Australian Government
Department of Health
Therapeutic Goods Administration

An introduction for external clinical evaluators

Welcome to TGA

Version 1.3, October 2017

TGA Health Safety Regulation

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From the Head, Prescription Medicines Authorisation Branch

Thank you for your interest in undertaking clinical evaluations for the TGA.

I cannot stress enough the importance of having you and your expertise available to produce Clinical Evaluation Reports for prescription medicines. I appreciate you may not be familiar with the work of TGA, and expect that you will find a bewildering array of acronyms, regulatory language and processes. Rest assured, in time you will become familiar with them.

This document contains a series of **Questions and Answers (FAQs)** which we have produced to help orientate you with the work of the TGA.

The FAQs are intended to be a lead into a set of structured **Learning Modules** to help you develop the skills necessary to produce evaluation reports of a standard required by the TGA to meet its regulatory needs. The Learning Modules will be provided to you as part of your training.

Resources that are available to you include:

- the Clinical Evaluation Report template and associated guidelines – this is the template that must be used for all evaluation reports you prepare for us;
- fact sheets setting out the TGA's administrative practices;
- links to international regulator websites – these sites are a valuable source of information about the outcomes of evaluations undertaken overseas and any recent regulatory action taken on the product you are evaluating for us; and
- links to EU guidelines – these guidelines are adopted by the TGA and set out best practice for sponsors for demonstrating quality, safety and efficacy of medicines.

These resources are available online or from the External Evaluation Management Team upon request.

The TGA website also has a news item link which will inform you about any updates to, or recently adopted, guidelines.

Of course we are always looking to improve the information we make available to you and so welcome any feedback you have regarding your interactions with us. Please contact ExternalEvaluations@health.gov.au for matters relating to training and support.

I encourage you to explore and use these resources and trust that your time working with the TGA will be both enjoyable and fulfilling.

Adrian Bootes
Head, Prescription Medicines Authorisation Branch

What does the TGA do?

The TGA is part of the Commonwealth Department of Health, and is responsible for regulating therapeutic goods in accordance with the *Therapeutic Goods Act 1989* and associated regulations.

The types of therapeutic goods regulated by the TGA include prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products.

Before a therapeutic good can be supplied to the Australian market, a company (referred to as the 'sponsor' or 'applicant') must obtain pre-market approval from the TGA and the good must be entered in the Australian Register of Therapeutic Goods (ARTG). The TGA's decision maker (the 'Delegate') must be satisfied that the product meets requisite standards of quality, safety and efficacy before approval can be given. This requires a rigorous scientific evaluation of data submitted by the sponsor and uses expertise from several scientific fields, and includes contributions from external evaluators.

The TGA's pre-market evaluation activities are supported by post-market monitoring and enforcement of standards, and by licensing of Australian manufacturers and verifying overseas manufacturers' compliance with the same standards as their Australian counterparts.

Who will I be interacting with at the TGA?

The TGA is arranged in three major Divisions – Medicines Regulation Division; Medical Devices and Product Quality Division; and Regulatory Practice and Support Division.

You will be producing clinical evaluation reports for the Prescription Medicines Authorisation Branch (PMAB), which sits in the Medicines Regulation Division.

PMAB evaluates new prescription medicines, leading decisions approve or reject the registration of prescription medicines. PMAB contains 6 clinical streams and is responsible for the decision-making for the following types of prescription medicines (amongst other products):

- *Stream 1*: Analgesics, anaesthetics, gastrointestinal and psychoactive products, skin disorder products
- *Stream 2*: Vaccines, anti-infectives and agents for immunological disorders
- *Stream 3*: Cardiovascular, musculoskeletal and renal/urinary tract products
- *Stream 4*: Oncology (solid tumours)
- *Stream 5*: Respiratory products, endocrine, ophthalmic and reproductive products
- *Stream 6*: Haematological disorders

There are 3 groups of people you will be engaging with at the TGA during the course of your work with us:

- **External Evaluation Management Team** – this team comprises administrative staff who deal with:
  - Request for Quotes
  - Outcomes of Quotations
  - Conflicts of Interest
  - Contracts and Contract Variations
  - Issues adhering to due dates
  - Payments

Contact: ExternalEvaluations@health.gov.au or +61 2 6232 8150.

- **TGA Delegates** – these are the people who use your evaluation reports to make decisions about whether or not to approve a medicine for supply in Australia. They review evaluation reports once completed, ensuring that the reports are complete and meet the required standard. Delegates are typically senior Medical Officers in PMAB.

  Note: in the Official Order (which serves as the contract between you and the TGA) the Delegate is identified as the 'Project Officer'. Talk to the Delegate about:
  - Technical issues in relation to the evaluation of an application, including use of the Clinical Evaluation Report template
  - Seeking guidance around requirements of an evaluation
  - Formulating Quotations
  - Feedback on your evaluation report

- **IT support staff** – these are IT specialists who can help you with access and issues arising with the use of TGA software. Contact: +61 2 6232 8900.

NOTE: Always copy ExternalEvaluations@health.gov.au on all correspondence with all TGA contacts.

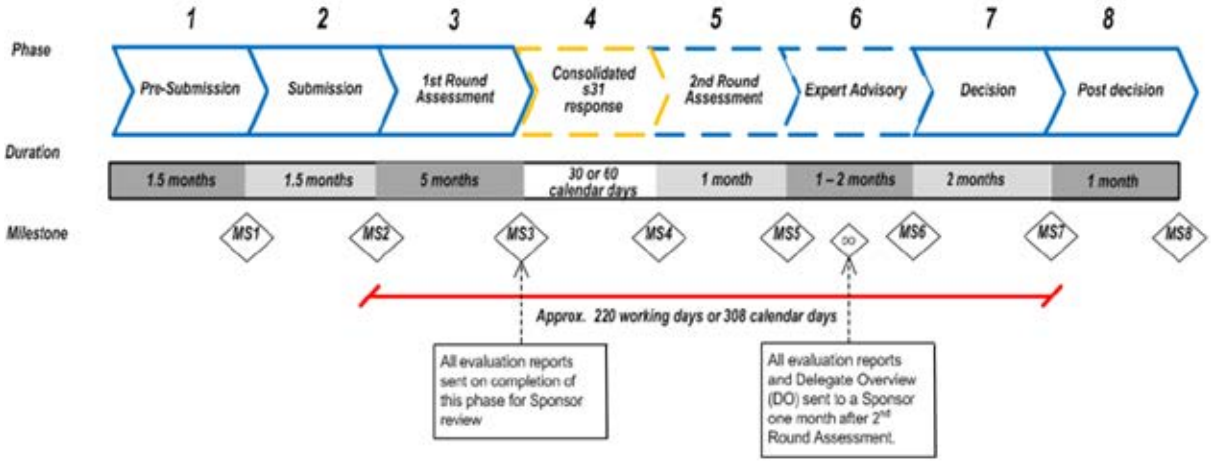
What does the medicines registration process look like?

The prescription medicines registration process comprises 8 basic consecutive stages:

Stage	Description
1. Pre-submission	Sponsor lodges a Pre-submission Planning Form (PPF) advising the TGA of the nature of their application. The sponsor may receive feedback from the TGA on any justifications or other aspects affecting the submission.
2. Submission	Sponsor lodges an application and submits the dossier to the TGA. The TGA considers the application and dossier against regulatory requirements. Applications not provided in accordance with regulatory requirements are not accepted for evaluation.
3. First round evaluation	All contents of the dossier are evaluated and draft evaluation reports are prepared. Each dossier is made up of a number of components including manufacturing, nonclinical, clinical and the sponsor's Risk Management Plan (RMP). Each component is evaluated separately and evaluation reports are prepared.
4. Consolidated questions (section 31)	Questions raised in all of the first round evaluation reports are consolidated and sent to the sponsor as a single formal request for information under section 31 (s.31) of the *Therapeutic Goods Act 1989*. The sponsor nominates in the PPF whether it will respond to the request in 30 or 60 working days. The sponsor is provided with a copy of the evaluation report for each of the components of the submission (with any identifying details removed) so that the sponsor has an opportunity to review each first round evaluation report for factual content.
5. Second round evaluation	The responses provided by the sponsor to the questions are made available to the evaluators. Each evaluator considers the s.31 response for their component (if applicable) and completes the second round of the evaluation. Any outstanding issues are identified in the report and subsequently considered by the Delegate.
6. Expert advisory review	The Delegate reviews the component evaluation reports. The Delegate may seek independent expert advice on aspects of an application if required, in which case a *Request for Advice* is written, containing an overview document which includes key data, a discussion about quality, efficacy and safety, and conclusions and proposed actions. The *Request for Advice* is sent to an advisory committee and copied to the sponsor. The sponsor has an opportunity to provide a response to direct to the committee, addressing issues raised in the Delegate's request for advice. The sponsor also has an opportunity to review the second round evaluation reports for factual content.

Stage	Description
7. Decision	The Delegate makes a decision about the application and informs the sponsor via formal correspondence. Prior to an approval, any outstanding issues pertaining to the Product Information, Consumer Medicine Information and Risk Management Plan are negotiated with the sponsor. For rejections, the Delegate prepares a *Statement of Reasons*, with an explanation of the sponsor's appeal rights.
8. Post decision	The medicine is entered on the Australian Register of Therapeutic Goods. An Australian Public Assessment Report (AusPAR) is also prepared. This document is published on the TGA website and provides information about the evaluation of the medicine and the considerations that led the TGA to approve or not approve an application.

The phases and timelines are shown in the figure below.



The decision to approve the sponsor's application or not is made by an in-house TGA Medical Officer acting under the delegation of powers from the Secretary of the Department of Health. Note: In the Official Order (which serves as the contract between you and the TGA) the relevant delegate is identified as the 'Project Officer'.

Each of the component evaluations (quality, nonclinical, clinical and RMP) are conducted over the course of the first and second rounds. All evaluation reports are reviewed internally by the TGA before they are authorised and sent to the sponsor.

Depending on the type of submission, the delegate's overview and all the evaluation reports are sent to an expert advisory committee for consideration:the Advisory Committee for Medicines (ACM) or the Advisory Committee for Vaccines (ACV). Submissions typically sent to the ACM or ACV include those supporting registration of new chemical entities (NCEs); novel dosage forms; fixed dose combinations of active substances, as well as variations to existing registrations where there are new indications/new patient groups; new routes of administration; and new dosage regimens.

Note: The medicines registration process is separate from, but a precursor to, listing of items on the Pharmaceutical Benefits Scheme (PBS). A medicine can only be considered by the Pharmaceutical Benefits Advisory Committee (PBAC) if it has been or is about to be entered in the ARTG. PBAC accepts that products included in the ARTG have adequate safety and efficacy to allow marketing in Australia. This is the starting point for consideration of effectiveness and cost-effectiveness by the PBAC. Products are registered by the TGA for specific therapeutic

indications and, in general, PBAC does not recommend a product to be listed on the PBS for indications beyond those stated in the ARTG.

The current PBAC process requires the presentation of the TGA delegate's overview for the ACM or ACV at the time a major submission is lodged. (*Note*: Your report does not go to the PBAC.) Subsequently, the resolution of the ACM or ACV also becomes available and is provided to the PBAC prior to the PBAC's consideration of the major submission. The PBAC Secretariat monitors the final TGA indication for differences from PBAC recommended restriction, which may require, on a case-by-case basis, the PBAC to review its recommendation.

Where do external clinical evaluators fit in?

The table below outlines the involvement of clinical evaluators in the various stages of the prescription medicines registration process.

Stage	Description
Pre-submission	Selected external clinical evaluators are sent a Request for Quotation (RFQ) on the cost of providing evaluation services for a proposed submission. The RFQ includes a Statement of Requirement (SOR) that sets out the scope of the submission and its likely contents. Documents made available to the TGA (and provided to the evaluator in the RFQ) include the table of contents and a tabular list of clinical studies. The SOR also identifies the EU guidelines relevant to the evaluation and any issues that need to be covered by the evaluation. Copies of earlier evaluation reports and ACM or ACV advice received for the same or similar products may also be sent as part of the RFQ where appropriate. An Official Order is given to the successful respondent and this (when signed) forms the contract between the TGA and evaluator.
Submission of the dossier	Clinical evaluators are not involved in this stage.

Stage	Description
First round evaluation	Clinical (and other) evaluators perform the bulk of their evaluation during the first round evaluation phase. The evaluator typically has 3 months to perform the first round evaluation. At the end of the first round evaluation, the clinical evaluator is expected to submit a report of high quality using the Clinical Evaluation Report (CER) template. The report must demonstrate that all relevant submitted data have been critically appraised and set out the strengths and limitations of the data and the benefits and risks of the medicine. Sections 1 to 12 of the CER template must be completed at this stage. Section 12 of the template provides the evaluator with the opportunity to ask questions of the sponsor in order to clarify any uncertainties about the data. These questions require careful consideration and crafting by the evaluator to ensure that an adequate and appropriate response is obtained. This includes any comments/requests for amendment of the PI and CMI. The evaluator is expected to make a clear analysis of the risks and benefits of the medicine as demonstrated by the submitted data and to make a preliminary recommendation as to whether the application should be approved or rejected based on the balance of the benefits and risks. If the assessment of the risk-benefit assessment is dependent on the sponsor's answers to clinical questions, the evaluator should indicate this and provide a rationale. Documentation of the benefit-risk assessment and recommendations at the end of the first round evaluation is very important, because it provides the TGA Delegate and the sponsor with a clear picture of the situation as it stands at the end of the first round evaluation, helps to reinforce the importance of any questions raised in Section 12 of the CER, and contributes to the transparency of the evaluation process.
Consolidated s.31 response	Clinical evaluators are not involved in this stage. The Delegate assesses the acceptability of the s.31 response insofar as to whether the questions have been answered and if evaluation of the responses (by way of a second round evaluation) is required.
Second round evaluation	During the second round evaluation the clinical evaluator reviews the sponsor's answers to clinical questions raised in the consolidated s.31 request and completes the remaining sections of the CER (sections 13 to 16). The CER is then submitted to the Delegate for final clearance. At the completion of the second round evaluation, the evaluator is expected to have made a final recommendation based on the balance of the benefits and risks of the medicine demonstrated by the data that have been submitted and after taking into account the sponsor's answers to any clinical questions posed in the consolidated s.31 request. Note: On occasions, the second round evaluation may be completed by another evaluator. It is therefore very important that the first round evaluation report has a clear and comprehensive benefit-risk assessment, recommendation regarding registration and comments on the product literature, referring back to the submitted data as documented in the evaluation. This will identify any gaps that will need to be addressed to enable a final benefit-risk assessment.

Stage	Description
Expert advisory review	Clinical evaluators are not routinely involved. However, they may from time to time be asked to respond to the sponsor's pre-ACM or pre-ACV comments on the CER.
Decision	Clinical evaluators are not involved.
Post decision **(ARTG entry & AusPAR)**	Clinical evaluators are not involved. The decision-making process is documented in the publicly available AusPAR. Excerpts from the clinical evaluation report are included in the AusPAR (although with no identifying details).

What is clinical evaluation?

Clinical evaluation is the systematic critical appraisal and summation of the clinical pharmacology, efficacy and safety data for a medicine, undertaken to establish the balance of benefits and risks of the medicine in relation to its intended use. It is also undertaken to ensure that claims being made in prescribing information and other product literature for the medicine accurately reflect the scientific evidence.

How is my clinical evaluation report used by the TGA?

Your Clinical Evaluation Report (CER) is a critical component of the TGA's decision-making process. It is used by the TGA's decision-maker (the Delegate) and by the Advisory Committee for Medicines (ACM) or the Advisory Committee for Vaccines (ACV) as the main source of information about the clinical aspects of the submission.

It is also used for the preparation of the Australian Public Assessment Report (AusPAR), a document published on the TGA website that provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve an application.

A copy of your CER is released to the sponsor and, for international companies, may be forwarded to their head office for comment. In addition, your CER may be sent to other regulatory agencies.

Accordingly, it is important your CER is of a high standard and be able to withstand intense scrutiny by a variety of stakeholders. The CER must have consistent content and formatting and be an independent, objective and critical appraisal of the data, assessing the claimed benefits of the medicine relative to its risks or undesirable effects. Your report must also demonstrate that all the data have been appraised without bias.

What materials do I need to perform an evaluation?

The following documents are used routinely for clinical evaluations and will be sent to you, or made available to you, by the TGA:

- a copy of the submission in electronic format;
- an electronic copy of the Clinical Evaluation Report template (Version 3.1);
- the Clinical Evaluation Report Guideline (Prescription Medicines) Version 3.1;
- the Statement of Requirement (SOR) – this is sent to you by the TGA when you are asked to quote for the evaluation of the submission; and
- any supporting materials (e.g. TGA-adopted EU clinical guidelines, previous clinical evaluation reports and committee meeting minutes).

The TGA has a guidance document known as the *Australian Regulatory Guidelines for Prescription Medicines* (ARGPM) which sets out the scientific and administrative requirements that sponsors should follow when compiling and presenting a dossier for review by the TGA. You are encouraged to refer to the ARGPM to acquaint yourself with any requirements specific to the medicine you are evaluating. *Note:* You must address any issues or specific questions raised by the delegate in the SOR.

See below for related information about IT capabilities.

What IT capability do I need to undertake clinical evaluations?

The clinical component of regulatory submissions invariably contains large amounts of data. To be able to review the data and write your report efficiently and in a timely manner it is necessary that you have high IT capability.

As a general rule the TGA recommends you should have:

- A modern desktop computer which supports web browsing using MS Internet Explorer, Google Chrome, Safari, (or similar). Use of laptop computers may be challenging due to the small amount of screen space available to view such large amounts of data in text and tabular format.
- Dual 19" screens are recommended because this will allow you to review the data on one screen and compile your evaluation report on the other. However you may have personal preferences – a single large screen may suffice but it will be less efficient.

External evaluators are also strongly encouraged to use docuBridge software as the primary review tool for their evaluations. This software is made available by the TGA and provides:

- enhanced navigation of the dossier via table of contents, bookmarks and hyperlinks;
- faster searches and retrieval of information;

- the ability to insert highlights and annotations directly in the submissions without altering the original document; and
- the ability to copy information from the submission and paste it into your evaluation reports.

In order to use docuBridge you will need:

- Quality broadband internet access – docuBridge software can be accessed on the TGA's computer network and high quality internet access will improve the speed and reliability of your connections to the TGA when performing your evaluation work in docuBridge.
- A special web browser application called Citrix Receiver is needed for you to be able to access the docuBridge software in the TGA's computer network. Citrix Receiver is easy to install on any desktop device, including PCs and Macs. Login IDs, passwords and security tokens will be issued to you by the TGA.

What makes a good evaluation report?

A good Clinical Evaluation Report is one that:

- uses the prescribed evaluation report template, is well written and has been proof-read prior to submission to the Delegate;
- considers **all the clinical data** contained in the submission;
- contains an independent, objective and critical appraisal of the sponsor's data, rather than simply summarising the data;
- refers to and applies relevant TGA guidelines;
- includes succinct summaries of the pharmacology, efficacy and safety of the product;
- has a well-argued balance of the benefits and risks of the product in relation to its proposed use;
- contains a clear set of recommendations regarding approval or otherwise of the application;
- includes a detailed review of the adequacy of the sponsor's proposed Product Information and Consumer Medicine Information; and
- where necessary, contains clear questions to be asked of the sponsor to address any uncertainties about the clinical data package.

You may find it helpful to look at some clinical evaluation reports in AusPARs (available on the TGA website) to get a feel for what is expected in a clinical evaluation report.

What does a submission look like?

A submission for a prescription medicine is presented in a standardised, electronic, internationally harmonised format known as the **Common Technical Document** (CTD) and comprises 5 Modules. **Modules 1, 2 and 5** will be used by you to complete a clinical evaluation.

Module 1 This is a regional-specific module containing administrative information unique to each regulatory authority. Of most relevance to your evaluation are:

- the letter of application and application form;

- table of contents for Modules 1 to 5;
- the overseas regulatory status of the medicine;
- the draft Product Information (PI) and Consumer Medicine Information (CMI) documents; and
- the draft Risk Management Plan (RMP).

Module 2 This module contains overviews, written summaries and tabulated summaries of the data contained in Modules 3, 4 and 5. These documents are written by the sponsor and should be looked at critically. Of most relevance to your evaluation are the overviews and summaries of clinical pharmacology, efficacy and safety.

Module 3 This module contains quality data relating to the active substance and medicinal product – its chemistry/biology, quality controls and manufacturing processes:

- composition of the medicinal substance and the medicine product;
- batch consistency;
- stability data;
- sterility data (if applicable); and
- impurity content.

These data are evaluated by chemists, biochemists, microbiologists and other scientists working at the TGA. External evaluators are sometimes used to evaluate this type of data for the TGA.

Module 4 This module contains nonclinical data:

- in vitro data;
- in vivo animal pharmacology data; and
- in vivo animal toxicology data.

These data are evaluated by toxicologists working at the TGA. External evaluators are sometimes used to evaluate this type of data for the TGA.

Module 5 This module contains clinical data and is the main data source for the clinical evaluation. The data comprises:

- clinical pharmacology (pharmacokinetics and pharmacodynamics) data;
- efficacy data generated from the clinical development program; and
- safety data generated from the clinical development program and from post marketing surveillance in other jurisdictions when the product is already approved there.

These data are evaluated by clinical evaluators in the Prescription Medicines Authorisation Branch. External clinical evaluators, such as yourself are often used to evaluate this type of data for the TGA.

A detailed analysis of how the contents of the various Modules can be used to compile a clinical evaluation report can be found in the Learning Module titled ***Introduction to Clinical Evaluation*** which will be made available to you..

What does a safety evaluation involve?

Clinicians are most probably familiar with reading reports of clinical trials in journal articles which often contain limited information about the safety outcomes of a trial and even less information on the methodology employed to generate safety data.

The safety data generated across clinical trials conducted as part of a clinical development program is much more extensive and detailed. Results from individual trials may run into many pages, supplemented by thousands of pages of appendices of tabulations and analyses. The amount of information contained in the dossier can be quite daunting for someone who is unfamiliar with data presented in this way.

The overall purpose of the TGA's safety evaluation is to:

- identify the major risks associated with use of the product;
- document the frequency and severity of specific risks;
- identify factors which alter the risk for individuals;
- identify the limitations of the data; and
- minimise overall risk from use of the product.

It is important that you take a rigorous approach to the examination of these data, including aspects such as patient exposure; the elucidation of adverse event data and analytical methods employed; appraisal of all deaths, treatment related adverse events and events of special interest; and whether safety concerns can be mitigated through risk minimisation activities.

The Clinical Evaluation Report template is structured so that these key aspects can be assessed systematically by you. Also, the Prescription Medicines Authorisation Branch has produced a detailed a Learning Module titled ***Evaluation of Premarket Safety*** to help you assess these aspects of a submission; this Learning Module will be made available to you.

Do I have capacity to undertake this clinical evaluation for the TGA?

Before you are asked to submit a quote for performing an evaluation for the TGA, the TGA's External Evaluation Management Team will contact you to see if you are available to undertake the work. The sorts of information available to you at that stage will be the name of the product and active ingredient; the nature of the submission (e.g. new chemical entity or extension of indication) and proposed indication; and the **anticipated** timelines for evaluation of the submission.

When considering your availability you should consider the following questions:

- *Will I be able to commit to working regularly on the first round evaluation report over a period of three months?*

  First round evaluations are usually completed over a three month period and you need to check that you will be available to work on the evaluation over most (if not all) of that period. The TGA recommends that you allow yourself enough time to read through all the documentation and produce a detailed report; start work well ahead of the completion date; and work regularly on your evaluation over the three month period rather than trying to do it in one or several large sessions. Note: The question of how much actual time needed for

the evaluation can be addressed if you are subsequently asked to submit a quote (see How much time do I need to set aside for the evaluation?)

- *Will I be contactable and able to amend the report (if required) in the one month period after submitting the first round evaluation report?*

  The TGA needs to be able to contact you with questions about your evaluation report prior to it being sent to the sponsor. The TGA Delegate may request that you amend the report to clarify issues or statements; include more detailed appraisal of some of data or sponsor's documentation (such as the Product Information); or address errors of fact or omissions. The Delegate may also wish to discuss the clinical questions that should be posed to the sponsor. It is important that the TGA be able to resolve such matters as quickly as possible to meet the deadline for sending the report and consolidated s.31 questions to the sponsor, so your availability during this period is paramount.

- *Will I be available to perform the second round evaluation (if required)?*

  At the time a submission is made to the TGA, a sponsor will choose to respond to the TGA's s.31 questions in either a 30-day or 60-day timeframe. You will not be required to undertake any work during that time. However, once the s.31 responses are received, there is a one month period to complete your assessment of the sponsor's answers. It is not possible to predict how much actual time will need to be devoted to the assessment and the production of the second round evaluation report as this depends on the number and complexity of questions asked of the sponsor, so you will need to be generally available over that one month period. However, if you know that particular one month period of the year is generally a very busy time for you (for example, because of examiner commitments; overseas commitments etc.) it may be prudent to decline to undertake the evaluation.

- *Will I be contactable and able to amend the report (if required) in the one month period after submitting the second round evaluation report?*

  Again, the TGA needs to be able to contact you with questions about your second round evaluation report prior to it being sent to the sponsor. The TGA Delegate may request that you amend the report to clarify issues or statements; include more detailed appraisal of the sponsor's s.31 responses; or address errors of fact or omissions.

If you answer 'no' to any of these questions, you are unlikely to be able to complete the work required by the TGA.

Conflict of interest

You will also need to consider whether there would be any conflicts of interest if you were to undertake this piece of work for us. If there is, you should decline to undertake the work. If you are unsure whether a conflict of interest exists, please discuss the details with the External Evaluation Management Team.

How much time do I need to set aside for the evaluation?

(Or what do I need to take into account when formulating a quote?)

As a general observation, evaluators who are new to the appraisal of clinical development dossiers for prescription medicines underestimate the amount of time required to read, process and distil large amounts of clinical data into a concise high-quality scientific report. It is easy to become overwhelmed by the number of studies and their supporting documentation. It is

therefore important that you allow yourself enough time to read through all the documentation and produce a detailed report; start work well ahead of the completion date; and work regularly on your evaluation rather than trying to do it in several large sessions.

When performing a clinical evaluation you will need time to read:

- the Statement of Requirement (SOR) – this is sent to you by the TGA when you are asked to quote for the evaluation of the submission and outlines the nature, scope and size of a sponsor's proposed submission as well as identify any relevant guidelines, TGA materials (e.g. previous evaluation reports) and issues that need to be addressed in the evaluation;

- any supporting materials sent to you by the TGA (e.g. TGA-adopted EU clinical guidelines, previous clinical evaluation reports and committee meeting minutes);

- Module 1 – although this contains mostly administrative information, there are several key pieces of information you will need to read through to complete the evaluation report, including the sponsor's application letter; the overseas regulatory status of the medicine; the overview of paediatric data; and the Risk Management Plan (specifically the Safety Specifications within);

- Module 2 – this module contains various summaries, including a Nonclinical Overview, a Clinical Overview, a Summary of Clinical Efficacy and a Summary of Clinical Safety. You will need to read these to gain an overall appreciation of the clinical data and relevant nonclinical data contained within the submission. These documents may also contain analyses (e.g. summaries of adverse events amalgamated across studies) that are not presented elsewhere in the dossier but which need to be appraised during the evaluation process. These summaries are commissioned, and often written, by the sponsor or its parent company. As such, the documents may not present or critique the data in an entirely unbiased manner, and you will need to look for this. You need to take into account any arguments made by the sponsor in support of the medicine in these documents and your report will need to respond to any assertions about the data that you do not agree with;

- Module 5 – you must review each clinical study in the sponsor's submission:

  - The length of study reports can vary, and the main body of text may run into several hundred pages. (*Note*: Reading only the study synopsis is not sufficient for performing the depth of appraisal that the TGA requires.) From a practical perspective, the evaluation deadline will seldom allow you to read every word of every study report, so you should allocate your time according to the importance of the study (e.g. pivotal vs. supporting study or pharmacology studies). Studies identified by the sponsor (or you) as being pivotal to the submission require a very detailed analysis (as reflected in the structure of the template) and so will take more time to write up. In contrast, supporting studies and pharmacology studies (which tend to have shorter reports), can be written up in a more abbreviated manner (again reflected in the report template).

  - When you first start working for the TGA you may feel most uncertain about how long it will take you to work through the study reports. As a general rule it would be wise to start off by allowing yourself a generous amount of time for the various study types, for example 8-24 hours for a pivotal efficacy/safety study, noting that you need to evaluate efficacy and safety aspects of each study separately; 4-12 hours for a supporting study and pharmacokinetic study. As you become more proficient, these timeframes may be adjusted downwards. Alternatively, you may know your reading speed and be able estimate the time based on page counts for the main body of each study report (if available);

  - The study reports are often accompanied by appendices which can total several thousand pages. The appendices usually contain the actual trial protocols and any amendments, statistical analysis plans, analytical/assay performance reports and

tabulations of summary statistics and analyses and sometimes individual patient data. Generally, the appendices do not need to be scrutinised at the same level as the main study report and are consulted if there is a particular issue where you need to "drill down" to look at the actual analyses that have been undertaken by the sponsor. However, you should at least determine whether the study was conducted as intended in the protocol and examine possible impacts of protocol amendments on the validity of the data in the final study report.

You will also need time to write the report:

- You may make use of copied and pasted text from the study reports in Module 5 where you can, but in the knowledge that you will often need to edit the text to make it more concise and/or or to remove any elements of bias. It is expected that the presentation of each study will be accompanied by your own critical appraisal of the trial design, highlighting any limitations or uncertainties around the results observed.

- With regard to the sponsor's Module 2 documents, it is acceptable to copy tables, figures and sections of text from these summaries, provided you have checked that the copied material accurately reflects the original data in the relevant study report(s), and edited if necessary. Uncritical and unattributed copying of text from these summaries is not acceptable – it serves only to repeat possibly biased statements by the sponsor and does not provide the essential critical appraisal of the data.

- You also need to remember that when finalising your report there are additional tasks over and above the analysis of data from individual clinical trials, that will add to your overall evaluation timeframe:

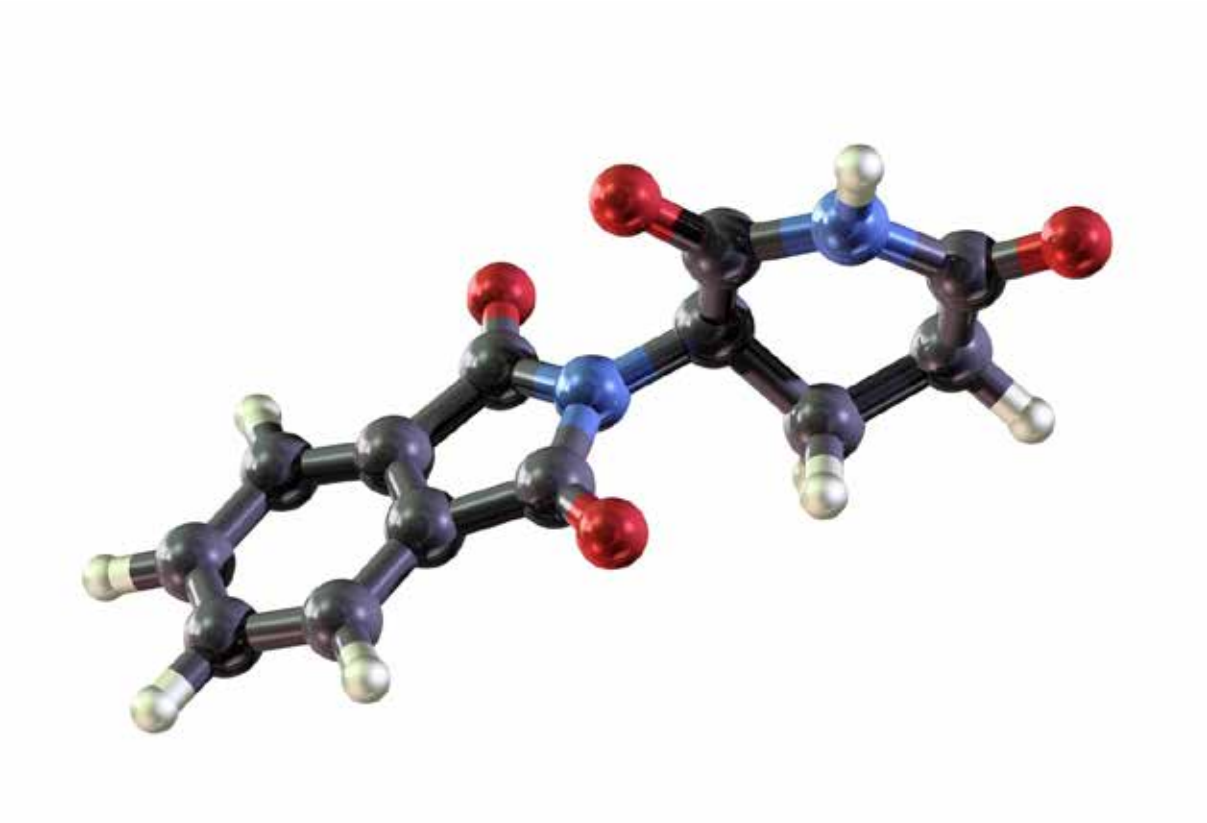
  – You need to formulate and write up your conclusions about the pharmacology, efficacy and safety data, based on the results observed across all the clinical studies, pointing to any outstanding issues that may need to be resolved (and reflected elsewhere in your report as clinical questions that should be asked of the sponsor);

  – You should review the PI and CMI (located in Module 1.3) – you need to consider these documents in depth to check that statements made in them are reflective of and supported by data in the submission;

  – You need to review the Safety Specifications of the Risk Management Plan (RMP - located in Module 1.8). This is a complex document, but very important as it highlights safety concerns raised in the clinical data that need to be proactively managed. Your role is to review the listed "important identified risks", "important potential risks" and "important missing information" in the Safety Specifications section of the RMP and ensure that it represents important adverse events that may affect the risk-benefit balance as identified through your evaluation of the clinical data; and

  – You need to formulate and write up your considerations of the benefit-risk balance of the medicine in relation to its proposed use and any uncertainties with regard to either the benefits or risks and how this can be mitigated; and make a recommendation about approval of the application or not.

Finally you will need time to proofread the document or have someone proofread it for you, particularly checking table and figure sequencing and cross referencing within the report.



Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	PMAB	2016
V1.1	Update references	PMAB/Evaluation Management	01/09/2016
V1.2	Update references	PMAB/Evaluation Management	22/11/2016
V1.3	Inclusion of Stream 6 and corrections	PMAB/Evaluation Management	12/10/2017

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