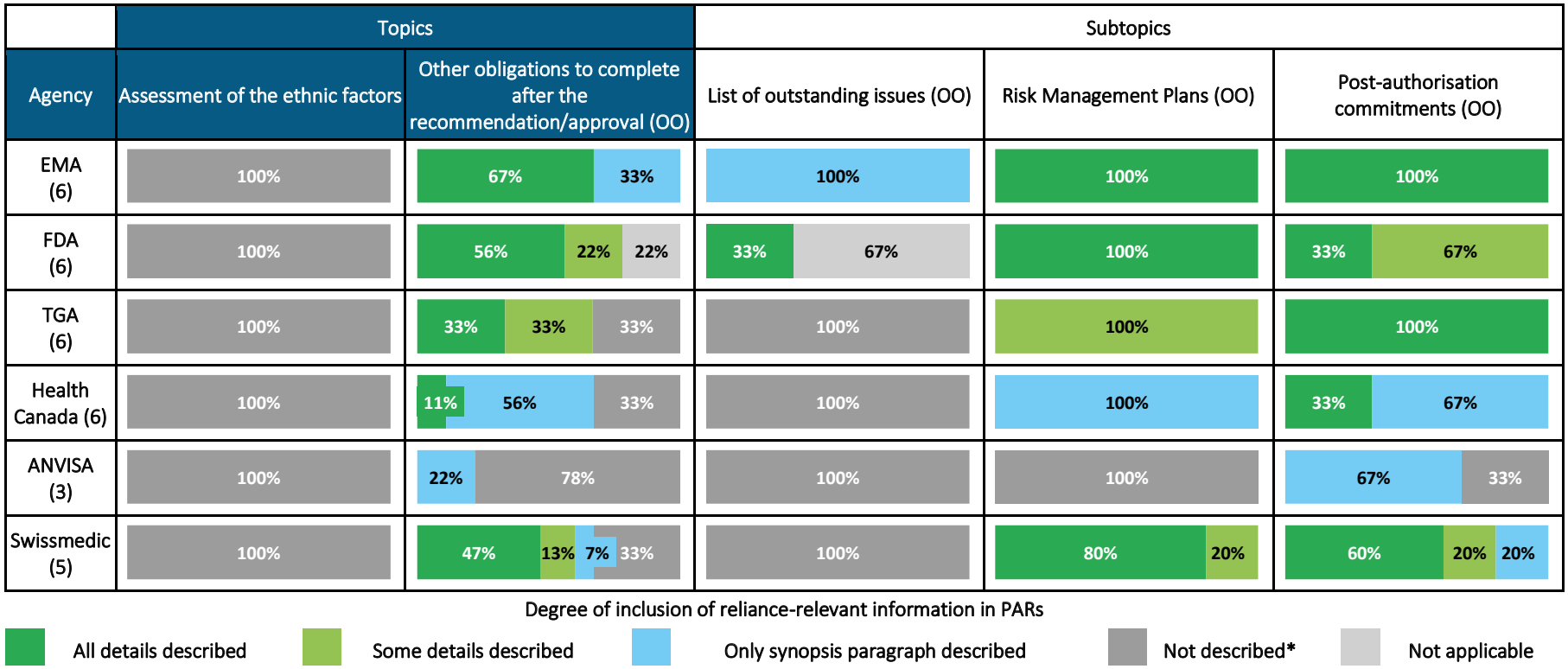
*Figure 15. Inclusion of reliance-relevant information in PARs, by agency, topic and subtopic for the Benefit-Risk Assessment (B-R) section (cont.)*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

*Figure 16. Inclusion of reliance-relevant information in PARs, by agency, topic and subtopic for the Benefit-Risk Assessment section (cont.)*




*(n): Number of public assessment reports (PARs).*

**: Not described in the PAR, but it should be noted that this information may be included in other documents (e.g., the MAA dossier, CPPs, and/or the respective non-public assessment reports). As an example, a summary of a mapping exercise conducted by a pharmaceutical company to show the "list of consolidated key information needed for reliance" against the CTD sections can be accessed here.*

## *Key messages:*

- In general, the Benefit-Risk Assessment section ranked 3rd in terms of degree of inclusion regarding reliance-relevant information compared to the other five PAR sections.
- Across the agencies, the PARs from EMA contained the highest proportion of reliance-relevant information, followed by FDA, TGA, Health Canada, Swissmedic and ANVISA.
- Regarding specific topics and subtopics:
    - In general, most of the reliance-relevant information related to the ***"benefit-risk assessment"*** topic was described in the agency PARs, where 100% of such information was described in EMA PARs, followed by TGA (85%), FDA (84%), Health Canada's (78%), ANVISA (67%) and Swissmedic (55%).
    - The results for the ***"benefit-risk assessment"*** topic were also displayed by subtopic to provide additional granularity.
    - All assessed PARs from EMA, FDA, TGA, and Health Canada, as well as 40% of Swissmedic's PARs detailed reliance-relevant information related to the ***"context in which the decision was taken"*** subtopic.
    - Additionally, the quality, non-clinical and clinical conclusions were generally described by the agencies in their respective PARs.
    - Most of the PARs assessed in this study contained reliance-relevant information relating to the ***"identified benefits",*** the ***"identified risks"***, and the ***"conclusion of the benefit-risk assessment"*** subtopics.
    - The reliance-relevant information regarding the ***"uncertainties associated with benefits"*** and the ***"uncertainties associated with risks"*** subtopics were generally not described or less well described except for all of EMA's PARs, followed by 40% of Swissmedic's PARs, 33% of TGA's PARs and 17% of the PARs developed by FDA and Health Canada (for the latter agency the percentage only applies to ***"uncertainties associated with risks"*** subtopic).
    - ***"Assessment of the ethnic factors"*** topic was not described within the specific summary benefit-risk section for these products.
    - In addition, the information regarding the ***"list of outstanding issues"*** subtopic was generally not found in agency PARs, except for FDA with 33% of PARs (where the rest were not applicable) and for EMA, where only a synopsis paragraph was described.
    - The reliance-relevant information about the ***"risk management plans"*** subtopic was found in all assessed PARs developed by EMA, FDA, TGA and Swissmedic when applicable.
    - In addition, the reliance-relevant information about the ***"post-authorisation commitments"*** subtopic was found in all PARs developed by EMA, FDA, and TGA, followed by 80% of Swissmedic's PARs and 33% of Health Canada's PARs.

# Conclusion

The WHO has recommended PARs as primary sources of information (WHO, Annex 10) to enable regulatory reliance, however, these documents were not initially developed for this purpose.

Therefore, this study sought to determine to what extent reference agency PARs can guide regulatory decision making by health agencies that use the documentation to undertake a risk-based review.

## Overall findings

In this study, 33 PARs developed by seven reference agencies (FDA, EMA, Health Canada, Swissmedic, TGA, ANVISA and MHRA) were assessed. One of the limitations of this study is the relatively small cohort of compounds assessed and the depth of data analysed. This should be particularly highlighted for ANVISA, which started to publish PARs only very recently and therefore, only three PARs were assessed. In addition, although the analysis of PARs for major line extensions was initiated, this was not possible as only selected agencies produce PARs relating to these products. Therefore, utilising PARs beyond initial authorisation and during the product lifecycle is currently a challenge.

In general, based on the new active substance PARs assessed, the study found that publicly available reference agency documentation contains the majority of information that relying agencies may require for reliance, particularly for the Clinical, Benefit-Risk Assessment and Regulatory Background sections. However, a certain level of detail was missing, for example, “Questions and answers raised during the scientific assessment”, “Description of GCP certifications”, “Uncertainties associated with benefits and risks” as well as “assessment of ethnic factors”.

In addition, the information relating to Non-clinical and, more importantly, the CMC section was less complete, particularly “Certification of the manufacturing facilities” and “Raw materials (e.g., manufacture, quality and stability of the API, excipients)”. Consequently, agencies that require the detailed information found in those two sections will need additional information beyond the PAR, obtained directly from the reference agency (e.g. non-public assessment report) or the applicant (e.g. the dossier), to undertake a reliance review.

Important information for agencies’ risk-based decision making may be included in other documents, particularly the dossier submitted in the MAA to the relying agency, CPPs, and/or the respective non-public assessment reports, including the Q&A developed by the reference agency and the applicant. The dossier will contain relevant data, while the assessment report details how this information was considered by the agency. These other documents were not assessed in this study, which was limited to PARs only.

In conclusion, there is no single PAR that contains all the reliance-relevant information based on the generic list utilised in this study. PARs contain useful information that can be leveraged to enable reliance, and together with other documents such as the dossier, can be used to inform regulatory decisions. However, their usability for risk-based review will depend on the relying agencies’ guidelines and requirements.

Additional efforts should focus on raising awareness of the importance of PARs for the purpose of reliance; improving the availability, completeness and usability of PARs; and advocating for a common harmonised PAR template or comparable relevant elements within a PAR, which can be used by current and emerging reference agencies. Additional recommendations based on this study are outlined below.

# Recommendations

## For reference agencies

Reference agencies should consider:

- Becoming more cognisant of how relying agencies use their PARs for reliance purposes. To enhance risk-based decision-making activities, reference agencies may consider reviewing their PARs' content while keeping relying agencies in mind and the information they require. This can help support future PAR revisions and strengthen collaboration between agencies.
- Establishing communication channels and platforms for addressing questions the relying agency may have relating to the decision making as well as sharing additional reliance-relevant information with agencies, not published as part of a PAR (e.g. Interim assessment reports, questions and answers, scientific advice). This will help relying agencies to understand further the decision-making process of a reference agency.
- Ensuring that PARs are published not only relating to the initial authorisation of the product but also for extensions of indications, and quality and manufacturing changes to enable the use of PARs for reliance throughout the lifecycle of a medicine.
- Aligning PARs across agencies regarding the content/format of the PAR and the information included.

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## For applicants

Applicants should consider:

- Establishing communication channels and platforms for sharing additional reliance-relevant information with the relying agency.
- Being transparent on any product differences between applications to the reference and relying agency, and providing justification for those differences.

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## For relying agencies

Relying agencies should consider:

- Understanding the decision-making approach and context of the reference agency and the grounds in which a PAR was developed.
- Utilising PARs or other publicly available documents as sources of information for reliance purposes if permitted by the national regulatory framework.
- When the information cannot be obtained from publicly available documents, it may need to be obtained from the dossier or from the reference agency directly (e.g. non-public assessment report). Nonetheless, for the latter scenario, before requesting information from the reference agency, memorandums of understanding or cooperation agreements may need to be in place.
- Applying caution where the product was reviewed by the reference agency itself through a reliance or a work-sharing project (e.g., Access Consortium) as there may be gaps in certain PARs if a reference agency did not review certain information in full. In this case, all the relevant sections of the PARs – of all work-sharing agencies or the initial reference agency- might need to be reviewed and considered.

# Future work

- Expand this study to additional PARs to further confirm the generalisability of the findings from this analysis. This would also enable a deeper analysis of the key product and agency specific factors that impact the availability and completeness of information in a PAR.
- Analyse other documents such as the dossier or non-public assessment reports to determine whether reliance-relevant information, particularly where it cannot be found in a PAR, is included elsewhere, and whether this is documented systematically across different products.
- Survey relying agencies as users of the reference agency PARs to uncover additional challenges and opportunities in utilising publicly available documents for reliance purposes. Such a survey could also explore what additional non-publicly available information is needed by relying agencies to support reliance decision making and how the information is being used.
- Explore the feasibility of a standardised PAR template that could be implemented by current and future reference agencies with common PAR headings and acceptable content. The latter could be done through dialogue in existing multistakeholder (including the applicant) and cross-agency fora.
- Develop a manual on how agencies can utilise PARs for their decision making when undertaking a reliance review.

# Appendix

## Definitions

**Accelerated/ Conditional/ Provisional approval.** Type of approval granted to promising drugs for serious conditions, using available information, surrogate endpoint(s) from phase 2 trials or interim phase 3 data; confirmatory trials with hard clinical endpoints required.

**Advanced therapy medicinal product (ATMP).** Medicine for human use that is based on genes, tissues or cells that offers groundbreaking new opportunities for the treatment of disease and injury.

**Biological product.** A substance isolated from animal tissues or product produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants) for therapeutic, prophylactic or in vivo diagnostic use in humans.

**Collaborative review (Project Orbis).** An initiative of the FDA Oncology Center of Excellence (OCE) that provides a framework for concurrent submission and review of oncology products among international partners –Australia-Brazil-Canada-Singapore-Switzerland-UK-US.

**Earlier/ Intensive dialogue review.** Enhanced interaction and early dialogue with developers of promising medicines to optimise development and speed evaluation (e.g., PRIME for EMA, Breakthrough and Fast-track designations for FDA).

**Expedited review.** Refers to the 'Accelerated Assessment' of EMA, the 'Priority Review' made by FDA, Health Canada, Swissmedic, and TGA, and the priority review described in RDC 204/2017 made by ANVISA.

**Facilitated regulatory pathway (FRP).** A regulatory pathway designed to facilitate availability, review and/ or approval of medicines where there is an unmet medical need by providing alternatives to standard regulatory review routes.

**List of outstanding issues.** A set of questions addressed to a company during a procedure, such as the evaluation of a marketing authorisation application. Lists of outstanding issues are prepared after a company has already responded to a list of questions.

**Major line extension (MLE).** Modification to an authorised medicinal product that is sufficiently great enough that it cannot be considered a simple variation to the original product but requires a new product authorisation. Such modifications include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system.

**New active substance (NAS).** A chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a prescription-only medicine, to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. The term NAS also includes:

- An isomer, a mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available.
- A biological or biotech substance previously available as a medicinal product, but differing in molecular structure through changes to the nature of source material or manufacturing process and which will require clinical investigation.
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

Applications that are excluded from the study:

- Vaccines.
- Biosimilars.
- Any other application where new clinical data were submitted.
- Generic applications.

Those applications where a completely new dossier was submitted from a new company for the same indications as already approved for another company.

Applications for a new or additional name, or a change of name, for an existing compound (i.e., a "cloned" application).

Emergency use or Special authorisations derived from an emergency (e.g., COVID-19 pandemic).

**Public assessment report (PAR).** A set of public resources that provide information regarding the results of the evaluation process of a marketing authorisation application for a new drug or additional indication of a medicinal product.

**Redact.** The act whereby a regulatory authority removes confidential information from texts before making it available to the public.

**Reliance.** The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessment performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

Reliance refers to the Art 13 TPA procedure for Swissmedic, the comparable overseas regulators type A procedure (COR-A) for TGA and EC decision reliance procedure for MHRA.

**Relying agency.** Regulatory authority that takes into account and gives significant weight to the assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision.

**Work-sharing review (Access Consortium).** Coalition to maximise international cooperation, reduce duplication, and increase each agency's capacity ensuring timely access to high-quality, safe and effective medicines for patients. As part of the work-sharing process, the agencies review different parts of the dossier. Although the review is shared, each regulator makes an independent decision regarding approval (market authorisation) of the new medicine.

**Small-molecule drugs/ Chemical entities.** An entity produced by chemical synthesis.

## Data sources

For the development of this study, CIRS consulted the following data sources:

**CIRS' Regulatory Review Times Database.**

**For FDA:**

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

**For EMA:**

https://www.ema.europa.eu/system/files/documents/other/medicines_output_european_public_assessment_reports_en.xlsx

https://www.ema.europa.eu/system/files/documents/other/medicines_output_summaries_of_opinion_en.xlsx

https://www.ema.europa.eu/system/files/documents/other/medicines_output_orphan_designations_en.xlsx

**For Health Canada:**

https://hpr-rps.hres.ca/reg-content/summary-basis-decision.php

https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

**For Swissmedic:**

https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/swisspar.html

https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/public-summary-swisspar.html

**For TGA:**

https://www.tga.gov.au/resources/auspar

https://www.tga.gov.au/resources/auspmd

https://www.tga.gov.au/resources/artg

**For ANVISA:**

https://consultas.anvisa.gov.br/#/medicamentos/

https://consultas.anvisa.gov.br/#/bulario/

https://consultas.anvisa.gov.br/#/pareceres/

**For MHRA:**

https://www.gov.uk/government/collections/marketing-authorisations-lists-of-granted-licences

https://products.mhra.gov.uk/

## Documents that formed part of the assessed PAR documentation.

For most agencies, PARs are not single documents but information resources containing several components, including a core set of regulatory documents. Consequently, multiple documents were assessed for each agency, as outlined below:

**For FDA:**

- **Approval Letter(s).**
- **Printed Labeling.**
- **Chemistry/Product Quality Review(s).**
- **Summary Review(s).**
- **Clinical/Medical Review(s).**
- **Non-Clinical Review(s).**
- **Statistical Review(s).**
- **Clinical Pharmacology and Biopharmaceutics Review(s).**
- Proprietary Name Review(s).
- Officer/Employee List.
- **Other Review(s).**
- **Risk Assessment and Risk Mitigation Review(s).**
- Administrative and Correspondence Documents.

**For EMA:**

- **Medicine overview.**
- **Public summary of opinion on orphan designation (for orphan drugs).**
- **Orphan maintenance assessment report (for orphan drugs).**
- **CHMP summary of positive opinion.**
- **CHMP assessment report (EPAR).**
- **Risk management plan summary.**
- **Product information.**
- **For Health Canada:**
- **Summary basis of decision (SBD).**
- **Product monograph.**

**For Swissmedic:**

- **Swiss public assessment report (SwissPAR).**
- **Public Summary SwissPAR.**
- **Summary of the risk management plan.**
- **Product information for human medicinal products.**

**For TGA:**

- **Australian public assessment report (AusPAR).**
- **Australian product information (AusPI).**
- **Consumer medicine information (CMI).**
- **Public Summary**.

**For ANVISA:**

- **Public opinion of drug assessment (PPAM).**
- **Patient information leaflet (Bula do paciente).**
- **Healthcare professional information leaflet (Bula do profissional).**

**For MHRA:**

- **Public assessment report (MHRA PAR).**
- **Patient information leaflet (PIL).**
- **Summary of Product Characteristics (SmPC).**

The documents highlighted in **bold** represent the documents that were found, following the evaluation of the PARs, to contain information relevant to reliance.

## List of topics and subtopics - reliance relevant information

| Section | Topic | Subtopic |
|---|---|---|
| 1. Regulatory Background | 1. List of steps taken in the regulatory process of the product within the individual agency. | 1. List of steps taken in the authorisation process of the product.<br>2. The dates on which the steps were taken in the authorisation process of the product. |
| | 2. List of countries in which the product has been approved, withdrawn, or rejected. | 1. A list of the countries where the product was approved.<br>2. The dates on which the countries approved the finished pharmaceutical product. |
| | 3. Questions and answers raised during the scientific assessment. | 1. The questions and answers that were raised before the final decision of the agency. |
| | 4. Summaries of meetings (e.g., within the agency, with companies). | 1. The dates when meetings took place.<br>2. The topics addressed in meetings. |
| | 5. Discussion of a divergent decision within the agency. | 1. The reasons why a divergent decision occurred. |
| | 6. Labelling (e.g., Package insert and leaflet). | 1. Description of the information aimed to be shared with healthcare professionals.<br>2. Description of the information aimed to be shared with patients.<br>3. Description of what must be shown on the label of the product. |
| | 7. Final decision of the agency. | 1. Description of the nature of the final decision of the agency.<br>2. The date of the final decision of the agency. |
| | 8. Rationale for orphan designation. | 1. May not be applicable. Description of whether the medicine has been granted an orphan drug status.<br>2. May not be applicable. The date when the orphan drug status was granted.<br>3. May not be applicable. The reasons why the orphan drug status was granted. |
| | 9. Rationale for using FRPs by the agency. | 1. May not be applicable. Description of whether FRPs were used by the agency when authorising the product and its rationale for using FRPs. |

| Section | Topic | Subtopic |
|---|---|---|
| 2. CMC | 1. Certification of the manufacturing facilities. | 1. For the drug substance: Date(s) on which the manufacturing facilities were inspected or certified.<br>2. For the drug substance: Description of the activities that were done for the inspection or certification of the manufacturing facilities.<br>3. For the drug substance: The address(es) of the inspected or certified manufacturing facilities.<br>4. For the finished pharmaceutical product: Date(s) on which the manufacturing facilities were inspected or certified.<br>5. For the finished pharmaceutical product: Description of the activities that were done for the inspection or certification of the manufacturing facilities.<br>6. For the finished pharmaceutical product: The address(es) of the inspected or certified manufacturing facilities. |
| | 2. Raw materials (e.g., manufacture, quality and stability of the API, excipients). | 1. Description of the analytical methods.<br>2. Description of the container closure system.<br>3. Description of the critical quality attributes (CQA).<br>4. Description of the manufacturing process.<br>5. Description of the storage conditions.<br>6. List of intermediate products.<br>7. List of reference materials. |
| | 3. Finished pharmaceutical product (e.g., manufacture, quality and stability of the finished dosage form). | 1. Description of the analytical methods.<br>2. Description of the container closure system.<br>3. Description of the critical quality attributes (CQA).<br>4. Description of the manufacturing process.<br>5. List of reference materials.<br>6. Qualitative list of raw materials, including excipients.<br>7. Quantitative list of raw materials, including excipients. |
| | 4. Transportation and storage conditions. | 1. Description of the atmospheric conditions to be kept when storing finished pharmaceutical product.<br>2. Description of the time in which the finished pharmaceutical product can be stored without compromising its integrity. |

| Section | Topic | Subtopic |
|---|---|---|
| 3. Non-clinical | 1. Non-clinical studies. | 1. List of studies performed.<br>2. Description of the purpose of each study.<br>3. Description of the study setup.<br>4. Description of the models used.<br>5. Description of the analytical methods used.<br>6. Description of granular results.<br>7. Description of GLP certifications.<br>8. Description of overall results. |
| 4. Clinical | 1. Therapeutic indication and dose. | 1. Description of the approved dose and its dose modifications if applicable.<br>2. Description of the approved therapeutic indication. |
| | 2. Clinical studies (e.g., pivotal and supplemental). | 1. Description of GCP certifications.<br>2. Description of granular results.<br>3. Description of overall results.<br>4. Description of the analytical methods used.<br>5. Description of the purpose of each study.<br>6. Description of the size of studied populations.<br>7. Description of the study setup.<br>8. Description of the types of studied populations.<br>9. List of studies performed. |
| | 3. Effects and precautionary actions in diverse populations. | 1. Description of the effects of the finished pharmaceutical product among different types of populations.<br>2. May not be applicable. Description of the precautionary actions when using the finished pharmaceutical product by different types of populations. |

| Section | Topic | Subtopic |
|---|---|---|
| 5. Benefit-Risk Assessment* | 1. Benefit-Risk Assessment. | 1. Description of the context in which the decision was taken.<br>2. Description of the Quality conclusion.<br>3. Description of the Non-clinical conclusion.<br>4. Description of the Clinical conclusion.<br>5. Description of the identified benefits.<br>6. Description of the uncertainties associated with benefits.<br>7. Description of the identified risks.<br>8. Description of the uncertainties associated with risks.<br>9. Description of the conclusion of the Benefit-Risk Assessment. |
| | 2. Assessment of the ethnic factors. | 1. Description of a section dedicated to the assessment of the ethnic factors within the Benefit-Risk Assessment. |
| | 3. Other obligations to complete after the recommendation/approval. | 1. May not be applicable. The list of outstanding issues.<br>2. Description of the Risk Management Plans.<br>3. Description of the post-authorisation commitments. |

*: These data are unique to assessment reports, and are not included in the MAA dossiers.

# About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS provides an international forum for industry, regulators, health technology assessment (HTA) and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science and to facilitate access to pharmaceutical products. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

## Briefing prepared by

**Juan Lara,** Senior Research Analyst

**Magda Bujar,** PhD, Senior Manager, Regulatory Programme & Strategic Partnerships

**Neil McAuslane,** PhD, Scientific Director

**Mario Alanís,** PhD, Senior Consultant

**Anna Somuyiwa,** Head

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### Centre for Innovation in Regulatory Science (CIRS)

70 St Mary Axe, London EC3A 8BE, UK

cirs@cirsci.org

www.cirsci.org

www.linkedin.com/company/centre-for-innovation-in-regulatory-science-ltd/

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