CMC variations: Navigating the Grey Zones (PCVS perspective)

Mr Jeff Webb

Principal Evaluator (Acting)

Scientific Evaluation Branch

Department of Health and Aged Care, TGA

CMC variations:
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- Introduction
- Applications
- Workflow
- Grey Areas

Agenda

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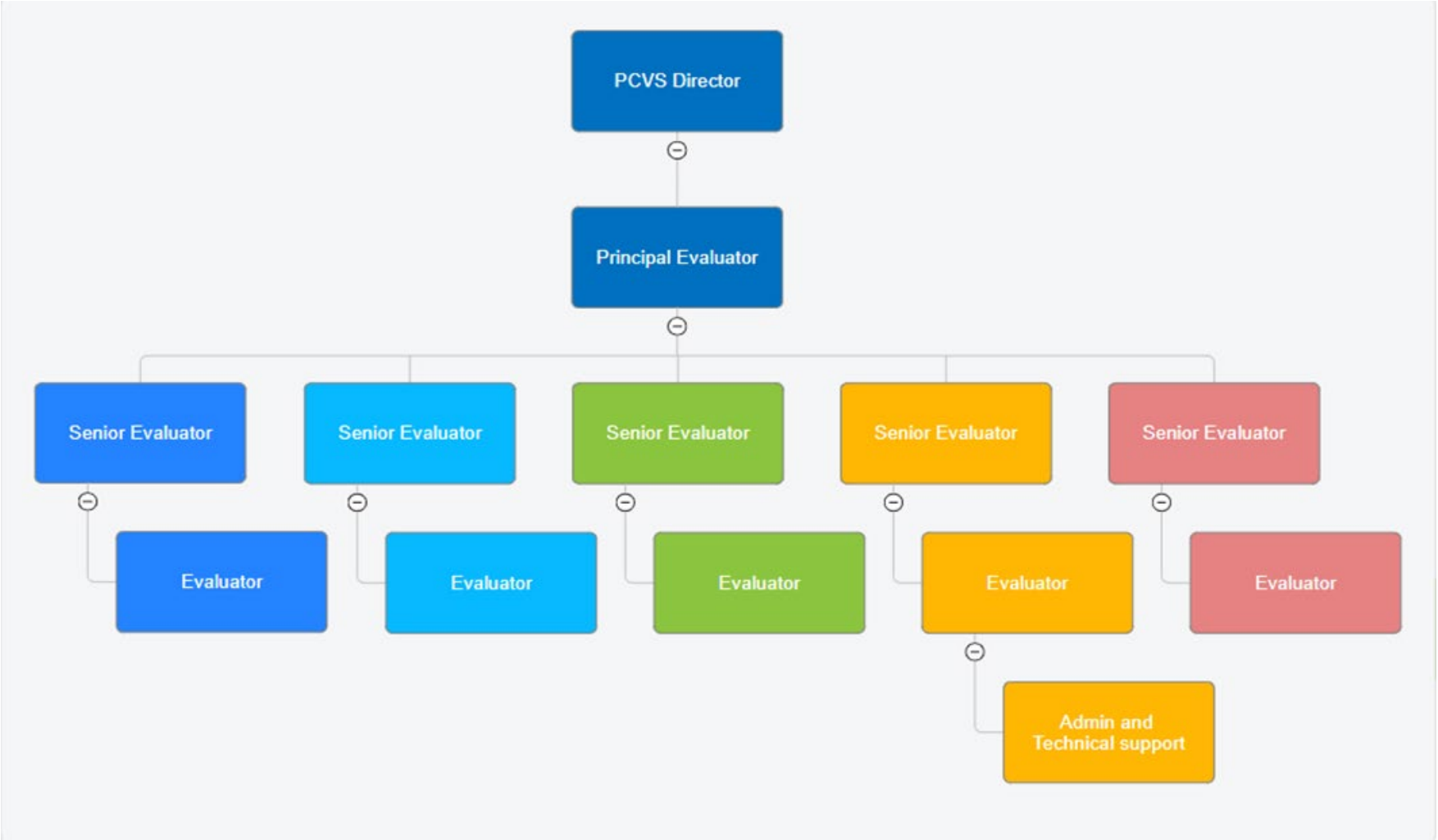
Pharmaceutical Chemistry Variation Section: an introduction

- **Changes** to chemistry, manufacturing, quality controls, labelling and packaging of currently supplied prescription medicines

- Evaluation and approval of minor variation applications including:
  - variations which require the submission of data for evaluation
  - Corrections to information
  - consent to import or supply therapeutic goods that do not comply with standards

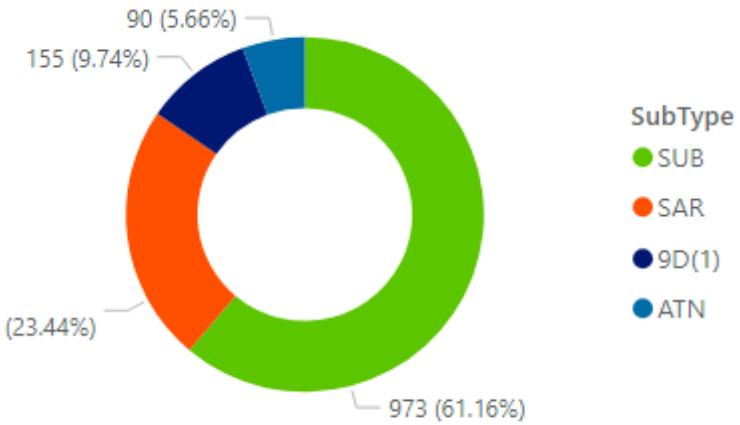
Pharmaceutical Chemistry Variation Section: introduction

Who are we?



How many variations do we see?

- In 2022/23 – 1597 Decisions completed by PCVS
- This financial year to date – 1555 (May 29)



- 1589 Notifications approved by the system in 2022
- 1376 to date for this financial year

2 years experience with PCVS:

- **Cat 3**
- LOW (0.5 day): → 4 Hrs
- Med B (1 day): → 9 hrs
- Med A (2 days): → 18 hrs
- High (3-5 days): → 28 hrs

- **SAR:**
- Low → 4 hrs
- Medium, High → 9 hrs

- **ATN**: Equivalent to Medium B

- **S14:** 2-3 days

- **Stakeholder engagement (PCS inbox/ talking to sponsor/peer review…) –** 1 hr/day

Key aspects of minor variations

1. No **reduction** to quality, safety or efficacy of the medicine
2. TGA approval is required **before** implementing a change
3. All ‘standards’ must be met

Medicines must meet certain standards

What are standards?

- British Pharmacopoeia
- European Pharmacopoeia
- United States Pharmacopoeia
- Therapeutic Goods Orders
  - E.g. TGO 91 – Standard for labels of prescription and related medicines

If standards are not met

Potential for

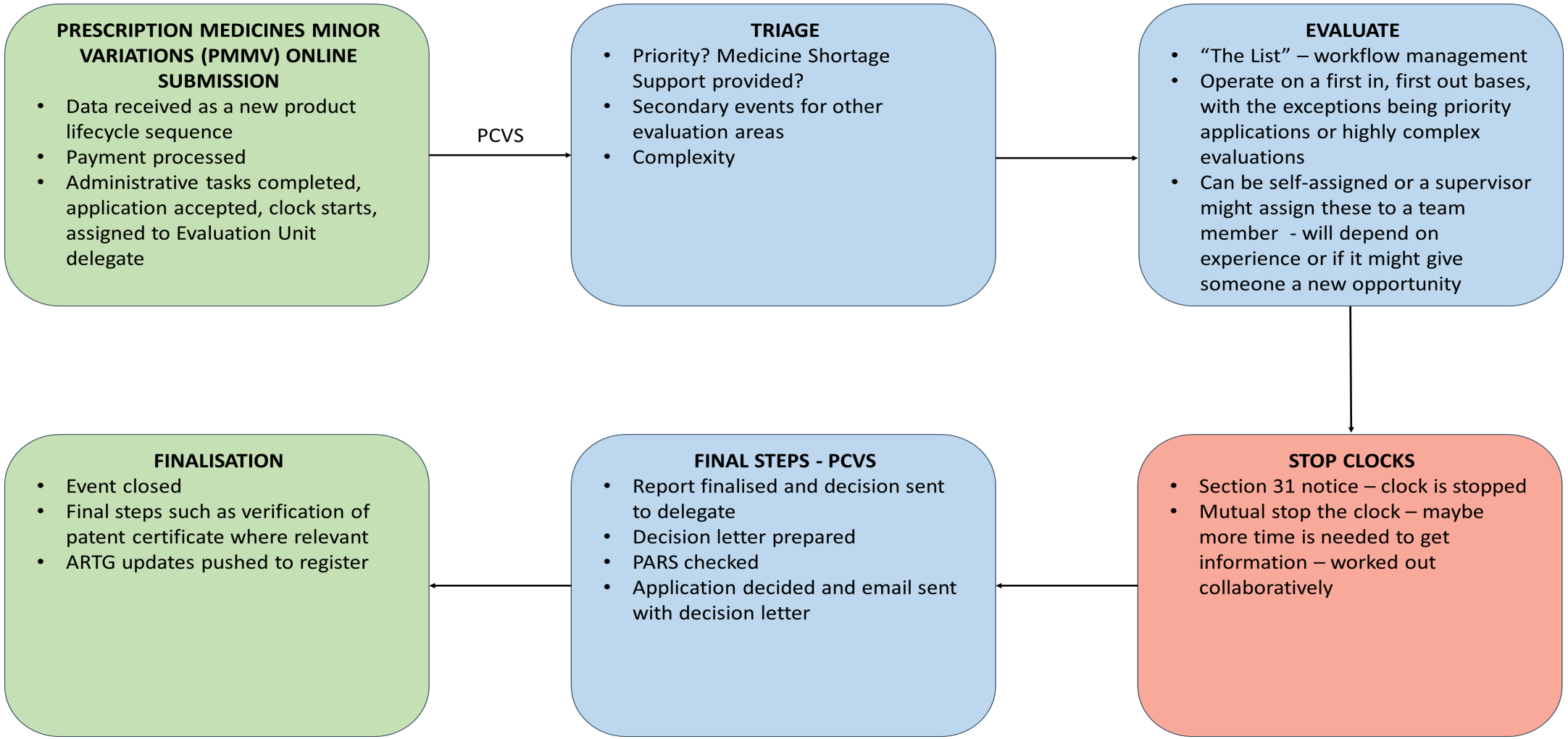
- Criminal offences
- Civil penalties

Application types and timeframes

Application types	Evaluation timeframe	Reference
s9D(3) application	45 working days	Regulation 16F, Schedule 9 Part 2 table of fees (TG Regulations 1990)
s23 application	45 working days	Regulation 16G of TG , Schedule 9 Part 2 table of fees (TG Regulations 1990)
s14	No statutory timeframe Target working days: 45	Schedule 9 Part 2 table of fees (TG Regulations 1990)
s9D(1)	No statutory timeframe	Schedule 9 Part 2 table of fees (TG Regulations 1990)

These changes are called minor because they do not require support of clinical, pre-clinical or bio-equivalence data

Application workflow



Grey Areas – PCVS perspective

Corrections to the dossier under 9D(1)

- Difference between editorial change (i.e. typo or missing punctuation) and a correction – adding in a decimal point or fixing an aspect of a method that was incorrect.
- If it is correcting data that was wrong through either by omission or being incorrectly recorded at the time, this is a correction.
- If it is typo, it is an editorial change and can be mentioned in a cover letter
- If it is an actual change due to drift in a process over time, it is a change. If this is being submitted retrospectively (NOT encouraged), it should be a Category 3 application as a notification should not be used for a change already applied.

Grey Areas – PCVS perspective

Multiple applications for new products under s25, use of z codes

- When submitting an application for a new product, you may have associated changes to other aspects of the medicine, which will cause changes to the PAR.
- Instead of creating separate associated submissions, we have codes available for associated changes across all change types.
- These are covered under the Z-Codes, and can be found from page 111 of Appendix 1. These codes ensure that all the changes you are making will be applied to the new product.
- Otherwise there is a risk that the associated changed, especially notifications, will be processed before the new product and actually associated only with the old product and not the new one!

Grey Areas – PCVS perspective

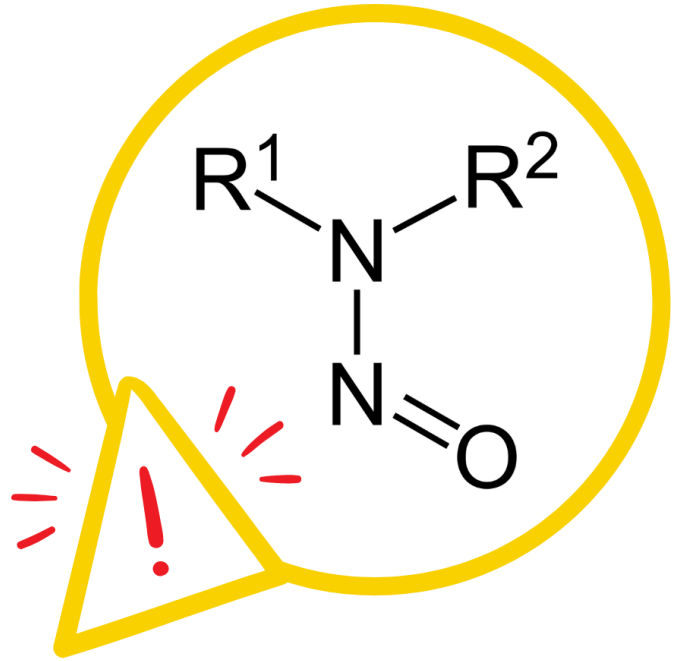
Bundling applications

- We frequently see the submission of separate applications for the same product made at the same time, with notifications, SARS and Category 3 applications submitted separately. Often submitted under the same cover letter.
- These applications can be bundled under the one Category 3 submission and they can all be processed/approved together. This ensures all changes get applied at the same time, especially when the change/s is actually related to the Category 3 change. For example, a Notification change related to the Category 3 change shouldn't be approved before the Category 3 change.
- This is where the cover letter is critical – and we can help with that, as we are working on a cover letter template that we hope will act as a guide for you.

Grey Areas – PCVS perspective

CEPs with nitrosamine changes

- As we all know (and you can hear later) nitrosamines are a constantly evolving space.
- At this stage, CEP updates that include the addition or removal of nitrosamine test limits and methods, need to be submitted as a Category 3 change.
- This is for us to capture what is happening and how the impurity is being reduced or measured in at risk products.



Grey Areas – PCVS perspective

GMP clearance prior to manufacturing changes and ATNs

- A submission without GMP is not a valid submission
- There are some instances where TGA will make an allowance, but that needs to be discussed prior to the submission of the application. This should only be for exceptional reasons (e.g. medicine shortage).
- An ATN is a new product, and therefore all GMP needs to be validated the time of approval.
- If you are making a change to an existing manufacturing site and the GMP has expired, the application is not valid.

Grey Areas – PCVS perspective

Dissolution data requirements

- Many change codes have comparative dissolution data requirements.
- These are considered essential to demonstrate particular changes have not impacted the release of the medicine.
- These can be associated with manufacturing changes, either new sites or processes for both Drug Substance and Drug product, changes to the final dosage form such as the shape, embossing or dimensions.
- Requirements are outlined in Minor Variations Process Guidance as well as Appendix 1 under the relevant variation change code.

Grey Areas – PCVS perspective

Dissolution data requirements

- At least 12 dosage units (tablets, capsules) of each batch must be tested individually, and mean and individual results reported.
- The percentage of nominal content released should be measured at a minimum of three suitably spaced time points (excluding the zero time point).
- The batches should be tested using the same apparatus and, if possible, on the same day.
- Test conditions should be those used in routine quality control.
- Data should include comparative profiles of pre- and post-variation products and the f_2 values need to be between 50 and 100. No f_2 where >85% release in 15 min.

Grey Areas – PCVS perspective

Others for discussion

- SOP revisions in Europe can be filed as notifications/ "Do & Tell". Such changes require prior approval in Australia. Even minor changes when categories are not specified would be classified as Cat 3 (i.e., changes that are editorial in nature and improve method clarity).
- Addition of another machine for ID or visual inspection or changes to consumables (e.g., Waters filters to Millipore) , where there is no change to the process, but the documentation has been updated.
- What level of change in the manufacturing process needs to be reported? Is it only when it impacts validation?

Website and link references

Clinical trials	https://www.tga.gov.au/clinical-trials
Clinical trials handbook	https://www.tga.gov.au/resource/australian-clinical-trial-handbook
Role of the sponsor	https://www.tga.gov.au/role-sponsor
Priority determination for prescription medicines	https://www.tga.gov.au/publication/priority-determination-eligibility-criteria
Provisional approval for prescription medicines	https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines
ARTG	https://www.tga.gov.au/australian-register-therapeutic-goods
How we regulate medicines	https://www.tga.gov.au/how-we-regulate-medicines
Compliance management	https://www.tga.gov.au/hubs/compliance-and-enforcement/compliance-management
TGA guidelines email list	https://www.tga.gov.au/tga-guidelines-email-list
TGA business services	https://www.tga.gov.au/tga-business-services
Schedule of fees and charges	https://www.tga.gov.au/schedule-fees-and-charges

Therapeutic Goods Administration (TGA)

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