Prescription Medicines: Navigating evaluation issues and common deficiencies

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Navigating evaluation issues and common deficiencies

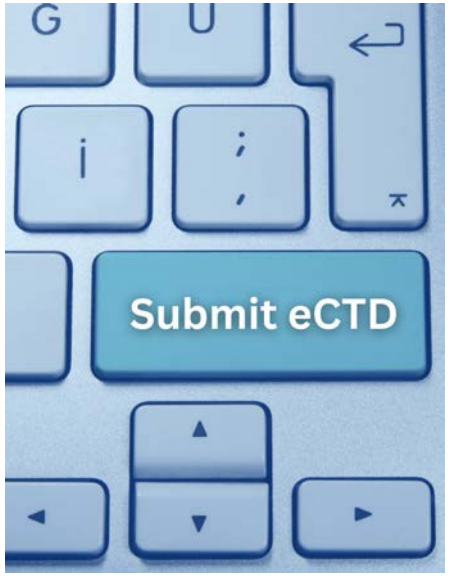
Focus on

- Two scenarios – Pre-approval and Post-approval
- Hierarchical considerations and decision making during the evaluation process
- Need for good cover letters
- Suggestions for good S31 responses

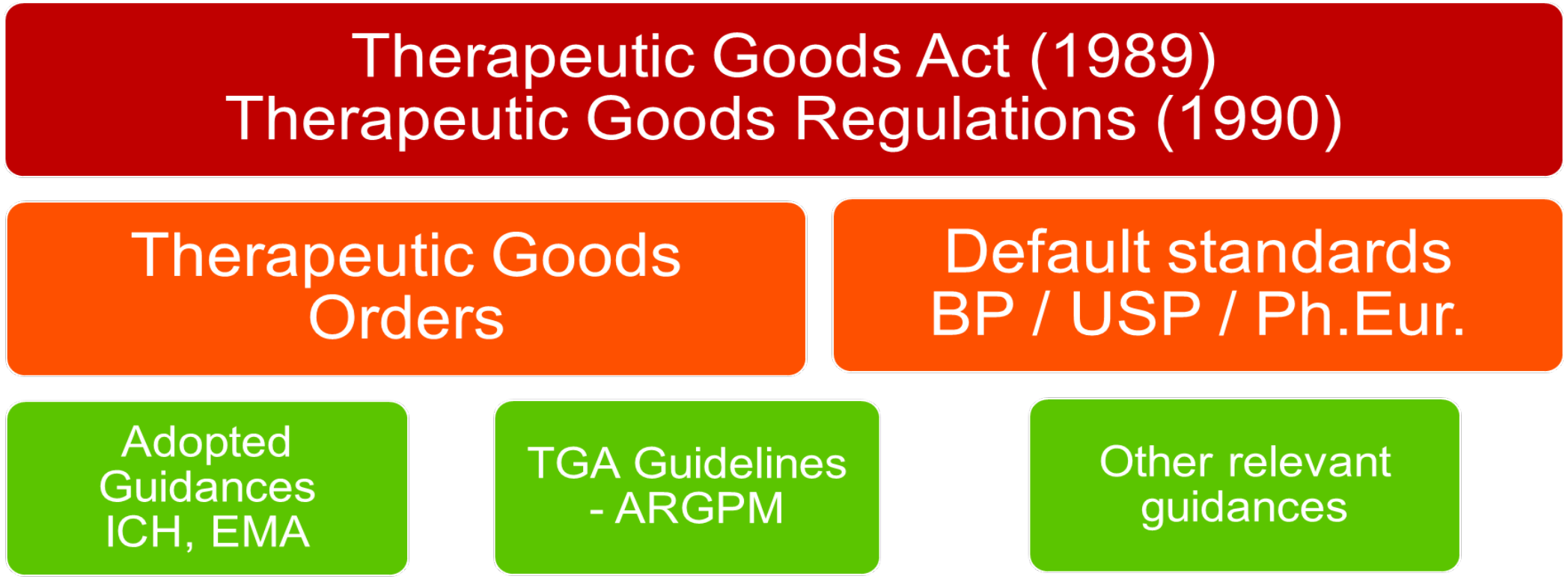
Regulatory framework: Prescription medicines

Applications must be made through the prescription medicines registration process

- Submissions in eCTD format
- Require supporting Quality (Module 3), Non-clinical (Module 4) and Clinical (Module 5) data
- Module 1 is for country specific information including presentation materials (PI, labels CMI)
- Submissions must be in eCTD format



Decision hierarchy



Scenario 1: Category 1 submission

LAXITINE active 10 mg and 20 mg tablets

Cover letter states it is a generic medicine

Reference product on ARTG
REFATINE 5 mg, 10 mg and 20 mg

Indication: *For the treatment of moderate to severe depression*

Requested shelf life – 36 months

BP monograph for ACTIVE Tablets

No drug product monograph when product developed.

However, BP monograph effective at time of submission

Assay limits for ACTIVE in drug product monograph
95.0 – 105.0%

Scenario 1: Category 1 submission

Drug product specification → Release and Expiry Assay limits proposed are the same - **90.0 – 110.0%**

Stability data for LAXITINE active Assay → Dossier states “All results meet specification limit”

Assay (%)	T0	T12	T18	T24	T36
Batch #1	100.4	99.5	98.7	96.9	95.7
Batch #2	98.2	97.6	96.1	95.6	94.1
Batch #3	97.9	97.0	96.9	95.8	93.9
Max. degree of change Δ from T0		↓ **0.9%**	↓ **2.1%**	↓ **3.5%**	↓ **4.7%**

Scenario 1 – Sponsor considerations before submission

Is there an applicable monograph at the time of submission?

- If YES, then expiry limit **must** meet monograph limit as BP, PhEur and USP are legislated default standards.
- Work with the DP manufacturer to change DP expiry specification if required.

Are there any increasing or decreasing trends observed with the stability data provided?

- If YES, then you cannot have the same release and expiry limits.
- In Scenario 2, there is a BP monograph for the DP so the expiry limit = monograph limit
  and is FIXED.

Do the drug product release and expiry Assay limits allow for any trends?

- If NO, then you cannot have the same release and expiry limits
- If there is a difference between release and expiry limits, is that difference enough to support requested shelf life?

Scenario 1 – QUALITY evaluator considerations

Assay (%)	T0	T12	T18	T24	T36
Batch #1	100.4	99.5	98.7	96.9	95.7
Batch #2	98.2	97.6	96.1	95.6	94.1
Batch #3	97.9	97.0	96.9	95.8	93.9
Max. degree of change Δ from T0		↓ **0.9%**	↓ **2.1%**	↓ **3.5%**	↓ **4.7%**

BP Assay limit: 95.0 – 105.0%
Proposed release and expiry limit: 90.0 – 110.0%

- There is an applicable BP monograph for drug product.
- The proposed release and expiry Assay limits are **wider** than BP limits and **do not** meet monograph.
- The expiry Assay limit for LAXITINE tablets must be changed to meet BP monograph i.e. **95.0 – 105.0%.**
- Batches #2 and #3 at 36 months **FAIL** the BP limit → **36-month shelf life not possible.**
- Is there a trend over time? YES - what is the maximum or average Δ?
- Is the trend the same for both the 10 mg and 20 mg tablets or different?
- Based on the LAXITINE tablet stability data, the release Assay limit would need to be revised to allow for ↓3.5% over **24-months** i.e. release limit **98.5 – 105.0%** and expiry limit **95.0 – 105.0%.**

Scenario 1 – CLINICAL Pharmacist considerations

Dosing and Efficacy information

- Remove data related to 5mg – dependant on context.
- If retained, footnote stating available in other brands required

Safety information

- Retain adverse effects and warnings related to the 5mg - dependant on clinical data
- Footnote required

PI Mandatory Text

- Refer to TGA Form for Providing Product Information

CMI document

- New CMI template
- Must reflect safety information in the PI - does not have to mirror the innovator
- Ensure document is easy to read and understand for consumers

Dossier considerations

- Separate file for PI/CMI documents for multiple trade names – not combined please

Scenario 1 Questions?

Scan the QR code with your device to submit a question.

Scenario 2: Category 3 post-approval change

Sponsor filed a submission to vary an ARTG entry under subsection 9D(3) for LUVLE activemab 10 mg/0.5 mL ready-to-use (RTU) liquid vial

Other Type IB variations already approved by EMA

Change	Current	Proposed
New alternate DP site	XYZ, India	QPR, USA
Add new manufacturing process	Ready to use (RFU) bulk liquid for injection	Lyophilisation step introduced to produce a lyophilised powder for injection
Change in activemab quantity	10 mg in 0.5 mL vial	12 mg in 0.5 mL vial
Change DS shelf life	36 months when stored at -20°C	60 months at -20°C
Extend shelf life of DP (RTU)	24 months at 2-8°C	48 months at 2-8°C
Approved temperature excursion condition during shipping.	Up to 5 days at -20°C or 25 days at 35°C	but not in combination – no change

Scenario 2:

Sponsor considerations before submission

1. What should I include in the cover letter/note for evaluator?

2. What type (category) of submission should this fall under? Why?

3. What should I consider when putting together data/justifications for the stability request?

Scenario 2:

What to include in Cover Letter?

HINT – For minor variations, a Cover Letter template is available on the TGA website (a guide only)

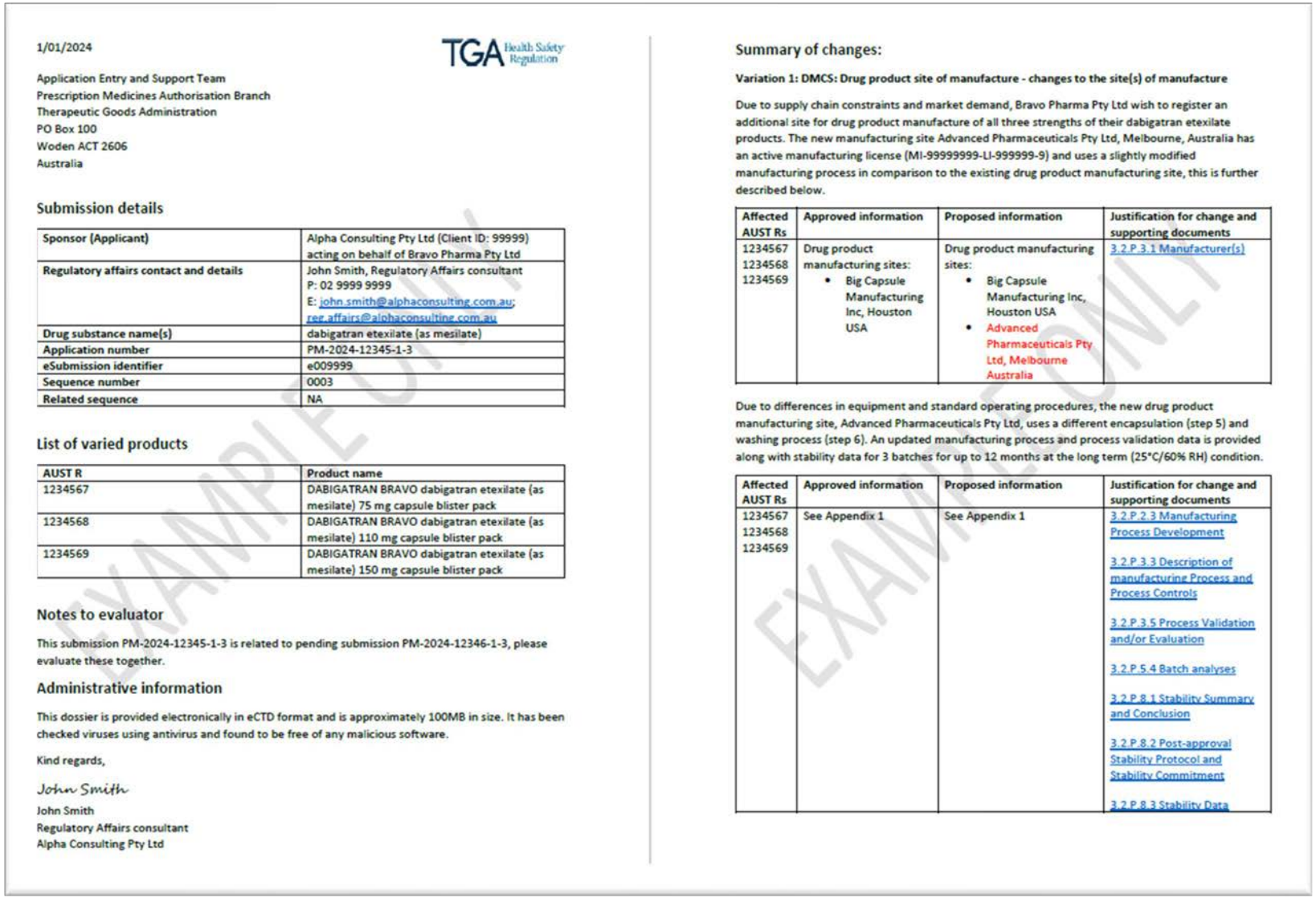
Itemise all changes in the letter

- Itemised changes are required for the decision letter.
- It is not enough to simply refer to ‘other Type IB variations already approved by the EMA’.

A clearly outlined Summary of Changes is helpful and should include

- current situation
- proposed changes
- rationale/justification
- supporting data with link to location

Cover letter template: Example



1/01/2024

TGA Health Safety Regulation

Application Entry and Support Team
Prescription Medicines Authorisation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

Submission details

Sponsor (Applicant)	Alpha Consulting Pty Ltd (Client ID: 99999) acting on behalf of Bravo Pharma Pty Ltd
Regulatory affairs contact and details	John Smith, Regulatory Affairs consultant P: 02 9999 9999 E: john.smith@alphaconsulting.com.au; reg.affairs@alphaconsulting.com.au
Drug substance name(s)	dabigatran etexilate (as mesilate)
Application number	PM-2024-12345-1-3
eSubmission identifier	e009999
Sequence number	0003
Related sequence	NA

List of varied products

AUST R	Product name
1234567	DABIGATRAN BRAVO dabigatran etexilate (as mesilate) 75 mg capsule blister pack
1234568	DABIGATRAN BRAVO dabigatran etexilate (as mesilate) 110 mg capsule blister pack
1234569	DABIGATRAN BRAVO dabigatran etexilate (as mesilate) 150 mg capsule blister pack

Notes to evaluator

This submission PM-2024-12345-1-3 is related to pending submission PM-2024-12346-1-3, please evaluate these together.

Administrative information

This dossier is provided electronically in eCTD format and is approximately 100MB in size. It has been checked viruses using antivirus and found to be free of any malicious software.

Kind regards,

John Smith

John Smith
Regulatory Affairs consultant
Alpha Consulting Pty Ltd

Summary of changes:

Variation 1: DMCS: Drug product site of manufacture - changes to the site(s) of manufacture

Due to supply chain constraints and market demand, Bravo Pharma Pty Ltd wish to register an additional site for drug product manufacture of all three strengths of their dabigatran etexilate products. The new manufacturing site Advanced Pharmaceuticals Pty Ltd, Melbourne, Australia has an active manufacturing license (MI-99999999-LI-999999-9) and uses a slightly modified manufacturing process in comparison to the existing drug product manufacturing site, this is further described below.

Affected AUST Rs	Approved information	Proposed information	Justification for change and supporting documents
1234567 1234568 1234569	Drug product manufacturing sites: • Big Capsule Manufacturing Inc, Houston USA	Drug product manufacturing sites: • Big Capsule Manufacturing Inc, Houston USA • Advanced Pharmaceuticals Pty Ltd, Melbourne Australia	3.2.P.3.1 Manufacturer(s)

Due to differences in equipment and standard operating procedures, the new drug product manufacturing site, Advanced Pharmaceuticals Pty Ltd, uses a different encapsulation (step 5) and washing process (step 6). An updated manufacturing process and process validation data is provided along with stability data for 3 batches for up to 12 months at the long term (25°C/60% RH) condition.

Affected AUST Rs	Approved information	Proposed information	Justification for change and supporting documents
1234567 1234568 1234569	See Appendix 1	See Appendix 1	3.2.P.2.3 Manufacturing Process Development 3.2.P.3.3 Description of manufacturing Process and Process Controls 3.2.P.3.5 Process Validation and/or Evaluation 3.2.P.5.4 Batch analyses 3.2.P.8.1 Stability Summary and Conclusion 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment 3.2.P.8.3 Stability Data

Scenario 2:

What type (category) of submission?

This is a Category 1 submission because it is

- a change of presentation/dosage form (injection solution) to (lyophilised powder for injection)
- a change in strength – RFU 10 mg/0.5 mL to powder for injection 12 mg in 0.5 mL

Refer to *Therapeutic Goods Regulations section 16G*

Clinical data/justifications will require evaluation

Scenario 2:

Considerations for stability request

Changes in dosage form and strength

- Requires appropriate stability data

Expand bracketing approach

- If introducing higher or lower strength of the product than what already has been registered.

For Biological medicines

- No extrapolation of stability data. You must provide real time data.
- Totality of shelf-life duration (for DS and DP) will be considered when shelf-life extension is sought.
- Think about the impact of shelf-life extension on already registered in-use (PI) and allowable temperature excursions during shipping.

For Chemical entities

- Extrapolation of stability data may be entertained.

Scenario 2:

Clinical Pharmacist considerations

Combined Submissions - SRR with Category 3 - not ideal!

- Consider the priority of changes to the PI
- Can cause delays in approval
- Separating of PI changes may be requested to allow for separate approval
- Submitting separately where possible is preferred
- Note in cover letter of concurrent submissions

Submission Type / Scoping

- If unsure, please reach out to Application Entry team for advice
  (you may attach an annotated PI to assist)
- Information to aid in correct submission type will be given only, no evaluation on acceptability at this stage
- The pre-submission advice is non-binding - the evaluator/delegate may query aspects of the submission during the evaluation phase

Scenario 2 Questions?

Scan the QR code with your device to submit a question.

Tips for improving the quality of S31 responses

1. Use the same deficiency question numbering as TGA evaluation report.

2. Provide a full response to each question in Module 1.0.3, not just a link to revised sections of dossier.

3. What have you changed in dossier? If you don't agree with evaluator assessment, provide a justification. If your justification cites references, then you should provide copies of those references for consideration.

4. Hyperlink or cross reference to the correct updated section and exact **page/location** in the dossier.

5. Do not provide unsolicited variations/data

6. Follow eCTD lifecycle conventions and label all files with a distinguishing name – e.g. not 32 individual 'Label' in Module 1.3.3!

Help US to help YOU

Takeaway messages

- Provide a clear Cover Letter and Note for evaluator – it really helps!
- Read our evaluation reports and continually evolve your dossiers to incorporate knowledge gained.
- Don’t forget presentation issues – consider updates to and consistency across ARTG, PI, CMI and labels.
- If you are unsure of a submission pathway, variation type, please contact us before you submit.

Contact us

General submission type questions

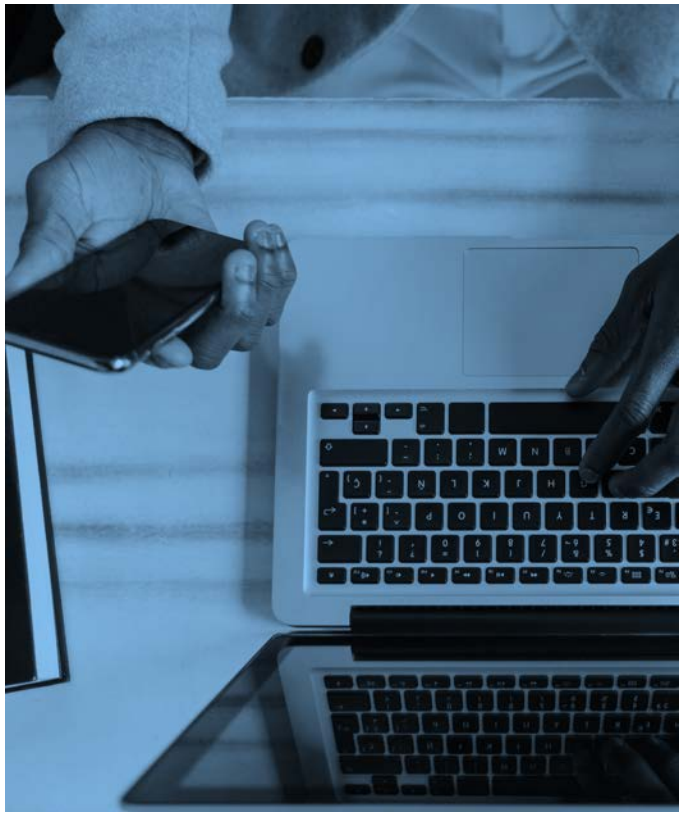
Aet.application.entry.team@health.gov.au

Specific pre-submission questions

biological.medicines@health.gov.au
(for biological medicines quality issues)

biomedicines.evaluation@health.gov.au
(for vaccine quality)

PCSinbox@health.gov.au
(for small chemical molecule queries – new applications and post-approval changes)



Questions?

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