Operational Procedures (OP)

Access Consortium
New Active Substance Work-sharing Initiative (NASWSI)

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Introduction

This document outlines operational procedures and recommendations for the planning and implementation of the New Active Substances Work-sharing Initiative (NASWSI) for the regulatory agencies within the Access Consortium:

- Therapeutic Goods Administration (TGA) – Australia
- Health Canada (HC) – Canada
- Health Sciences Authority (HSA) – Singapore
- Swissmedic (SMC) – Switzerland
- Medicines and Healthcare products Regulatory Agency (MHRA) – United Kingdom

As part of the NASWSI, a joint review may be considered for new chemical entity or new biological entity applications, or new indication applications that are submitted to two or more Access agencies.

For new chemical or biological entity applications, the submission will be divided into modules, with each module, or in some cases designated sections within a module, reviewed by a specific agency. Other participating agencies conduct a peer review of the assessment reports for each module. Each agency is also responsible for the review of their relevant Module 1.

For new indications applications, generally one agency will evaluate Module 5. Other participating agencies conduct a peer review of the assessment reports and also evaluate their respective Module 1.

Each agency makes its own sovereign decision based on the recommendations contained in the assessment reports. Where during the process, it becomes apparent that there are insurmountable issues with the data that the participating agencies are unable to reconcile, the agencies have the option to seek additional information and undertake further review.

Applicant and application selection

Applicants considering taking part in the NASWSI should initiate early communication with the Access agencies in the countries where they propose to submit their application to discuss the suitability of their application.

Potential applicants will be required to work collaboratively with the agencies throughout the procedure.

Requirements for applications

Applications should be submitted simultaneously to at least two, but preferably more, of the Access agencies. The formal work-sharing procedure described in this Operational Procedures document will commence on submission of an Expression of Interest (EoI) form (see below).

A joint review may be considered for:

- new chemical entity or new biological entity applications
- new indication applications.

Applications submitted under the standard or priority review pathways may be eligible for the NASWSI. The same assessment pathway (standard or priority) must be used in all participating jurisdictions. Applicants are required to indicate the pathway they intend to use in the EoI.

A joint review will not be considered for:

- applications for provisional or conditional approvals
- variations to products previously authorised through the NASWSI procedure (other than new indications applications).

Dossier requirements

The dossiers submitted should comprehensively address the requirements of all jurisdictions proposed for work-sharing.

It is expected that the applicant submits the same data set for Modules 2-5 to all agencies. However, if there are differences, the completed "Summary of Differences" table (included in the EoI form) should be submitted, outlining the differences in the information provided to each participating agency. The participating agencies will consider these differences to determine if the application is suitable for the NASWSI. It is acknowledged that Module 1 will continue to be different for the dossiers filed in the different Access jurisdictions (as per regional requirements).

Dossiers must be submitted in eCTD format to all agencies where eCTD is allowed.

Phase 1: Pre-procedure – confirmation of operational approach

The pre-procedure covers the process steps and issues that will be considered before an application is accepted for the NASWSI. These steps need to be completed concurrently within the regulatory systems of the participating agencies.

Technical (scientific) pre-submission meeting/teleconference

A technical pre-submission meeting or teleconference with the applicant is recommended. It is recommended that these meetings be held bilaterally for each jurisdiction. Joint meetings, with two or more regulators can be requested, but may not be granted due to operational and resource challenges.

Applicants are required to follow the usual procedure of their local agency when requesting a technical pre-submission meeting.

Note the technical pre-submission meeting can occur after the submission of the EoI.

Submission of EoI

Interested applicants should submit an EoI at least 3 months in advance of their anticipated filing date to each agency proposed for work-sharing. Once an EoI form has been submitted, the participating agencies will discuss the suitability of the application for the NASWSI and the next steps via email and/or teleconference.

Priority review request

Where applicable[1], applicants should submit their priority review request at least 3 months in advance of filing. Priority review status, where it is available, will generally need to be determined in each jurisdiction before Access partners allocate review responsibilities.

[1] Note that only TGA, HC and SMC have formal priority pathways. However, in appropriate circumstances, HSA and MHRA may agree to an expedited review to enable participation in the NASWSI.

Role determination for Access partners

The Access agencies will consider their operational needs when allocating review responsibilities for the dossier.

There will be models for 2, 3, 4 and 5-way work-sharing. As an example, for a new chemical entity application involving three regulators the joint review could consist of one agency reviewing module 3 data, one agency reviewing module 4 data and another agency reviewing the module 5 data.

Responsibility for the review of aspects related to more than one module (e.g. impurities) or where the data is evaluated by different groups within the Access agencies (e.g. bioavailability) will be determined on a case-by-case basis. As an example, if a toxicological assessment of impurities is required, it will be directed to the agency that is responsible for the non-clinical review.

Note – The lead for the clinical review will coordinate the logistical pre-submission meeting on behalf of Access partners, where one is requested (see below).

Development of an evaluation plan and timeline

Access agencies will develop an evaluation plan with specific milestones that allows each agency to meet their legislative obligations and/or performance standards.

In addition to the expected evaluation timeline, the Access agencies will also confirm the approach for agency questions raised during the assessment phase:

- For joint review of an application under the standard pathway, agency questions will generally be issued as part of a consolidated list of questions (LoQ) at the end of the round 1 evaluation (Milestone 3). Access agencies may, however, indicate a preference to issue evaluation questions throughout the evaluation period (via "rolling questions") for the module they are responsible for.[2]
- For joint review of an application under the priority review pathway, agency questions will be issued as "rolling questions" throughout the evaluation period (i.e. during Phase 2).

Logistical pre-submission teleconference

In addition to the technical discussions that may occur between each agency and the local applicant, a logistical pre-submission teleconference between the applicant and the Access agencies is recommended.

The aim of the logistical pre-submission teleconference is to discuss and confirm the logistics and expectations related to the requirements, timelines and processes specific to work-sharing, and allow the agencies to respond to any queries from the applicant.

It is recommended that the teleconference takes place at least two months prior to the filing of the application.

The applicant will be requested to:

- provide a list of queries for the Access agencies at least two weeks in advance of the pre-submission teleconference
- complete a meeting record summarising the agreed outcomes and actions arising within two weeks of the meeting.

[2] Note the NASWSI does not allow rolling submission of data by applicants during the evaluation phase. Applicants must lodge a complete dossier at the time of submission.

Phase 2: Application submission and assessment

All timelines described below should be interpreted as "calendar days". If a milestone falls on a weekend or a national holiday, the milestone will be the preceding business day.

The evaluation timeframes outlined below are the default timeframes for a NASWSI application using the **standard pathway**. These are *target timeframes* that will allow all Access agencies to meet their legislative obligations and/or performance standards. Participating agencies may agree to modified timeframes in consultation with applicants.

If any changes to the evaluation plan are required during the evaluation, e.g. changes to applicant response times or delays to reviews, the Access agencies will correspond with the applicant to seek agreement.

For a NASWSI application using the **priority pathway**, the evaluation plan will be customised for each application.

Milestone 1: Submission of the application

Applications should be submitted to each agency simultaneously or as agreed with the agencies.

Milestone 2: Acceptance of Application

Timeframe: 30 to 45 days [3]

After receipt of the application, the agencies will:

- independently perform the technical and administrative screening of the application to ensure that their legislative and data requirements are met (e.g. application forms, user fees)
- inform the local applicants of the acceptability of the application for assessment following their usual procedure.

The day of acceptance of the application for assessment is "Day 0" of the NASWSI process.

Note – screening timeframe may vary between agencies, however the goal is to have the submission enter review on the same date in all participating jurisdictions.

Assessment of dossier — **Timeframe: 90 days**

Access agencies will review and prepare an Assessment Report (AR) and a List of Questions (LoQ) for the module(s) they are responsible for using their own national guidelines.

Each agency will follow their usual procedure for reviewing its respective Module 1.

Where an application (priority review pathway) or individual module is being reviewed using rolling questions rather than a LoQ:

- The Access agencies will issue rolling questions throughout the evaluation at set time points wherever possible. For example, one scenario could be, starting at day 60 and then once a month until day 150 (i.e. 4 rounds in total).
- Applicants are required to provide responses to rolling questions within 15 days.

Peer review — **Timeframe: 25 days**

The Access agencies will conduct a peer review of the AR and LoQ:

- consulting the modules (as needed) and sharing additional questions on relevant modules

[3] From filing to acceptance for assessment.

with the reviewing agency
- undertaking any necessary supplemental evaluations of the relevant module(s) where there are additional country-specific requirements or guidelines that need to be considered.

Evaluator teleconferences will be scheduled to discuss aspects of the review as necessary. Feedback and any additional questions may be provided to the reviewing agency for consideration and discussion.

Finalisation of the ARs and LoQ **Timeframe: 5 days**

Access agencies will finalise the consolidated LoQ on Modules 2-5 (excluding any questions issued by rolling questions) and their respective LoQ on Module 1 as applicable (including questions on product information and labelling).

Milestone 3: Consolidated LoQ issued to the applicants

Each agency will send to their local applicant:

- the consolidated LoQ
- a copy of the AR(s) they have prepared, where this is part of their usual procedure.[4]

The LoQ will be divided into a common set of questions (common to all participating agencies), and country-specific questions (relating to Module 1 as well as any country-specific questions for the other modules). The country-specific questions will be identified using prefix letters A (Australia), or C (Canada), S (Singapore), CH (Switzerland), UK (United Kingdom), e.g. A1, A2 etc.

Note that the agencies will not provide copies of assessment reports prepared by another agency.

Milestone 4: Response to the consolidated LoQ **Timeframe: 30 or 60 days**

Applicants are required to send complete responses to the consolidated LoQ to each agency as follows:

- responses to all common questions should be submitted to each agency
- responses to country-specific questions for Modules 3-5 need only be submitted to the applicable agency, unless requested as an FYI.

The dossier must be updated in all jurisdictions to ensure that the application is complete. If required, a 'catch-up' sequence can generally be provided towards the end of the evaluation process that includes any updated data for Modules 3-5.

The time for the response to the consolidated LoQ will be either 30 or 60 days as nominated by the applicant in the EoI.

Note – participating agencies may agree to modify the LoQ response period in consultation with the applicant.

Assessment of responses to LoQ **Timeframe: 25 days**

The Access agencies will:

- review the responses to the LoQ and update the ARs for the module(s) they are responsible for
- prepare an AR of responses to their respective LoQ on Module 1 and any supplemental

[4] TGA and MHRA will share their AR at Milestone 3.

evaluations of the other modules.

Peer review **Timeframe: 15 days**

The agencies will conduct a peer review of the AR of the responses.

Milestone 5: Finalisation of the ARs **Timeframe: 5 days**

Where there are no outstanding issues the report(s) will be finalised and the agencies will proceed to follow Phase 3 National Steps.

If necessary, the agencies may prepare an additional (second) LoQ to seek further clarification on any outstanding issues, which each agency sends to their local applicant.

If the additional LoQ are country-specific, the other agencies may elect to proceed to follow Phase 3 National Steps.

Submission of responses to additional LoQ by applicant **Timeframe: 15 days** [5]

If required, the applicant sends responses to any additional questions to all participating agencies via the respective local applicants.

Assessment of responses to additional LoQ **Timeframe: 15 days** [5]

The reviewing agencies will review the responses to the LoQ and update the ARs as necessary.

Where relevant, Access agencies conduct a peer review of AR of the responses and provide feedback. Access agencies will finalise the AR(s).

Milestone 6: Conclusion of formal work-sharing

Total maximum elapsed time from acceptance of the application to the start of the national steps: 225-255 calendar days [180 days excluding applicant time/stop-clocks]

The work-sharing process formally concludes at the end of the evaluation phase as the process enters into Phase 3 National Steps. Each agency will progress towards making a final decision (or seeking further clarification on issues separately before making a final decision) by undertaking necessary administrative steps to finalise the application process domestically.

Phase 3: National steps

National steps may include expert advisory committee meetings, and the finalisation of product labelling. To ensure all agencies can follow their national steps in a timely manner, the agencies may customise the evaluation plan beyond Milestone 5.

During the national steps, the Access agencies may continue to share information, such as outcomes of expert advisory committee meetings, and discuss issues concerning the labelling and packaging material.

Note: While there may be discussions between regulators about product labelling during the evaluation phase, different laws and frameworks exist in each country which affects regulatory decisions related to product labelling. It is likely that product labelling will differ from one jurisdiction to another.

[5] Depends on nature of unresolved issues.

Milestone 7: Separate sovereign decisions

The Access agencies will:

- independently inform the local applicant of their decision to grant or refusal to grant market authorisation
- publish a public assessment report or similar document in accordance with their usual procedures.

These communications may not be simultaneous.

Market authorisation or refusal of market authorisation by one regulator will not affect the decision or the timing of the decision by the remaining participating regulators.

Where a submission is not considered approvable by an Access agency, its national procedures will apply.

Target evaluation plan of the Access NASWSI standard procedure

All timelines described below should be interpreted as "calendar days" including applicant time/stop-clocks [or calendar days excluding stop-clocks].
If a milestone falls on a weekend or a national holiday, the milestone will be the preceding business day.

Milestone	Timeframe	Action	Comments / Agency-specific information
Phase 1: Pre-procedure – confirmation of operational approach			
	>3 months pre-submission	Submission of EoI	
	~3 months pre-submission	Technical pre-submission meeting	Between Access agency and applicant within each jurisdiction Can occur before submission of EoI
	3-4 months pre-submission	Priority review request	If pursuing priority pathway (only TGA, HC, SMC have formal pathway)
		Role determination & development of evaluation plan	Occurs between Access agencies
	>2 months pre-submission	Access logistical pre-submission meeting (optional)	Involving all participating Access agencies and applicants
1	Day -45 to Day -30	Submission of application for screening	TGA: applicant to also submit PPF before (timing can be negotiated) MHRA: 14 days for screening HC: 45 days for screening (standard submission); 25 days for screening (priority review submission)
Phase 2: Application submission and assessment			
	Target timeframes for standard pathway – Calendar days [Calendar days excluding stop-clocks]		
2	Day 0	Acceptance of application / Commencement of evaluation	
	Day 60, 90, 120, 150	*Rolling Qs issued*	*If applicable for a particular Module. Attempts will be made to develop a schedule for rolling questions where possible.*
	Day 75, 105, 135, 165	*Response to rolling Qs*	
	Day 90	Rd 1 reports exchanged and Access agencies begin peer-review	
3	Day 120	Finalisation of Rd 1 reports Consolidated Rd 1 LoQ issued to applicant	
4	Day 150 / 180 [120]	Response to consolidated Rd 1 LoQ / Commencement of evaluation of response	Applicant nominates response time (30/60 days) in EoI All agencies except HC: clock is stopped during response
	Day 175 / 205 [145]	Rd 2 reports exchanged and Access agencies begin peer-review of Rd 2 reports	
5	Day 195 / 225 [165]	Finalisation of Rd 2 reports Consolidated Rd 2 LoQ issued (if necessary)	SMC: Rd 2 LoQ corresponds to pre-decision

	Day 210 / 240 [165]	Response to consolidated Rd 2 LoQ / Commencement of evaluation of response	All agencies except HC: clock is stopped during response
6	Day 225 / 255 [180]	Conclusion of formal work-sharing	
Phase 3: National steps			
		Expert advisory committee meeting (except HC)	TGA: if required, meetings are held bi-monthly HSA: if required, meetings are held every 3 months SMC: if required, meetings are held monthly and are integrated into Phase 2 MHRA: if required, meetings are held monthly and are integrated into Phase 2
		Finalisation of labelling etc.	
7	Day 300	Separate sovereign decisions	MHRA: decision by Day 255 / 285, i.e. 210 days excluding stop-clocks
		Prepare, review and publish public assessment reports	MHRA: PAR published within 60 days of approval/refusal