GMP Clearance - Addressing Application Deficiencies

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GMP FORUM 2024

Agenda

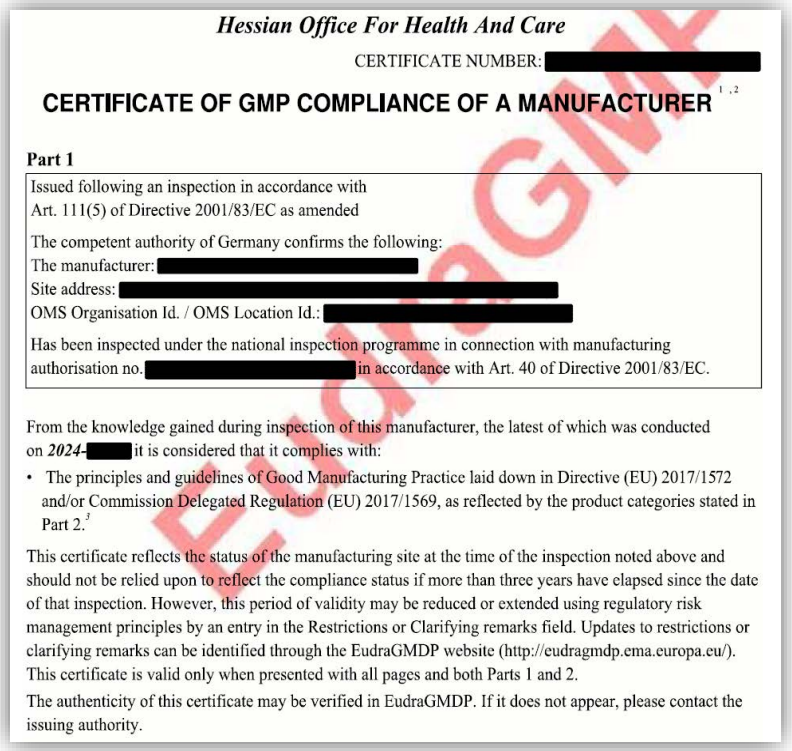
- Introduction
- MRA Pathway
- CV Pathway
- Top 5 Tips
- Questions

Introduction

GMP Clearance Overview

- Is used to verify the GMP compliance of an overseas manufacturing site with the principles of GMP.
- GMP Evaluators often identify several evidence deficiencies within GMP Clearance applications.
- Sending Requests For Information (RFI) or Proposal to Not-Issue (PNI) can increase the assessment time of your applications.
- You may be able to streamline your application by addressing the common deficiencies before applying.

MRA Pathway



Hessian Office For Health And Care

CERTIFICATE NUMBER: [redacted]

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1,2]

Part 1

Issued following an inspection in accordance with
Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of Germany confirms the following:
The manufacturer: [redacted]
Site address: [redacted]
OMS Organisation Id. / OMS Location Id.: [redacted]

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. [redacted] in accordance with Art. 40 of Directive 2001/83/EC.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2024-***[redacted] it is considered that it complies with:

- The principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572 and/or Commission Delegated Regulation (EU) 2017/1569, as reflected by the product categories stated in Part 2.[3]

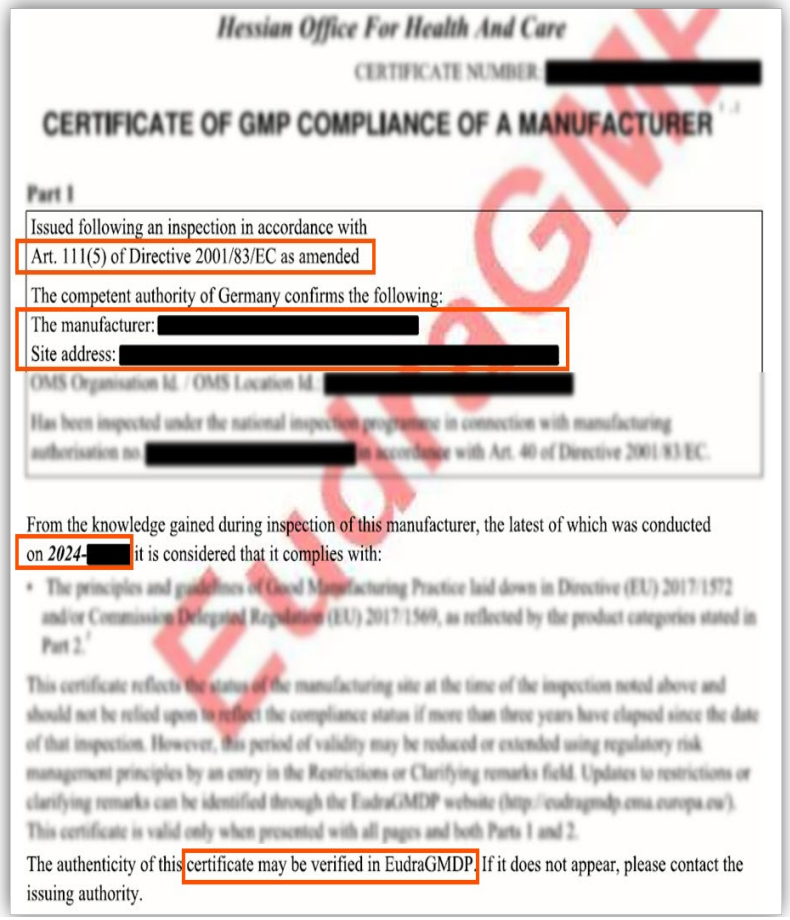
This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. Updates to restrictions or clarifying remarks can be identified through the EudraGMDP website (http://eudragmdp.ema.europa.eu/). This certificate is valid only when presented with all pages and both Parts 1 and 2.

The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

GMP Certificate

- Primary evidence to support your application scope
- Insufficient evidence will result in clearance not issued
- Planning your application to ensure success
- Example: EU GMP Certificate
  - Follows standard format
  - Publicly available databases – Eudra GMDP / MHRA / Swissmedic

MRA Pathway



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Site address: [redacted]
OMS Organisation Id. / OMS Location Id.: [redacted]

Has been inspected under the national inspection programme in connection with manufacturing authorisation no [redacted] in accordance with Art. 40 of Directive 2001/83/EC.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on *2024-[redacted]* it is considered that it complies with:

- The principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572 and/or Commission Delegated Regulation (EU) 2017/1569, as reflected by the product categories stated in Part 2.

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The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

GMP Certificate - Part 1 Acceptable

- EU GMP certificate
- Issued for Human Medicinal Products
  - Directive 2001/83/EC
- Other regulatory authorities have similar GMP standards
- Manufacturer name & address aligns with your application

MRA Pathway

Hessian Office For Health And Care
Regierung Von Oberfranken

CERTIFICATE NUMBER [redacted]

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with :

Art. 15 of Directive 2001/20/EC

The competent authority of Germany confirms the following:

The manufacturer: [redacted]

Site address: [redacted]

OMS Organisation Id. / OMS Location Id: [redacted]

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. [redacted] in accordance with Art. 13 of Directive 2001/20/EC.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on *2022*[redacted] it is considered that it complies with:

- The principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572 and Commission Delegated Regulation (EU) 2017/1569

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and

Part 2

Human Investigational Medicinal Products

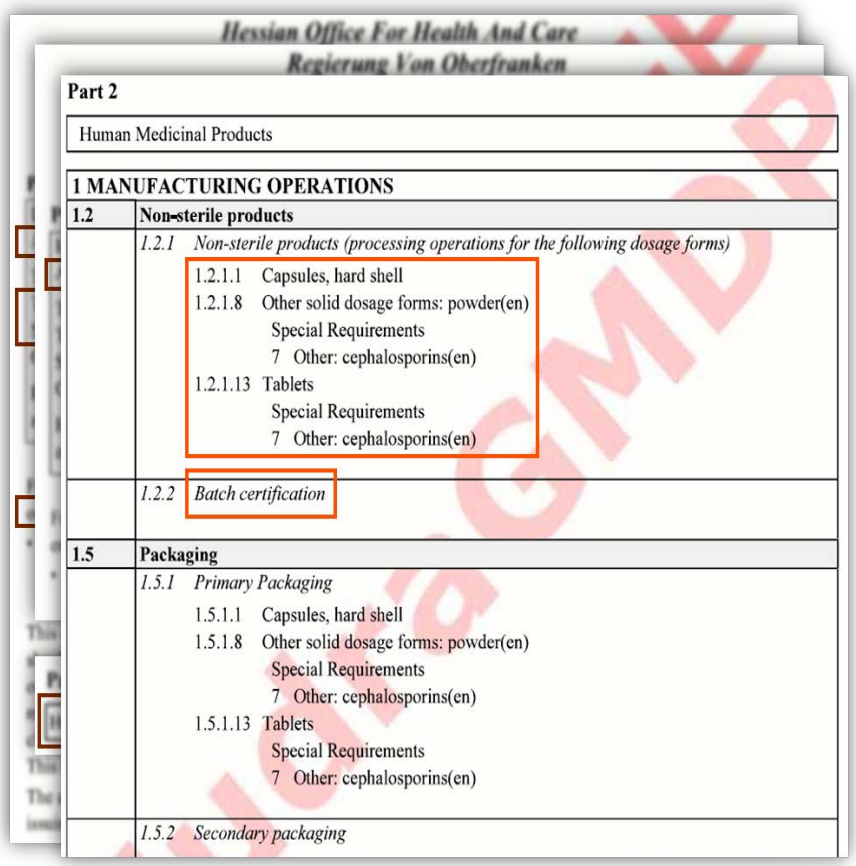
This certificate is valid only when presented with all pages and both Parts 1 and 2.

The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

GMP Certificate - Part 1 Unacceptable

- Clinical trials / investigational medicines
  - Directive 2001/20/EC
- Veterinary medicinal products
  - Directive 2001/82/EC / Regulation (EU) 2019/6
- Inequivalent GMP standards
  - Food / devices

MRA Pathway



Hessian Office For Health And Care
Regierung Von Oberfranken

Part 2

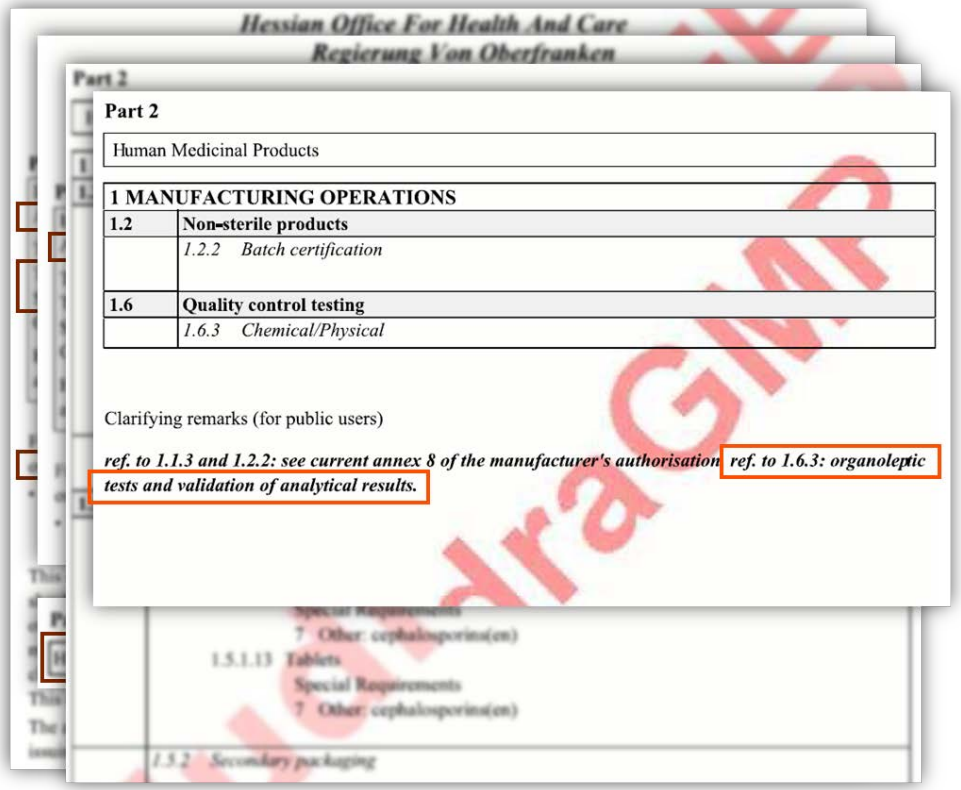
Human Medicinal Products

1 MANUFACTURING OPERATIONS	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms)
	1.2.1.1 Capsules, hard shell
	1.2.1.8 Other solid dosage forms: powder(en)
	Special Requirements
	7 Other: cephalosporins(en)
	1.2.1.13 Tablets
	Special Requirements
	7 Other: cephalosporins(en)
	1.2.2 Batch certification
1.5	**Packaging**
	1.5.1 Primary Packaging
	1.5.1.1 Capsules, hard shell
	1.5.1.8 Other solid dosage forms: powder(en)
	Special Requirements
	7 Other: cephalosporins(en)
	1.5.1.13 Tablets
	Special Requirements
	7 Other: cephalosporins(en)
	1.5.2 Secondary packaging

GMP Certificate - Part 2 Dosage forms

- Must support the clearance application scope
- This example supports:
  - Manufacture of hard capsules, powder and tablets
  - Release for supply
- Does not cover:
  - Manufacture of soft capsules, liquids, etc.
  - Manufacture of any sterile dosage forms

MRA Pathway



GMP Certificate - Part 2 Steps and remarks

- Certificate supports:
  - Release for supply (non-sterile)
  - Chemical / Physical testing
- Does not cover:
  - Manufacture of dosage form
  - Microbiological testing
- Clarifying remarks can limit application scope
  - Site only performs ‘organoleptic tests’ (visual, odour, texture, etc.)
  - Chemical assay may not be covered

CV Pathway

General Application Issues

- Evidence does not meet the general documentary requirements
  - Not the most recent version
  - Inspection report translations are not certified
- No attachments / appendices provided for each document
- Information is redacted to the point where it hinders assessment

CV Pathway

Inspection Report

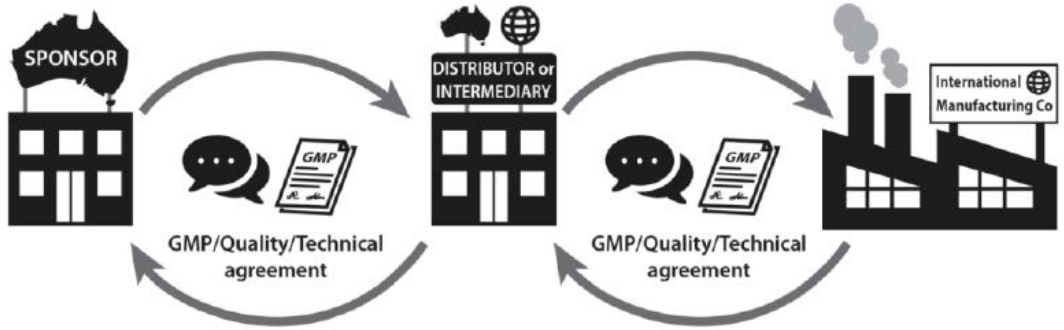
- List of inspection observations provided instead of the full report
- The inspection doesn’t cover the scope of the application
- The inspection was conducted under the wrong compliance program
  - E.g Food / device / clinical
- Not from a recognised regulatory authority

CV Pathway

Site Master File / Validation Master Plan

- Appendices / attachments not provided
- Diagrams / floor plans not legible
- Validation schedule not provided or has insufficient details
- Unclear which buildings / suites are used to manufacture specific APIs or dosage forms

CV Pathway



Quality Agreements

- Australian sponsor is not included
- Not all agreements in the supply chain are provided
- The parties are not clearly identified / have not signed or are missing contact details
- The roles and responsibilities are unclear
  - e.g. Both parties marked as responsible
- Does not cover the required dosage forms or manufacturing steps

CV Pathway

Release for Supply Procedure

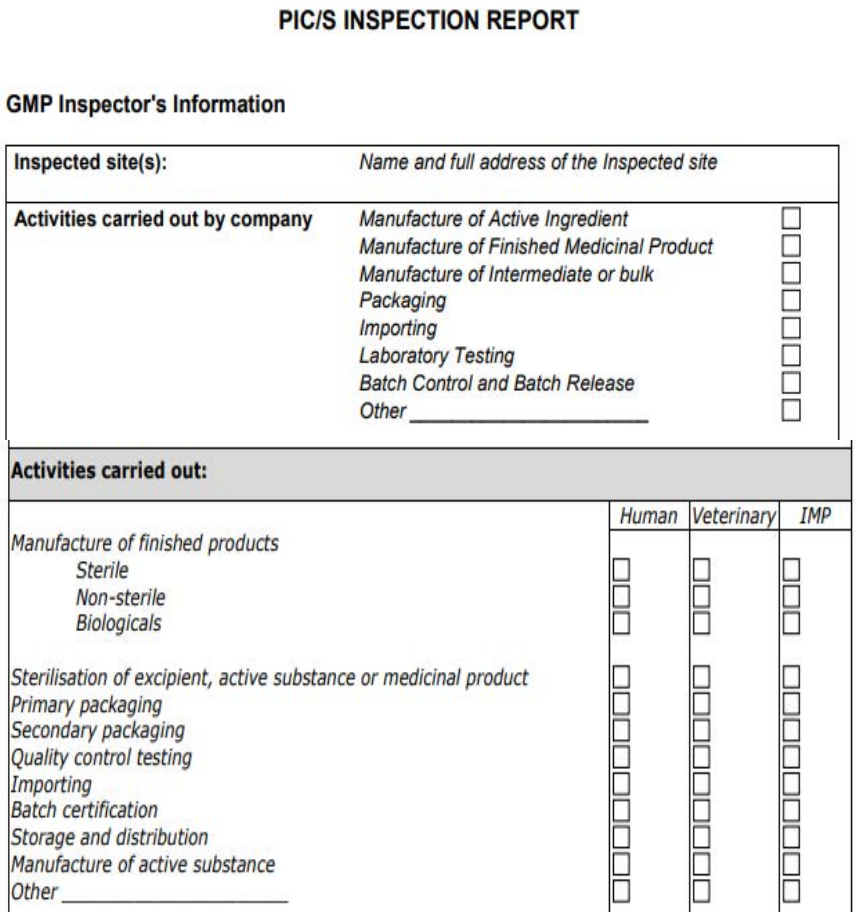
- The document provided is a system interface procedure
  - e.g. SAP
- Release checklist / appendices related to the procedure are not provided
- Does not detail how the Australian MA requirements are considered by the AP
- Unclear or inconsistent between site procedures and GMP agreements
  - e.g. Release under quarantine

Top 5 Tips to Improve GMP Clearance Applications

1. Complete documentary evidence

- The full copy of the most recent document version or evidence is provided
- The documents and any drawings are legible and able to be understood clearly
- They are not excessively redacted
- All appendices provided for each document
- Documents are signed and effective

Top 5 Tips to Improve GMP Clearance Applications



PIC/S INSPECTION REPORT

GMP Inspector's Information

Inspected site(s):	*Name and full address of the Inspected site*	
Activities carried out by company	*Manufacture of Active Ingredient*	☐
	Manufacture of Finished Medicinal Product	☐
	Manufacture of Intermediate or bulk	☐
	Packaging	☐
	Importing	☐
	Laboratory Testing	☐
	Batch Control and Batch Release	☐
	Other _____	☐

Activities carried out:			
	Human	*Veterinary*	*IMP*
Manufacture of finished products			
Sterile	☐	☐	☐
Non-sterile	☐	☐	☐
Biologicals	☐	☐	☐
Sterilisation of excipient, active substance or medicinal product	☐	☐	☐
Primary packaging	☐	☐	☐
Secondary packaging	☐	☐	☐
Quality control testing	☐	☐	☐
Importing	☐	☐	☐
Batch certification	☐	☐	☐
Storage and distribution	☐	☐	☐
Manufacture of active substance	☐	☐	☐
Other _____	☐	☐	☐

2. Supporting your scope

- Ensure scope of the inspection / GMP certificate align with your application scope
- Ensure you understand how other jurisdictions regulate your product
    - E.g. Vitamin supplements regulated as food, sunscreen regulated as cosmetics
- Understand the evidence requirements for GMP Clearance applications

Top 5 Tips to Improve GMP Clearance Applications

3. Effective communication with the site

- Know what evidence is available for your site
    - Confirm a recognised regulator has inspected the site
- Knowing what and when information is being provided by the manufacturer
- Ensure the manufacturer provides complete and timely responses to RFIs
- Ensure the GMP agreement roles and responsibilities are appropriate

Top 5 Tips to Improve GMP Clearance Applications

4. Understanding your registration / listing requirements

APIs/drug substances - biological medicines manufacturing step(s)	Recorded on ARTG
Master cell bank manufacture, storage and maintenance	No♥
Working cell bank manufacture, storage and maintenance	Yes
Manufacture of intermediates from higher risk starting material (e.g. sourced from animals, bacteria, viruses, recombinant material)	Yes
Active Material Manufacture	Yes
Chemical and Physical, biological or microbiological testing that is later used to inform release for supply of the finished product	Yes*
In-process control testing	No
Packaging	No
Storage of drug substance	No♥
Release for further processing	No

- Contact the relevant product registration and listing areas to confirm requirements prior to submitting a GMP Clearance
    - Understand which manufacturing steps need to be on the ARTG
- Ensure the dosage forms / manufacturing steps of your GMP Clearance align with your product registration / listing
- The product regulatory area will determine what manufacturing steps will require a GMP Clearance / evidence of GMP

Top 5 Tips to Improve GMP Clearance Applications

5. Streamline your application

- Include a cover letter in your application if clarification is needed
- Provide relevant information if requesting prioritisation
    - e.g. Medicine shortage notification, product submission details
- Communicate delays as early as possible
    - e.g. Requesting extensions to respond to Requests for Information
- Sponsor Information Dashboard (SID) has current links to information and user guides on how to submit a clearance

Questions?

Scan this QR code with your device to submit a question

GMP FORUM 2024

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration