Australian Government
Department of Health
Therapeutic Goods Administration

Management of GMP Compliance signals

For Sponsors and Manufacturers of Medicines and Biologicals

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TGA Health Safety Regulation

TGA Compliance Management

- TGA safeguards the health of the Australian community through effective and timely regulation of therapeutic goods. Appropriate regulation helps ensure that the medicines and medical devices that millions of Australians rely on are safe and fit for purpose.

- One function of the TGA is to monitor and enforce compliance with laws that regulate therapeutic goods in Australia.

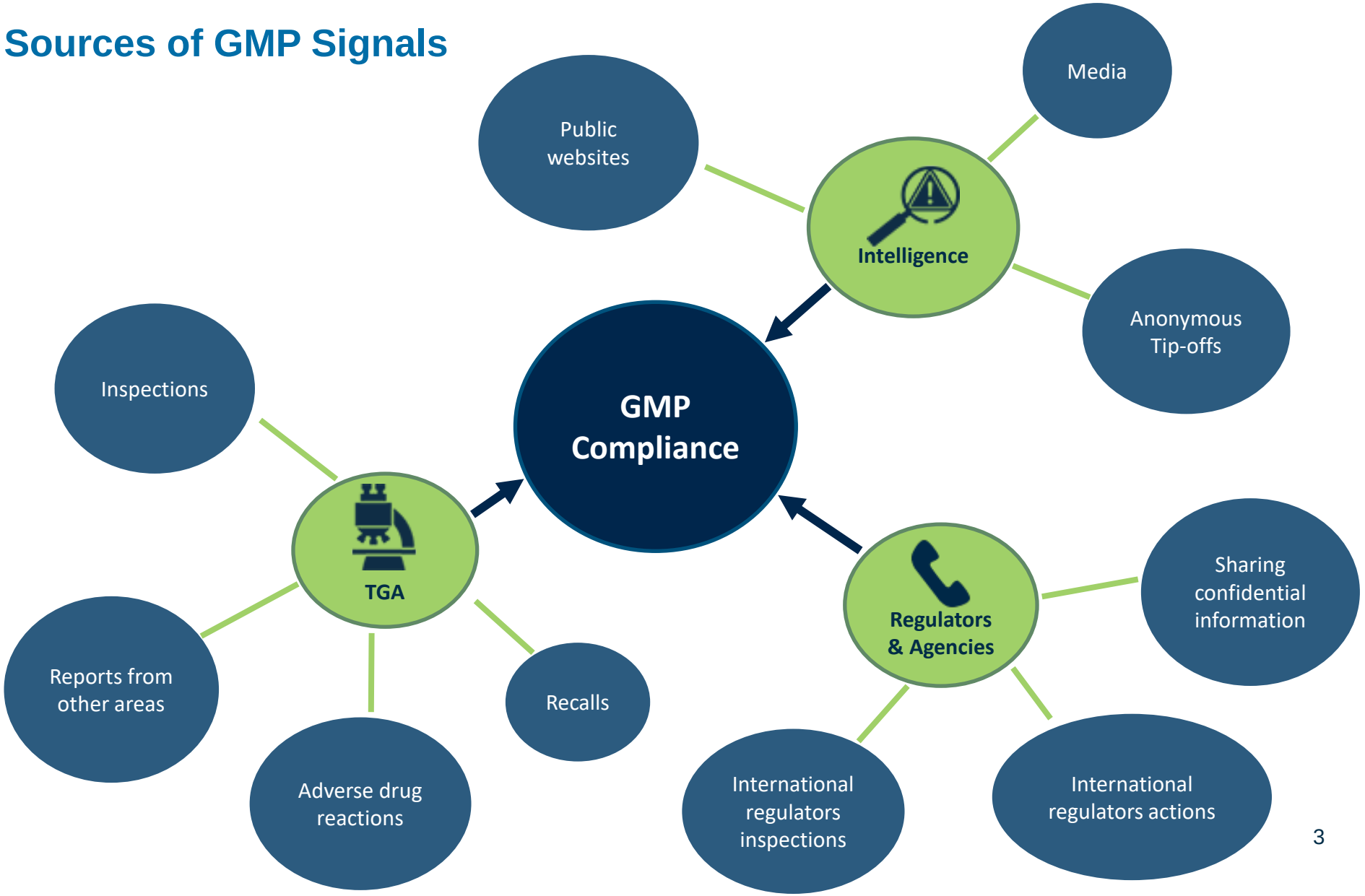
- Compliance and Enforcement Hub - https://www.tga.gov.au/hubs/compliance-and-enforcement/compliance-management
  - Manufacturing Quality Branch (MQB) - Manage GMP Compliance Signals for Manufacturers of Medicines and Biologicals

GMP Compliance Signals

- GMP compliance signals (non-compliance alerts) include but are not limited to intelligence, data and information that we receive from various internal and external intelligence sources, as well as our inspections and routine compliance monitoring process which indicate a departure from the manufacturing principles (or equivalent overseas standards) by a manufacturer.

- In addition, for overseas manufacturing sites we perform routine monitoring of overseas compliance systems and databases published by other overseas regulatory authorities.

Sources of GMP Signals



Who can report GMP Signal?

- Anyone can report a potential or actual GMP compliance signal.

GMPCompliance@health.gov.au

- Sponsors or manufacturers can report directly to TGA. This can also be done anonymously.

Sponsors/Manufacturer Responsibilities

- Sponsors and manufacturers **are expected to** report potential or known GMP compliance signals at their manufacturing sites and provide this information to the TGA when they become aware of such information.

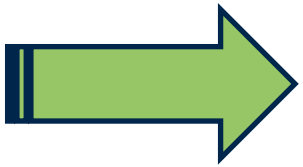
- It is expected that when sponsors / licensed manufacturers become aware of potential or actual GMP issues, GMP Compliance are advised as soon as practicable.

- The sponsor oversight of GMP compliance status of the manufacturing site should be stipulated in the GMP Agreement between the sponsor and manufacturer (we may ask for this if we need to).

Management of GMP Compliance Signals

- Manufacturing Quality Branch (MQB) manage GMP compliance signals related to the manufacturing of medicines and biologicals from:
  - licensed domestic manufacturing sites and
  - overseas manufacturing sites for products intended for supply in Australia.
  - We also manage signals relating to licence, certification and clearance applications.

- Once we receive and triage a GMP compliance signal, it undergoes a review and investigation process to determine if compliance action is required to address the signal.



Guidance on the Management of GMP Compliance Signals

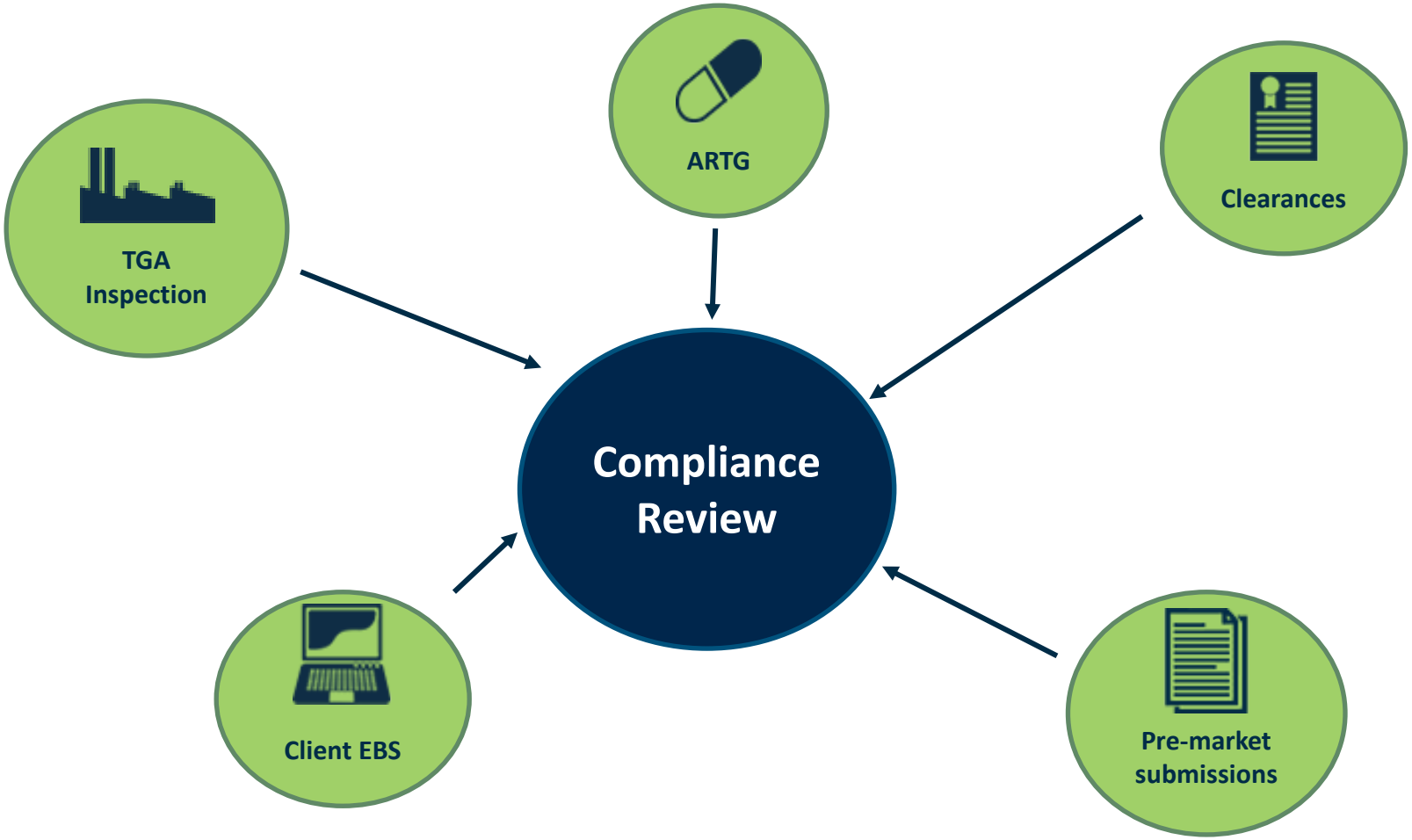
Guidance on the Management of GMP Compliance

- Guidance to be published – for Medicines and Biologicals
- Our framework for managing GMP compliance signals.
- The guidance is intended to inform sponsors and manufacturers of the process GMP Compliance follow when we get a signal, the types of information requested and the potential outcomes.

- Applies to:
  - All licensed manufacturers in Australia,
  - Sponsors responsible for overseas sites of manufacture of a medicine or active pharmaceutical ingredient supplied to Australia.

- Guidance Not Applicable to Medical Devices

Review of compliance signals



Review of compliance signals

- During investigation, we review a range of information relevant to the manufacturing site, products and supply to Australia market.

- Therefore, it is important to maintain your records

Keep manufacturing details of your ARTG up to date

Keep your Client eBS and contact details are up to date

Review of compliance signals

Signal received by Compliance team and an investigation begins.

GMP clearance applications related to the site are placed on hold pending the outcome of the assessment.

Sponsors are requested to provide risk assessments and other additional information relevant to the signal.

Assessment of information and documentation from sponsor and manufacturer.

Sponsors are notified of the outcome of the compliance investigation and regulatory actions

Request for Information

Request for Information

- Risk Assessment – Australia Market
- Supply Questionnaire which includes detail of your ARTGs, product supply info, clearance and pre-market info
- Additional information that may be relevant to the GMP compliance signal investigation and risk assessment process, e.g.
  - inspection report
  - post-inspection letter (PIL)
  - manufacturer's responses to the regulatory authority
  - evidence of corrective and preventative actions (CAPAs)
  - Site Master Files (SMF)
  - GMP or Quality agreements (or equivalent), where appropriate
  - TGA manufacturer questionnaire

Risk Assessment

why we are asking for it

- The TGA ask for risk assessments when there is supply, or when there is going to be supply to ensure any product on the **Australian market** is safe.
- We need this to be able to determine whether continued supply is warranted. It also helps to ensure consistent determinations are made for similar types of issues.
- What should be considered?
  - A risk assessment which covers products actually or intended to be supplied in Australia.
  - A review of the observations related to the signal (e.g. warning letter, non-compliance report etc.) and discussion related to whether these will have an impact on products to be supplied to Australia.
  - Clearly details the impact on products, risks to consumers, if anything needs to be recalled
  - What is being done to mitigate risks and plans by the manufacturer to correct the issues.

Risk Assessment

- A document where the sponsor has reviewed the information provided by the manufacturer, and applies this to the local situation, or the manufacturer has provided a document which covers the Australian market.
- Clearly outlines what the problem is, what's being done to fix it, the impact on products supplied in Australia.
- Guidance - ICH guideline Q9 on quality risk management

Risk Assessment

- If there are serious issues, please acknowledge that and provide information around risks.
- If determined appropriate to recall the products, please notify TGA Recall.

  For example, a non-compliance report for a sterile manufacturer issued by a European Medicines agency. All sterile products were recalled from the EU market.

Risk Assessment - Pitfalls

- Information provided is too generic and not specifically detailing how the risks are mitigated
- Information provided was for a different regulator which did not address Australian market
- The report does not detail what the issues are/were, what has been done to address these, and what impacts these had on products supplied here

Enforcement Tools & Regulatory Actions for GMP Compliance

Regulatory actions - domestic licensed manufacturers

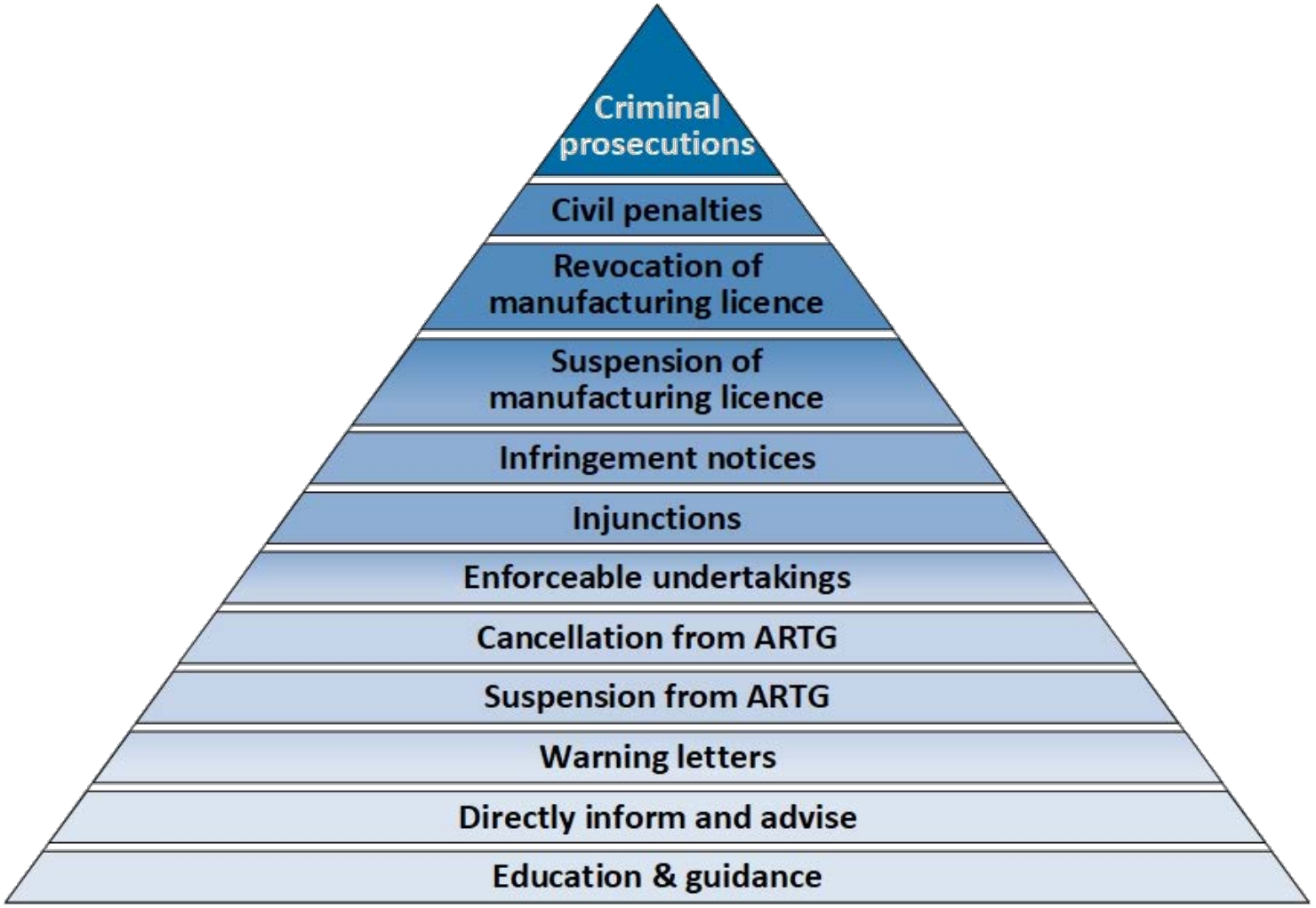
- For a domestic licensed manufacturer, the investigation may be through a request for information or a TGA inspection. Where required, a TGA inspection may be required to further investigate the claims (announced or unannounced).

- Any proposed actions may be taken in conjunction with the inspectorate section.

- Where information is received around a potential manufacturer of therapeutic goods who do not hold a manufacturing licence, the matter will be referred to the Regulatory Compliance Branch of the TGA for investigation and action.

- A range of compliance and enforcement tools are employed to address alleged GMP non-compliance, either individually or in combination, and to encourage compliance with the Act.

Domestic Licensed Manufacturers – Regulatory Tools

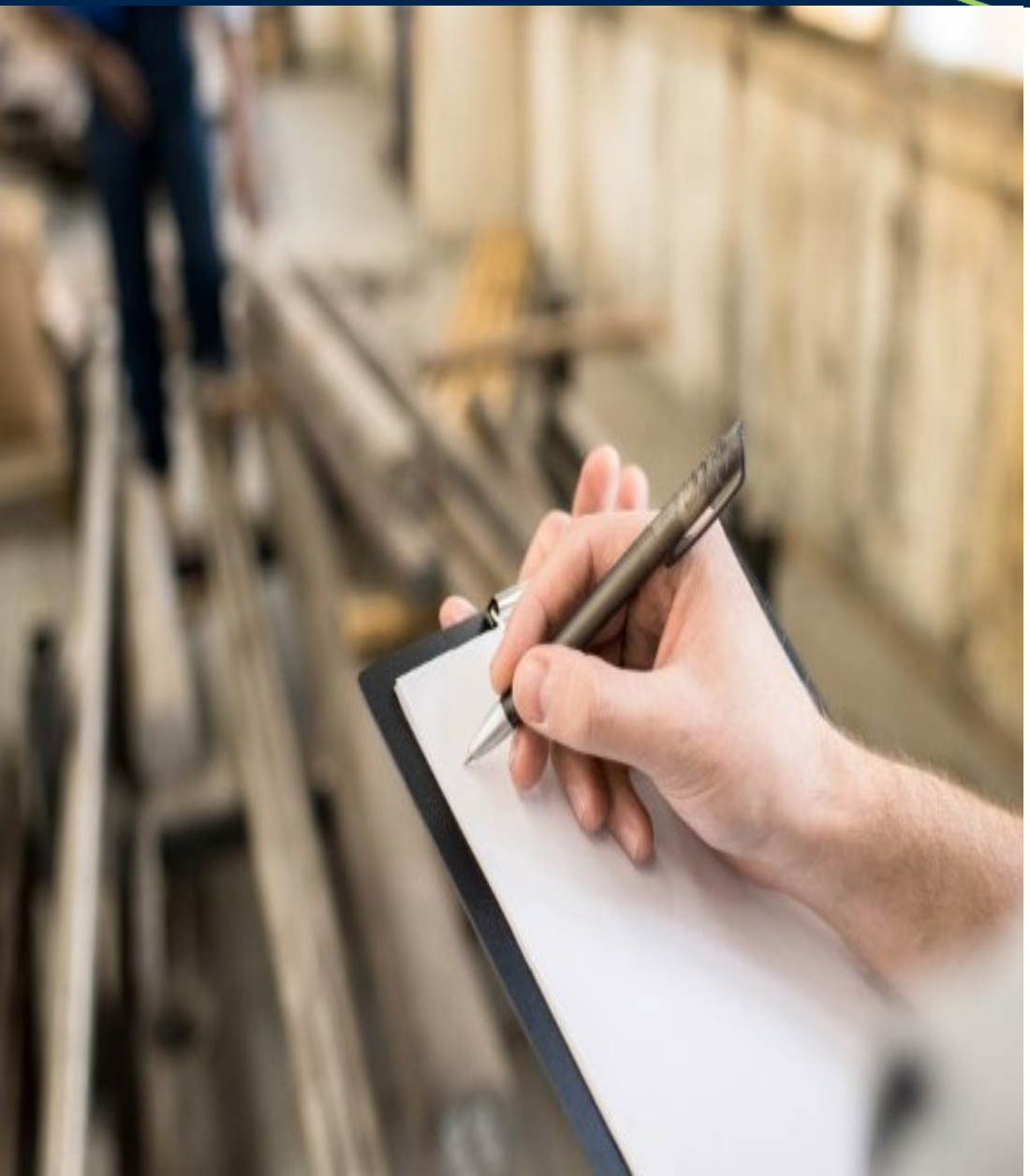


Regulatory actions for overseas manufacturers

- During review, all GMP clearance applications related to the site are placed on hold pending the outcome of the assessment.
- Sponsors will be requested to provide risk assessments and other additional information required.
- Where information is not provided by the due date, the case will progress based on the available information
- Sponsors will be notified of the outcome including any further compliance regulatory action that is required to be taken to address the signal.

Regulatory actions for overseas manufacturers

- The outcome of a compliance signal investigation may determine that action is required against a GMP clearance.
- The compliance action taken may be one or a combination of the following:
  - reduction of clearance validity
  - reduction of the clearance scope
  - addition of a condition or restriction to the clearance
  - suspension of clearance
  - cancellation of clearance
  - TGA compliance inspection (on site, remote or hybrid inspection)
  - product recalls
  - action against the ARTGs



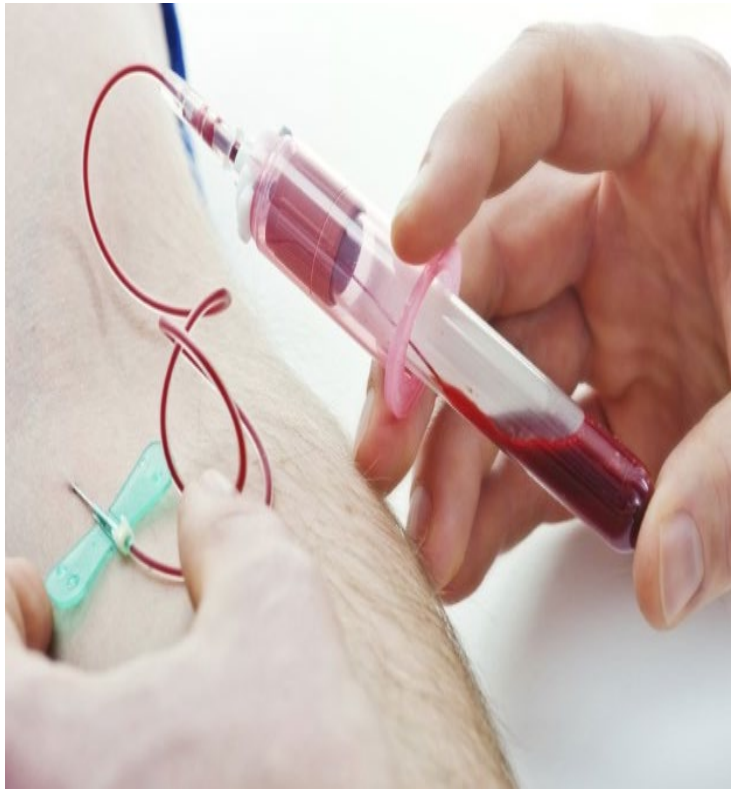
GMP Compliance Case Studies

Case Study 1 – Consumer Report

A consumer lodges a complaint to the TGA about AAA cool capsules product. The complaint is that they developed an allergic reaction (rash) after taking the product.

- The consumer reports it as an adverse drug reaction on the TGA website.
- The adverse drug reaction team would then conduct their review and determine whether there are concerns in relation to the manufacture of the product.
- If so, the matter gets referred to the GMP Compliance Team for further investigation
- Following our investigation and assessment, we confirm the issues around the manufacturing operation and Quality Management Systems at the site.
- It is determined that the re-inspection of the site should be brought forward and the inspection is to incorporate further review of the concerns identified during this compliance investigation.

Case Study 2 – Hazard Alerts



Hazard alerts for missing donor related medical history

- *Company C* is a medium scale human tissue processing facility that provides human tissue for implantation to surgeons operating within Australian hospitals.

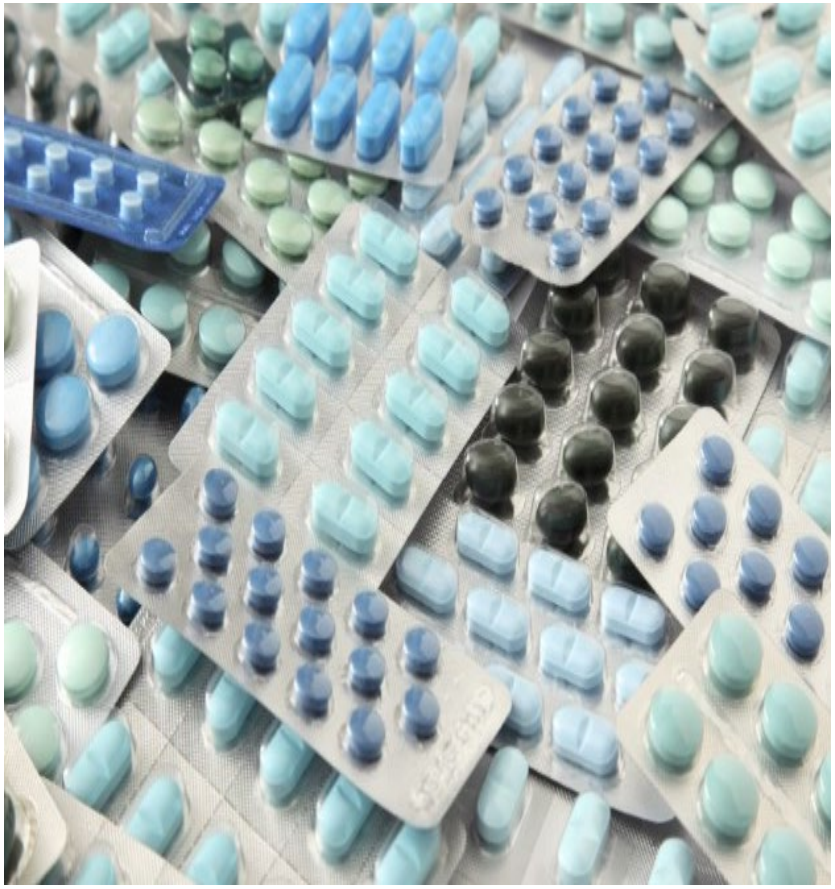
- The TGA received five consecutive hazard alerts for missing donor related medical history data. The manufacturer was contacted and asked to provide information on their risk assessment.

Case Study 2 – Hazard Alerts

- Following assessment of the information available, there was insufficient evidence to demonstrate that the risks are adequately managed.

- The following compliance actions were taken:
  - The GMP compliance signal was referred to the Lead Inspector for review at the next scheduled reinspection as the site was scheduled to undergo a TGA inspection within the following month.
  - The manufacturer's donor assessment processes and procedures were a focus of the inspection plan.

Case Study 3 – Overseas Regulator



Suspension of EDQM Certificate of Suitability (CEP)

- The European Medicines Agency (EMA)/European Directorate for the Quality of Medicines & Healthcare (EDQM) conduct a joint inspection of an active pharmaceutical ingredient (API) manufacturer.
- The EMA issue a non-compliance report. The EDQM suspend Certificates of Suitability (CEPs) for several APIs manufactured at this site.

Case Study 3 – O/S Regulator

Suspension of EDQM Certificate of Suitability (CEP) – Cont'd

- In this case we would contact relevant sponsors for further information, including details of products that they have registered on the Australian Register of Therapeutic Goods (ARTG), product supply details and risk assessments.
- Critical medicines and current/potential medicine shortages would be identified and confirmed.
- In this case, following a request for information, the manufacturer decides to suspend their manufacturing activities pending CAPAs implementation, while the CEPs are still suspended.
- Our Compliance Team assess the available information, including sponsor specific information, supply information and risk assessments.

Case Study 3 – O/S Regulator

Suspension of EDQM Certificate of Suitability (CEP) – Cont'd

- Requested information and risk assessments are provided by sponsors, but they do not address the risks for Australian supply.

- The following potential actions may be taken:
  - Suspension of existing clearances where there are no ARTGs or no products being supplied in Australia.
  - Suspension of existing clearances that are not related to medicines shortages or critical medicines.
  - Relevant sponsors are notified of the compliance actions to be taken, including advice regarding on-going or future supply and potential recall actions.
  - TGA continue to monitor for further compliance intelligence including the reinstatement of the CEPs.

Summary

- Industry Guidance to the Management of GMP Compliance Signals:
  - Provides information about the GMP compliance signal investigation and assessment process and information request
  - Highlights sponsors and manufacturers responsibilities in reporting of compliance signals and providing of information by the due date
  - Important to consider and address risk in context of products and supply for Australian market
  - Outlines regulatory compliance tools and actions (domestic and overseas sites)

Reporting of GMP Compliance Signal

- Email: GMPCompliance@health.gov.au
- Phone: 1800 020 653 (free call within Australia)

Australian Government

Department of Health

Therapeutic Goods Administration