Australian Government
Department of Health
Therapeutic Goods Administration

Good Manufacturing Practice (GMP) Clearance Applications - Common pitfalls

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Medical Devices & Product Quality Division
Health Products Regulation Group

6 December 2019

TGA Health Safety Regulation

Welcome | GMP clearance applications – common pitfalls

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Background

Mutual Recognition Agreement (MRA) pathway:

- Manufacturer is located within the borders of a MRA country
- Current target processing time: 30 TGA working days

Compliance Verification (CV) pathway:

- Manufacturer does not meet criteria for the MRA pathway but inspected by acceptable regulatory authority
- Stop clock implemented January 2019
- Target processing timeframes implemented 1 July 2019

Application type	Target processing timelines
CV Non-Sterile API	60 TGA working days
CV Sterile/Biotech API	75 TGA working days
CV Non-Sterile Finished Product	90 TGA working days
CV Sterile/Biotech Finished Product	120 TGA working days

Mutual Recognition Agreement (MRA) pathway

Scenarios when we do NOT seek further clarification resulting in clearance NOT issued…

- × Where the GMP certificate is not provided
- × Not a GMP certificate (e.g. Marketing Authorisation, licence)
- × Where the GMP certificate has expired (> 3 years since the inspection)
- × Is for the wrong manufacturing site
- × Has been issued using an inequivalent GMP standard
- × Does not cover the scope of your application

MRA pathway

MRA clearance applications not issued

May 2016 – October 2019

Reason	Number of applications
Expired GMP certificate	35
No acceptable supporting evidence	269
Wrong manufacturing site	31
Incorrect scope	32
Total	367

MRA pathway

Common deficiencies	What can you do?
Human Investigational Medicinal Products certificate provided	Watch out for Directive 2001/20/EC
Veterinary Medicinal Product certificate provided	Watch out for Directive 2001/82/EC
Good Laboratory Practice (GLP) certificates not accredited to International Standards Organisation (ISO) 17025	Watch out for GLP certificate that mentions ISO 17025

MRA pathway

One of the major factors contributing to delay in processing MRA applications:

NOT providing Active Pharmaceutical Ingredient (API) declaration upfront!

Why we require it?

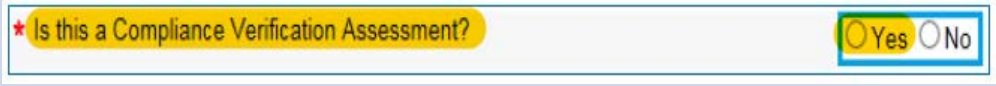
If API was not specifically mentioned in the GMP certificate, API declaration provides assurance from the manufacturer that the specific API(s) in your application is manufactured in the same facility and buildings as those inspected and referenced in the GMP certificate or inspection report

Example of deficiency	What can you do?
Scope: *Active material manufacture of Pegfilgrastim* GMP certificate: Only mentions *1.3 Biological medicinal products* Pegfilgrastim was not specifically mentioned in the GMP certificate, API declaration is required.	Determine if your API(s) are covered in GMP certificate, if not: **Provide API declaration/clarification upfront!**

CV – Application Receipt

Common pitfalls

1. **Relevant fees not paid (stop clock applied):**
   - 48% clearance applications* at receipting stage awaiting payment

Example of deficiency	What can you do?
If the application is a CV application and fee has not been paid	Select YES to this question: 

* Source based on October 2019 data

CV – Application Receipt

Common pitfalls

2. Incomplete applications (stop clock applied):

66% clearance applications* in assessment queue identified as incomplete

Common deficiencies	Example of deficiency	What can you do?
No clarification/justification provided upfront when certain evidence was not submitted with the application	List of products not provided however this may be located within the GMP agreement annexes	Provide clarification via cover letter upfront
Required evidence not provided by applicant	GMP agreement not provided for a contract testing laboratory	Understand the type of application you are selecting for your application
Awaiting for manufacturer to provide evidence directly to TGA	Sponsor cannot determine what evidence the manufacturer has provided directly to TGA	First point of contact: Talk to your manufacturer to ensure evidence has been submitted to TGA correctly

* Source based on October 2019 data

CV - Application Assessment

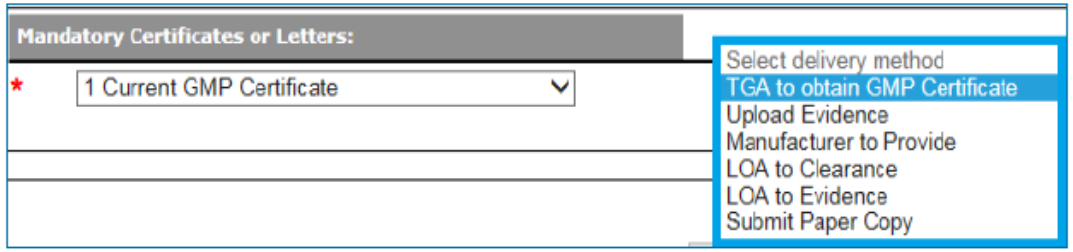
Majority of clearance applications at assessment stage identified deficiencies and require further information from the sponsor.

During assessment, you will be sent one request with a specified due date to provide information (stop clock applied)

Factors contributing to delay during assessment that may result in your application not issued:

- Response not provided by the due date
- Response provided does not address deficiencies raised
- New documents provided however there is no explanation on how it addresses the issues raised
  - **Include explanation and specific reference on how it addresses each of the deficiency**

CV – GMP certificate

Common deficiencies	Example of deficiency	What can you do?
US FDA cover letter provided as a GMP certificate	US FDA cover letter provided as a GMP certificate, liaison fee not paid	Ensure the following is selected: 
Pharmaceutical Inspection Cooperation Scheme (PIC/S) GMP certificate + European Directorate for the Quality of Medicines (EDQM) inspection report (outside the borders of PIC/S)	Manufacturing site: located in India GMP certificate: issued by Croatia with EDQM inspection report	Submit alternative evidence inspected by acceptable regulatory authority
Dosage forms or manufacturing steps in the GMP certificate not covered in the corresponding inspection report	GMP certificate: includes tablets and capsules Inspection report: only covered the manufacture of tablets	Understand the level of detail covered in the inspection report (relevant to the scope of your application)

CV - Inspection report

Common deficiencies	Example of deficiency	What can you do?
Inspection didn't cover specific buildings, systems, processes applicable to the scope of the application	Inspection report: covered manufacturing operations in Building A Scope: manufactured in Building B	**Communicate with your manufacturer before submitting your application to**: 1. Understand where your products are manufactured 2. Understand what was covered in the inspection report E.g. Specific buildings, systems, processes, products 3. How the scope of the inspection relates to your products 4. Provide justification upfront via cover letter!
Insufficient information on the suitability of facilities, utilities, processes relevant to the scope of the application	Primarily a list of deficiencies deficiency/Post Inspection Letter (PIL)	Provide alternate evidence (full inspection report) from recognised regulatory authority

CV - Inspection report

Common deficiencies	Example of deficiency	What can you do?
Heavily redacted	n/a	Request manufacturer to submit full unredacted inspection report directly to TGA
Not translated by an independent certified translator	Manufacturer translated the inspection report	• Ensure inspection report is translated by independent certified translator • Provide certified translation statement
PIC/S inspection report outside the borders of that country	Thai FDA inspecting a manufacturing site in India	Provide alternate evidence from recognised regulatory authority

CV - Regulatory inspections list

Common deficiencies	Example of deficiency	What can you do?
Not provided	List of inspections not provided however this information can be found in the Site Master File	Clarification is to be provided upfront where we can source this information. **Otherwise this may be identified as incomplete at receipting stage**
Inspection list identified a more recent inspection report, however no information on why this was not provided	Scope: tablets List of inspections included: - Jan 2018 US FDA - Jan 2019 US FDA Only the Jan 2018 US FDA inspection report was provided as this covered tablets however there was no explanation as to why Jan 2019 evidence was not provided	If the scope of your application is not covered in the latest inspection report, clarification/justification is to be provided upfront via cover letter

CV - Regulatory actions details

Common deficiencies	Example of deficiency	What can you do?
Declaration provided by the sponsor and not the manufacturer	Declaration with Australian sponsor's company letterhead and signed by the sponsor	Liaise with your manufacturer to sign this declaration before submitting your application
Only related to specific products for that particular application and not the entire manufacturing site	*"…No regulatory actions identified for product Z"*	Ensure the declaration is for the entire manufacturing site (not just specific to your products)
Refers to the outcome and deficiencies of inspections	*"…4 major deficiencies identified during May 2019 inspection"*	Liaise with your manufacturer to sign this declaration of all regulatory actions – not just the outcome of inspections before submitting your application
Regulatory actions occurred however no additional information about action/event	"…*Recall occurred in May 2019, however they are not related to products to Australia"*	Provide information around the following: • Regulatory action (include both voluntary and imposed) • Summary of the root cause analysis and investigations conducted • Corrective & preventative actions • Current status

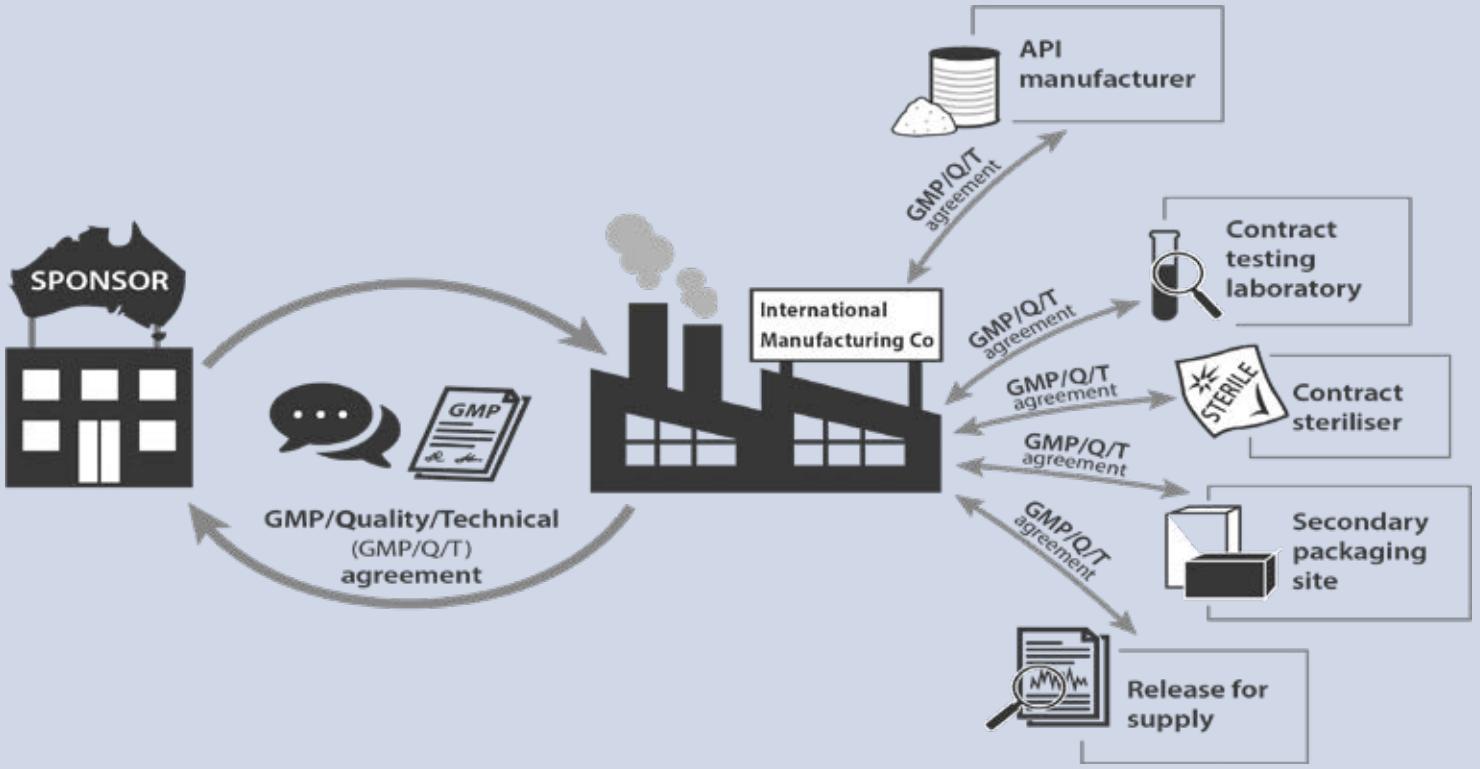
CV - Site master file (SMF), quality manual or equivalent

Common deficiencies	What can you do?
Not providing appendices	Ensure appendices included at application submission
Site layout not legible	Ensure site layout is legible –provide actual file size (not compressed)
Manufacturer's name and address in the SMF does not match the scope of your application	Ensure correct SMF provided at application submission
Insufficient information regarding manufacturer's operations, facilities and quality management system	Provide other documents that collectively contain the same details

CV - List of products intended for supply

Common deficiencies	Example of deficiency	What can you do?
Not provided	List of products not provided however this can be found in the GMP agreement	Clarification is to be provided upfront where we can source this information. **Otherwise this may be identified as incomplete at receipting stage**
Dosage form contradicts to what is in the application or GMP/Quality/Technical agreement	List of products: capsules, tablets Agreement: capsules Scope: tablets	Ensure list of products matches the agreement and the scope of your application.

CV - GMP agreement or equivalent

Common deficiencies	Example of deficiency	What can you do?
Convoluted supply chain		Provide clarification via cover letter upfront

CV - GMP agreement or equivalent

Common deficiencies	Example of deficiency	What can you do?
Missing signatures and dates	n/a	Ensure all parties have signed the agreement prior to application submission For new registrations or New Chemical Entity submissions, draft agreement is accepted. Provide clarification via cover letter upfront
Out of date agreements	Agreement provided is dated 2015	Provide updated agreement, otherwise provide justification via cover letter upfront (if applicable)

CV - GMP agreement or equivalent

Common deficiencies	Example of deficiency	What can you do?
Steps of manufacture not clearly defined in the agreement	Agreement: manufacture of dosage form Scope: full product manufacture	Ensure agreement is updated and relevant to Australian market
Sponsor proposes to apply for additional dosage forms to what is in the GMP agreement, however there is no information of this intention	Agreement: capsules Scope: capsules and tablets	Australian sponsor to provide a signed statement that the GMP agreement will be updated to reflect the relevant dosage forms prior to commercial supply to Australia. Appropriate condition may be placed on the GMP Clearance

CV - GMP agreement or equivalent

Common deficiencies

× Ambiguous terminology (Clarify upfront via cover letter!!)

Example:

CV - GMP agreement or equivalent

Common deficiencies

× Roles and responsibilities of all parties not clearly defined

Example

The table of responsibilities in the GMP agreement shows all parties are responsible for this function, however based on the application the Contract Acceptor is only responsible for Release for Supply step:

Responsibilities	Contract Giver 1 (Australian sponsor)	Contract Giver 2	Contract Acceptor
Release for supply	**X**	**X**	**X**

Please explain!

CV - GMP agreement or equivalent

For manufacturing sites responsible for Release for Supply (RFS) step:

Common deficiency	Example of deficiency	What can you do?
Roles and responsibilities of Australian Sponsor not defined when RFS step is conducted by the manufacturer	Missing post market responsibilities (e.g. recalls, complaints)	• Understand the supply chain supplied to Australia • Provide supporting documentation on the roles and responsibilities of Australian sponsor • Ensure it meets the full requirements of chapter 7 of the PIC/S guide (Good manufacturing practice for medicinal products – Part I)
	Australian sponsor does not meet the requirements regarding Product Quality Review (PQR) input and review	
	Shipping responsibilities for products to Australia not clearly outlined: • What happens if temperature excursions occur during shipping? • What happens to products shipped under quarantine?	

CV - GMP agreement or equivalent

When documentation provided is between the Global Head Quarters and manufacturer:

Common deficiencies	What can you do?
Roles and responsibilities of Australian Sponsor not provided	Provide a signed statement or global procedure from the sponsor that clearly outlines the roles and responsibilities of the Australian sponsor

CV - Release procedures

Common deficiencies	Example of deficiency	What can you do?
Manufacturing site is only responsible for release for further processing	Procedure is for releasing of bulk product	• Understand your supply chain • Ensure the scope of your application excludes RFS
Document provided is a procedure on how to use their system	System Interface Procedure provided- SAP	Communicate with your manufacturer to provide appropriate procedures
Unclear who is the Authorised Person	No information on who signs the batch documents	Communicate with your manufacturer to provide clear roles and responsibilities on who is responsible for this function
Unclear how batch records are checked according to relevant Marketing Authorisation	No information within the procedure	Provide supporting documents/procedures how batch records are checked to relevant Marketing Authorisation

CV - Validation Master Plan (VMP)

Common deficiencies	What can you do?
VMP for another site/building	Ensure VMP provided is applicable to the scope of your application
Missing dates of last qualification and proposed dates for re-qualification	Provide supporting documentation upfront, otherwise clarify via cover letter where we can source this information

CV - Product Quality Review (PQR)

Common deficiencies	Example of deficiency	What can you do?
PQR provided does not meet Chapter One of PIC/S Guide	PQR did not include a review of starting materials	As per PIC/S requirements (Clause 1.10 & 1.11), understand your responsibilities as an Australian sponsor
Statement and PQR procedure not provided for products that have not been subject to a review	n/a	Provide a statement if the substance or product has not yet been subject to a PQR Additionally provide the PQR procedure
Missing appendices	n/a	Ensure all appendices are included at application submission
Most recent PQR not provided	2014 PQR provided	Ensure updated PQR provided

Active Pharmaceutical Ingredients (API) declaration

Talk to your manufacturer before submitting the application!

MRA pathway:

- If the GMP certificate doesn't mention the specific API(s) in the scope of your application

CV pathway:

- If the inspection report provided only covered specific API(s) that is not relevant to the scope of your application

API declaration

Common deficiencies	Example of deficiency	What can you do?
Declaration signed by the sponsor	Declaration with Australian sponsor's company letterhead and signed by the sponsor	Liaise with your manufacturer to sign this declaration before submitting your application
Generic statement provided and building number not specified	*"…manufactured in the same facility (specific buildings) as those inspected and referenced in the inspection report or GMP certificate"*	Provide specific building number/name (e.g. Building B) your product is manufactured in
Declaration provided contradicts with other evidence	Inspection report: only covered building A Scope: Your product is only manufactured in building B	Provide relevant evidence

Letter of Access (LoA)

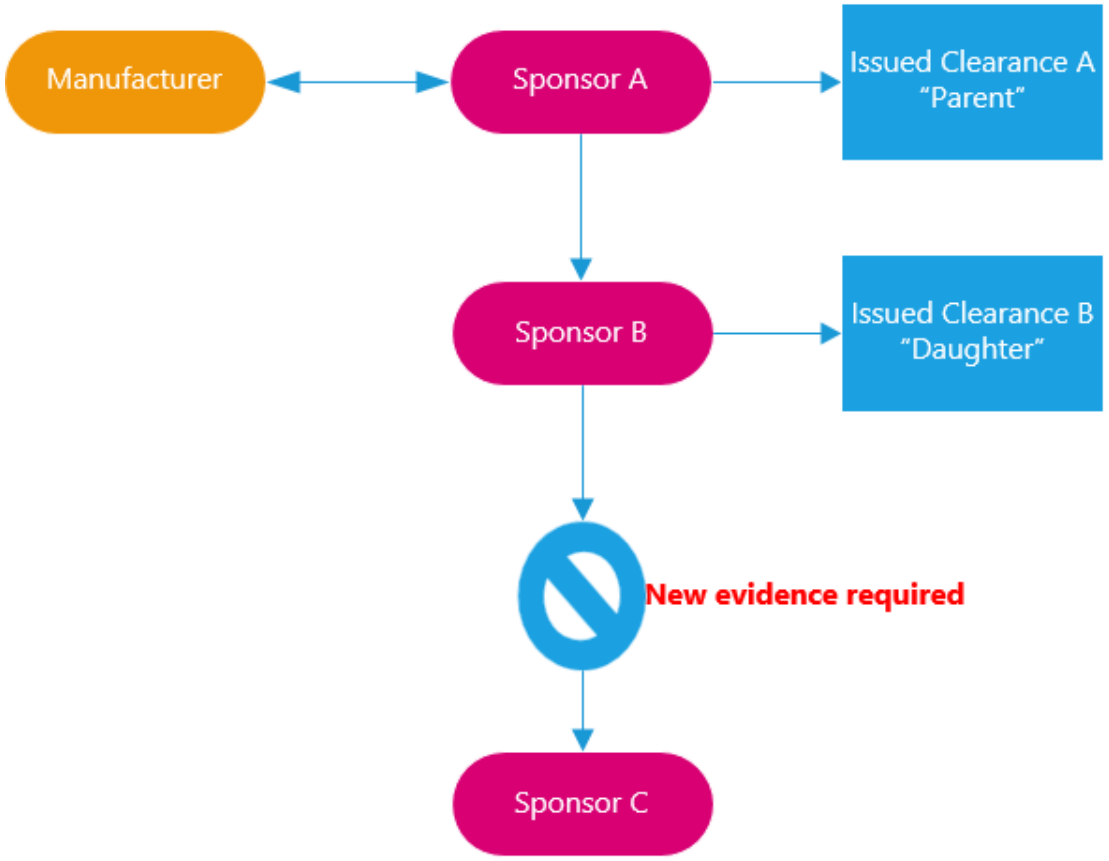
Common deficiencies	Example of deficiency	What can you do?
Sponsor specific evidence not provided	GMP agreement not provided	Ensure sponsor specific evidence is provided: • GMP agreement • List of products intended for supply • Latest Product Quality Review • API declaration (only applicable for LoA to evidence)
Unclear on the type of LoA	*"…LoA to clearance – grants access to evidence"*	**Clearly state the type:** • 'Manufacturer LoA to evidence'? • 'Sponsor LoA to evidence'? • 'Sponsor LoA to clearance'?

LoA to clearance

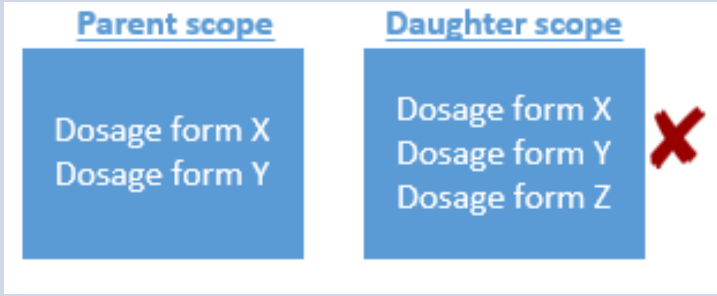
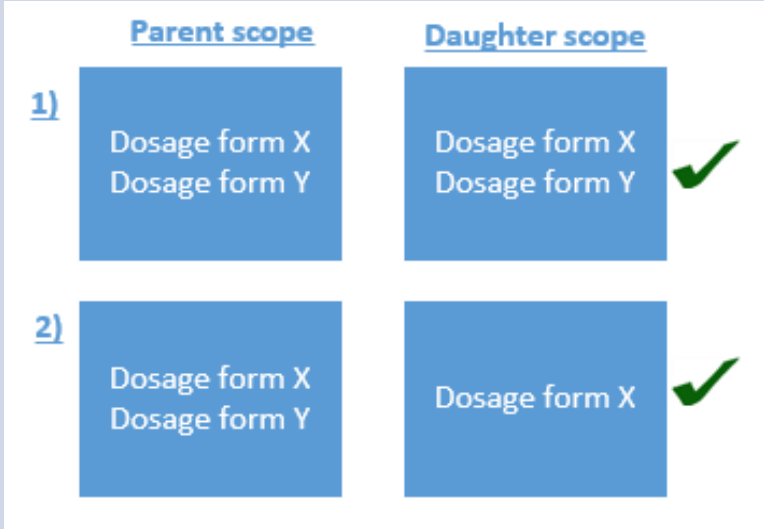
Common deficiencies

× Application it allows access to was issued using another LoA

Example:



LoA to clearance

Common deficiencies	Example of deficiency	What can you do?
Scope of application accessing the LoA (daughter) is **not** identical or less than the clearance scope providing the access to (parent)		Communicate with the sponsor granting you to access LoA and consider the following: 
API declaration provided (cannot be accepted if API is not in the parent application)	Parent: ibuprofen Daughter: ibuprofen, albumin (API declaration provided)	

Summary

Communicate with your manufacturer!!

- Understand what is in the evidence submitted with your application
- Understand where your product is manufactured
- Was the manufacturing line for your product covered in the inspection report? If not find out how the products/buildings/manufacturing lines in the inspection report relate to your products
- Understand your supply chain to the Australian market
- Any ambiguity in terminology, responsibilities or evidence provided should be clarified upfront via a cover letter
- If you have any questions, contact us before submitting your GMP clearance application

Website and link references

Information about the GMP Clearance process is available at:
https://www.tga.gov.au/publication/gmp-clearance-guidance

Information about international agreements and arrangements for GMP clearance:
https://www.tga.gov.au/international-agreements-and-arrangements-gmp-clearance

Regular updates about changes are provided through the Notices about GMP Clearance
https://www.tga.gov.au/notices-about-gmp-clearance

- Increases to fees and charges
- Timeframes

Enquiries regarding desk top assessments using overseas regulator evidence
GMPClearance@health.gov.au

Enquiries regarding general GMP enquiries, Australian manufacturers, overseas sites seeking a TGA inspection of their facility
GMP@health.gov.au

Karman is currently reading over your submitted questions.

We would appreciate your participation in our live polling.
We'll will be back shortly for **Q&A**

LIVE POLL

Question time

More information

- TGA website – tga.gov.au
- GMP Clearance https://www.tga.gov.au/manufacturing-medicines
- Facebook – TGA Australia
- Twitter - @TGAgovau
- YouTube
- TGA topics blog - tga.gov.au/blogs/tga-topics

Contact us

GMP Clearances

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