

Empowering Compliance: The Critical Role of QPs in API GMP Auditing

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Learning outcomes

- How Qualified Persons (QPs) are at the forefront of ensuring API GMP compliance
- QP Declaration Requirement for Regulatory Submissions
- Discussing the challenges surrounding QP declarations
- How audit assessments continue to pose significant hurdles.

Legal Backbone of QP API GMP Declarations

Directive 2001/83/EC

-  Initial Framework - No specific provisions for API GMP or QP declarations at this stage.

Directive 2004/27/EC

-  Turning Point – QP API GMP Declaration Introduced.

Directive 2011/62/EU (Falsified Medicines Directive)

-  Transport, Supply Chain, and Risk Controls – Written Confirmation, Registration and API GDP Transportation.

QP Declaration Requirement for Regulatory Submissions -1

Active substance manufacturer(s)	Finished product manufacturer(s)	Batch release site(s)
Name/address of new API manufacturer	Corresponding list of each registered product manufacturing site that uses active substance originating from the listed API site	Corresponding list of each registered batch release site releasing product containing active substance originating from the listed API site

New Active Substance Manufacturing Site

QP Declaration Requirement for Regulatory Submissions -2

Active substance manufacturer(s)	Finished product manufacturer(s)	Batch release site(s)
List each registered API manufacturer	Corresponding list of each registered (<i>and proposed new</i>) product manufacturing site that uses active substance originating from the listed API sites	Corresponding list of each registered batch release site releasing product containing active substance originating from the listed API sites

New Finished Product Manufacturing Site

QP Declaration Requirement for Regulatory Submissions -3

Active substance manufacturer(s)	Finished product manufacturer(s)	Batch release site(s)
List each registered API manufacturer	Corresponding list of each registered product manufacturing site that uses active substance originating from the listed API sites	Corresponding list of each registered (<i>and proposed new</i>) batch release site releasing product containing active substance originating from the listed API sites

New Finished Product Batch Release Site

QP Declaration Requirement for Regulatory Submissions -4

Depends on the Criticality of the Change ...

Marketing Authorisation (MA) Renewal

CEP Revisions or ASMF (DMF) Updates

**New Marketing Authorisation
(MA) Application**

QP Declaration Challenges – Focus on API Starting Materials

PART A: Concerned active substance manufacturing sites

Name of Active Substance:

Name and Address of Active Substance Manufacturing Site^{1,2}	Manufacturing Operation / Activity³

1. List each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting material, include intermediate manufacturing sites / part-processing sites.
2. State the site name and address in detail, including the building numbers (if applicable).
3. For example – Full or partial manufacture of the active substance, micronisation.

QP Declaration Challenges – Focus on API Starting Materials

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology : fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
“Classical” Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

Increasing GMP requirements



- An “Active Substance Starting Material” is a raw material, intermediate, or an active substance that is used in the production of an active substance and **that is incorporated as a significant structural fragment** into the structure.
- The Manufacturer should designate and document the rationale for **the point at which production of the active substance begins.**

QP Declarations – Challenges with Dossier Access and Redundant Sites

? Do You (QP) Have Access to the Dossier?

- QPs often do not have direct access to the entire ASMF or CEP, especially if it's under restricted part confidentiality

Should QP Declarations Include Redundant Sites?

- ✓ Best practice:
 - Include only active manufacturing sites in QP declaration
 - Redundant sites should not be included - Potential non-compliance if site is inactive and not maintained to GMP standards.



Is this API covered by a CEP or ASMF?

Search the API name in the EDQM CEP database:

https://extranet.edqm.eu/publications/recherches_CEP.shtml

 **1. ASMF
(Active Substance
Master File)**

- Also known as: DMF (Drug Master File)
- Consists of:
 - Open Part (Applicant's Part) – shared with the finished product MAH
 - Restricted Part – confidential, only seen by regulatory authorities
 - No reference to Ph. Eur. monograph or CEP.



Is this API covered by a CEP or ASMF?



2. Verify CEP Versions

- Cross-check all CEPs against the EDQM Certification Database, The API manufacturer holds a CEP number (e.g., R0-CEP 2023-123-Rev 00).
- Confirm that the latest valid version is held and referenced
- Ensure no expired, superseded, or withdrawn CEP is being relied on
- 🔍 Tools: EDQM Public CEP Database - https://extranet.edqm.eu/publications/recherches_CEP.shtml.

QP Declarations Must Reflect the Finished Product Context

- API GMP declaration depends on the finished product it is used in. The same API may need different declarations based on its intended dosage form and processing steps.

One API ≠ One Declaration for All Products

 Example: Salbutamol API

Used in	Formulation	Processing Requirement	CEP Covers It?	Declaration Must Include
Syrup	Oral liquid	None (standard API)	 Yes	API manufacturing site (from CEP)
MDI Inhaler	Pressurised inhalation	 Micronisation	 No	Micronisation site + API manufacturing site

QP Declarations – Who, When, and How Many

PART B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies

This QP declaration is applicable to the following registered MIAH(s), that use the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product, where the active substance is registered as a starting material and is manufactured at the sites listed in Part A:

MIAH Site	MIAH Number	Manufacturing Activity

-  Supporting Agreements:
 - Quality Agreement: Governs technical and GMP responsibilities
-  QP-to-QP Agreement Can support clarity on:
 - Audit reliance
 - Document/data sharing
 - Responsibility demarcation.

Basis of QP Declaration – What Must Be in Place? (Part C)

PART C: Basis of QP Declaration of GMP Compliance

Please tick section (i), complete the table in section (ii) and, if applicable, add the supplementary supporting information to section (iii).

(i) **On-site audit of the active substance manufacturer(s)**

(ii) **Audit(s) of the active substance manufactured at the site(s) listed in PART A has/have been completed either by the MIAH(s) listed below or by a third party auditing body(ies) i.e. contract acceptor(s) on behalf of the MIAHs i.e. contract giver(s) as listed:**

MIAH Site (or contract giver)	Auditing body (contract acceptor)	Site audited	Date of audit ⁴

⁴ Justification should be provided if the date of last audit exceeds 3 years:

Section (ii): Audit Details Must Answer...

 Question

 Notes to Clarify

Product-specific or site-specific audit?

Must include the API in scope

Full API supply chain documented?

From starting material → brokers/traders

Audit done by QP or delegated third-party?

Must be qualified, independent

Is the Technical Agreement in place?

Between MIAH and API manufacturer/supplier

Do they have incoming goods inspection?

Must include: CoA checks, sampling, rejection system

Are qualified auditors used?

Training + GMP Part II knowledge required



How Do You Scrutinise the Audit Report?

- To scrutinize an audit report conducted by others (especially when audit was conducted by non-QPs), a systematic and critical review is essential
- A checklist-style framework - use this to evaluate whether the audit report meets the EU GMP Part II and ICH Q7 standards and fulfils your due diligence obligations as a QP within the MIAH
- Refer the next slide ...

✓ 1. Audit Identity & Administration

- Full site address included.
- Auditor(s) name, employer, and audit organizing party (MIAH or third party) documented.
- Contact person at the site clearly named (email and phone).
- Audit date(s) clearly stated and justified (e.g., full days/partial days).
- Justification for audit duration provided (if shorter than standard).
- Site overview included – company ownership, age, headcount, GMP history.

✓ 3. Historical Context

- Dates of previous audits of the same site recorded.
- Negative outcomes, if any, summarized.
- Explanation of risk-based focus for any reduced-scope follow-up audits.

✓ 5. CAPA Review

- Manufacturer's responses to findings assessed.
- Review of corrective/preventive actions (CAPA) with timelines.
- Auditors' assessment of CAPA adequacy and supporting documentation.

✓ 2. Scope of Audit

- Clearly states whether full manufacture or partial process was audited.
- Lists specific APIs or intermediates covered under audit scope.
- Activities assessed under EU GMP Part II / ICH Q7 chapters are listed.
- Excluded activities explicitly stated.
- Buildings and stages audited are clearly identified.
- Access denial to any area noted and explained.
- High-risk areas flagged for focus (e.g., cross-contamination, validation, deviations, shipment control).

✓ 4. GMP Compliance Analysis

- Full assessment provided for each section of EU GMP Part II.
- Key observations, deficiencies, and compliance status detailed per section.
- Findings categorised (Critical / Major / Minor) with definitions of these terms.
- List of APIs made on multi-purpose equipment recorded.

✓ 6. Final Assessment

- Auditor provides summary of CAPA review status.
- Final recommendation on GMP compliance status provided.
- Statement on whether reduced goods-in checks at FP site are justified.
- Proposed re-audit interval stated.
- Signed and dated by lead auditor.

API GMP QP Declarations – Summary

Key starting materials,
Intermediates

Buildings references and
addresses agree with
CEP/ASMF

API Supply chain and
transportation?

Incoming Goods inspection
program

QTA between API
manufacturer and
Finished Product
Manufacturer

Trained or Qualified auditor
you can trust ?

QP-QP agreement

Any GMP certificates –
local, EU or MRA
partners?

QP Responsibility – Finished Product vs API GMP Declarations

■ Section 1: Finished Product Certification

- 🍌 Each batch must be certified by the QP
- 📄 Directive: Article 51 of Directive 2001/83/EC
- ⚖️ This is a legal duty and widely understood
- 👤⚖️ QP is responsible and accountable

■ Section 2: API GMP Declarations – Equally Serious

- 🌐 APIs are manufactured globally
- 🚫 Batch-by-batch certification not feasible
- EU Finished products are released in UK/EU
- 📄 QPs rely on GMP declarations for APIs

■ Section 3: The Reality of API GMP Declarations

- 📄 GMP declarations are based on 3-year audit frequency
- 🔍 If audits are delegated, they must be robust
- ⚠️ Even if delegated, QP remains legally accountable
- 👤 Signing = Legal responsibility

■ Final Callout :

⚠️ Do NOT take API GMP declarations lightly

→ They carry legal weight
→ They demand robust due diligence.

Useful tips

Awareness of the regulator and their role

- Medicines and Healthcare products Regulatory Agency (MHRA)
 - An executive agency sponsored by the Department of Health and Social Care - The “Competent Authority” in the UK for medicines for human use

MHRA sources of information:

- Blogs, Publications, Guidance Notes, Email alerts

International Focus

- Learn about other regulators and relevant guidance documents.

Events & Training courses

- Engage with industry peers to learn from best practices
- Approved courses delivering bespoke training to meet your learning needs

Consultancy services

- Tailor-made guidance from experienced consultants to achieve maximum compliance

SeerPharma UK

Our philosophy

Understanding the regulations is good, but understanding the Regulator is, we believe, the gold standard. As former MHRA inspectors and , we have both the insight and practical understanding of the regulatory regime as well as practical knowledge of how those regulations are interpreted.

Our aim

To share that inside knowledge to help you compete successfully in the regulated environments of pharmaceutical, biotechnology, medical devices and related industries.

Meet the Team



Mariam Naqesh-Bandi, Director & Senior Consultant



Shahbaz Sarwar, Director & Senior Consultant



Arvind Vijayabhaskar, Director & Senior Consultant



Alan Bentley, Director & Senior Consultant



Debra Stanfield, Office Manager

... Including Subject Matter Expert Associate Consultants

Consultancy services provided

Highly tailored and practical advice and solutions to help companies grow their business

Provide extensive knowledge of the regulatory environment to effectively communicate this to significant figures in industry (licence holder and Responsible Persons)

Ensure companies have in place the correct quality and productivity tools and techniques required to succeed. So whether that's improving their compliance history with the regulator, differentiating against national and international competition or driving greater profitability from operations, SeerPharma can provide the solutions.

Have provided services to pharmaceutical businesses ranging across different business models: Specialised distribution, cold chain, biologicals, marine, aesthetics, freight forwarders, virtual operators, NHS hospitals, manufacturers, pharmacies, UK and Global.

Training services provided

- Responsible Person Gold Standard training courses held every 4-6 weeks via remote, hybrid and face-to-face
- Training courses available:
 - Export and Import of Pharmaceuticals
 - Quality Risk Management in Distribution
 - Deviation, CAPA and Root Cause Analysis
 - WDA Holder – GDP and Licence Obligations
 - MIA Holder – GMP and Licence Obligations
 - Audit (self-inspection) training
 - Temperature Management
 - Responsible Person Import
 - Principles of Good Manufacturing and Distribution Practice
 - Wholesale in Community Pharmacy/GDP for Pharmacists (coming soon)
- Bespoke training tailored to a company's requirements or circumstances.
- Working collaboratively with other training providers, e.g. TOPRA and Key2Compliance
- Coming soon: GDP eLearning.

Any questions?

Let's chat! Please come and visit us at Stand 203

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