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EU Qualified Person:
Understanding the Role, Tasks, Responsibilities and EU procedures

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QP - Role, Tasks, Responsibilities and EU procedures

- The EU Directives, EU Regulations, and the EU Guides to GMP (Eudralex Vol. 4) define detailed requirements to be met by the Qualified Person (QP).
- Terminology
- QP Role, QP and Clinical trials
- Ethical duties of the QP
- QP vs QA

QP - Role, Tasks, Responsibilities and EU procedures

Regulations – Directives – Decisions – Recommendatons / Opinions / Guidelines

- A "regulation" is a binding legislative act. It must be applied in its entirety across the EU.
  Example: Clinical Trial Regulation •
- A "directive" is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals. Example: Directive 2001/83/EC
- A "decision" is binding on those to whom it is addressed (e.g. an EU country or an individual company) and is directly applicable.
- A "recommendation" is not binding.

- Directive 2001/83/EC
- Directive 2001/20/EC (Clinical Trials Directive, Articles 48, 49, 51 – qualification, education, responsibilities)
- Directive 2003/94/EC and Regulation (EU) No 536/2014 (Clinical Trials Regulation)
- EudraLex Volume 4 (Annex 16..)
- Local regulation frame (QP registrar....)

QP - Role, Tasks, Responsibilities and EU procedures

MIA – Market Import Authorisation

CTA – Clinical Trial Application

CTR – Clinical Trial Regulation

CTS – Clinical trial supply

IMP – Investigational Medical product

AMP – auxillary medicinal product

ImPD – Investigational medical product dossier

MA – market authorisation

PSF – Product Specification File

TQA – Technical Quality Agreement

QP - Role, Tasks, Responsibilities and EU procedures

- **Manufacturing and Importation Authorisation (Site Licence)**
    - EU pharmaceutical companies hold a Manufacturers' Importers Authorisation (MIA), which is essentially a "site license"
    - MIA details the manufacturing and packaging activities that a company is authorised to carry out, and also lists the personnel that are authorized to act as a Qualified Person at the site
    - Sanaclis is MIA holder (+ GMP certificate)
    - Periodically inspected

- **Wholesale Distribution Authorisation (Site Licence)**
    - Requires an EU Responsible Person to be named on the WDA
    - Issued by the local Regulatory Authority
    - Comply with GDP, inspected prior to issuance of WDA
    - Periodically inspected against Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01)

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- **Is packaging a manufacturing operation?**
    - YES
- **Is a labeling/clinical labeling a manufacturing operation?**
    - YES
- **Is import of IMP from a 3rd countries a manufacturing operation?**
    - YES

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QP vs QA

- QP = legal liability, batch-focused
- QA = system oversight
- Decision chain: QA → QP for final release

Feature	Qualified Person (QP)	Quality Assurance (QA)
Legal Status	Legally mandated by EU Directive 2001/83/EC.	Corporate function; not a specific legal requirement for individuals.
Liability	**Personal & Criminal liability**. The QP can be sued or imprisoned for a bad batch.	Corporate liability. The company is responsible for QA failures.
Focus	**Batch-specific.** "Is *this* specific batch safe and compliant for *this* trial?"	**System-specific.** "Are our processes, SOPs, and training programs robust?"
Main Duty	Batch Certification and formal release for use in humans.	Auditing, SOP management, CAPA oversight, and training.
Independence	Must be independent of Production (and often QA management).	Often reports to the Head of Operations or a Quality Director.

EU QP

- The QP role is **mandated by EU law**
- *no batch* can be released without formal QP certification
- This certification is a **legal requirement** (built into EU GMP and the MA and CTR framework

- Personal legal responsibility
- Scope: GMP compliance, MA/PSF/CTA requirements, testing documentation completness
- Import testing (if applicable)

QP - Role, Tasks, Responsibilities and EU procedures

The QP acts as a **personal guarantor** of:

- GMP compliance,
- regulatory compliance with the MA/CTA
- correctness of testing and manufacturing,
- appropriateness of imported batch controls,
- and the overall integrity of batch release

This is a **unique EU concept**: a single, identifiable individual carries personal responsibility and legal accountability for the release of every medicinal batch

QP - Role, Tasks, Responsibilities and EU procedures

Qualification and Education

- **Education:** A university degree in pharmacy, biology, or chemistry (or equivalent).
- **Experience:** Several years of experience working in pharmaceutical manufacturing operations
- **Residence:** Must reside within the EU
- **Delegation:** While they can delegate technical tasks, the final certification and release of a batch cannot be delegated

QP - Role, Tasks, Responsibilities and EU procedures

- **Before CT submission**
  - MSA, QTA, QP to QP
  - ImPD review
  - Audit of manufacturing sites
  - QP declaration (Template QP declaration has been issued by the European Medicines Agency (EMA))

- **After submission**
  - Import
    - testing in EU (after the import from 3rd country is obligatory only for commercial products
  - Certification/Release
    - **Step 1: Technical Release** - Qualified Person certifies batch compliance usingmanufacturing records, testing, audits, and PSF alignment.
    - **Step 2: Regulatory Release** - Sponsor ensures trial authorization, ethics approvals, andsite readiness in receiving country.

QP - Role, Tasks, Responsibilities and EU procedures

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Audit: *"I have personal knowledge that this site complies with GMP."*

- Each manufacturing, packaging, release testing site listed in ImPD
  - Every 2-3 years
- Audit delegation: 3rd Party report accepted - if they meet the defined requirements
- RA inspections – not accepted

<u>Reports should be sufficiently detailed for assessment to be made</u>

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QP - Role, Tasks, Responsibilities and EU procedures

PSF vs ImPD

Summary Table		
Feature	**IMPD**	**PSF**
Purpose	Regulatory submission for CTA approval	GMP reference file for QP batch certification
Audience	Regulatory authorities + Ethics Committees	Manufacturer + Qualified Person
Focus	Scientific evidence (quality, non-clinical, clinical)	GMP compliance, manufacturing documentation
Required by	Clinical trial legislation (Reg. 536/2014, guidelines)	EU GMP Annex 13
Level of detail	Broad, scientific, CTD format	Practical, GMP-operational quality documentation
When updated	With CTA changes or new data	Continuously to reflect current GMP and manufacturing status

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Clinical Trial: complicated and sophisticated project involving different subjects, companies, structures....

Qualified Person responsibilities: Directive 2001/83/EC lists the basic responsibilities

- In some EU countries no QP specific national legislation established yet
- Knowledge of the whole sypply chain is vital
- The QP must ensure compliance with any specific expectations for GMP as per the CTA and IMPD registered details
- This includes confirmation **that the correct version of the documents within the submission are available to the QP where any substantial amendments have been submitted**.

Cave: distinguish between QP and "Responsible Person"

QP - Role, Tasks, Responsibilities and EU procedures

IMP manufacture: The Qualified Person is in particular responsible for:

- Ensuring that there are systems in place that meet the requirements of respective regulation (e.g. Annex 13)
    - That a release of investigational medicinal products should not occur until after the QP has certified that the relevant requirements of § 39 have been met.
    - The assessment of each batch for certification prior to release is performed according Annex 13 Paragraphs 40-42.

In addition, the Qualified Person should:

- Have access to the Product Specification File (PSF, ImPD), a reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product".

- **Certification can involve extensive reviews of:**
    - Manufacturing & packing batch records for compliance with MA and EU GMP
    - Partial Manufacturing Certification, Deviations, OOS results or environmental failures from drug product sites
    - Temperature conditions during shipment to EU site

QP - Role, Tasks, Responsibilities and EU procedures

Clinical Trials: „most visible outcomes“:

1. QP Declaration
2. IMP import
   - Import License for IMP and Clinical Trial Supplies (MIA) required)
   - Distribution License (comparators)
   - Customs clearance services (VAT, customs fees)
3. Batch certification, QP release after the import

4. Other challenges:
   - Blinding, randomisation, Shelf life extension, Return&Destruction

QP - Role, Tasks, Responsibilities and EU procedures

QP Declaration

- The starting point for a QP declaration of EU GMP should be an audit conducted by or on behalf of the importing company
- QP confirms that the IMP manufactured in a third country meets EU GMP standards for IMPs. This is proved by :
    - a personal on-site audit
    - or an audit conducted by a third party
    - or by another QP employed by the importer
    - If no audit has been performed (e.g. COVID-19, expired audit report, etc...), a justification and explanation should be provided, describing how the QP knows that standards at least equivalent to EU GMP are being followed at the site
- All sites involved in manufacturing steps and including primary and secondary packing, any contract laboratories involved with release or stability testing should appear on the QP declarations…….and audited
- EuCT Number required
- CT Number required

QP - Role, Tasks, Responsibilities and EU procedures

QP Declaration

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy

Brussels,
SANCO/D/6/SF/mg/ddg1.d.6(2013)1104750

TEMPLATE FOR THE QUALIFIED PERSON'S DECLARATION EQUIVALENCE TO EU GMP FOR INVESTIGATIONAL MEDICINAL PRODUCTS MANUFACTURED IN THIRD COUNTRIES

This document provides the template for the *Qualified Person's Declaration Concerning GMP Compliance of the Investigational Medicinal Products* as per Commission guideline CT-1,[1] section 2.7.1, paragraph 62.

The aim is to harmonise this template and hence the dossier submitted with a request for authorisation of a clinical trial.

Document history:	
Date of discussion of draft by the ad-hoc group for the development of implementing guidelines for the "Clinical Trials Directive" 2001/20/EC:	30 April 2013
Date of publication:	See above
Date of coming into operation:	6 months date of publication
Supersedes:	N/A
Changes compared to superseded version:	N/A

[1] Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (OJ C82, 30.3.2010, p. 1)

Commission européenne/European Commission, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË - Tel. +32 22991111
Office: DM24 02/034 - Tel. direct line +32 229-67543 - Fax +32 229-98046; Sanco-pharmaceuticals-d6@ec.europa.eu

QUALIFIED PERSON'S DECLARATION EQUIVALENCE TO EU GMP FOR INVESTIGATIONAL MEDICINAL PRODUCTS MANUFACTURED IN THIRD COUNTRIES[2] (ARTICLE 13(3)(b) OF DIRECTIVE 2001/20/EC)

EudraCT number(s)	**Name of the IMP(s)**
Co-medication (EU origin):	

Manufacturing and/or Importation Authorisation (MIA) number[3] under which this declaration is made: _____

Part A

Name of the IMP(s)	**Manufacturing site(s)** **(Name and address where the activity is performed)**	**Activity performed at this site** **(including packaging, labeling and testing)**

Part B

I confirm that I am a QP and am authorised to make this declaration.
I declare that compliance with GMP at least equivalent to EU GMP has been verified on the basis of:

(i) Audit

Manufacturing site(s) (Name and address where the activity is performed)	**Auditing party**	**Date of last audit (completion)**

(ii) If an audit of the site has not been performed, please provide a brief justification and explanation on how the QP knows that standards at least equivalent to EU GMP are being followed at the site[4].

Manufacturing site(s) (Name and address where the activity is performed)	**Justification**

This declaration is submitted by:

Signatory _____ Date _____

Print name _____

[2] Countries other than EU Member States or contracting states of the European Economic Area (EEA).
[3] If no number is issued please state the name of the authorisation holder.
[4] E.g. assessment of documentation provided by the manufacturer, valid GMP certificate (EudraGMP), etc.

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IMP import

- **Import License for IMP and Clinical Trial Supplies (MIA)**
- **Distribution License (comparators)**
  - **Extra license for controlled substances (narcotic and psychotropic substances)**
- **Customs broker services**
  - Advice on required documents and invoice preparation/harmonisation
  - Customs declaration filling, payment of applicable duties and fees
  - Customs clearance
  - Payment of import duties (+VAT)

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QP Certification & Release - Annex 16 of the EU Guide to GMP

QP - Role, Tasks, Responsibilities and EU procedures

QP Certification and Release

List of general documentation

Regulatory Documents

- Clinical Trial Application for each country that the trial will take place in;
- Clinical Trail Application Approval Letter
  - *(For countries where there* is *no approval letter provided, a statement from company Reg Affairs department stating that application process is complete and no objections have been received from the competent authority to stop the trail from proceeding)*
- List of any special conditions that a competent authority has placed on the trial;
- IMPD
- QP Declarations for third country manufacturing and testing sites
- Temperature records (storage, transport)

Miscellaneous Documents

- Audit reports of manufacturing and testing sites in support of QP Declarations

QP - Role, Tasks, Responsibilities and EU procedures

QP Certification and Release

Batch Documentation

e.g. Bulk Active and Placebo Product (not previously QP released)

- The following documents, for the manufacture of the bulk product are required:
  - **Certificate of Analysis (CoA)** for the Active Pharmaceutical Ingredient {not required for placebo lots). For EU GMP the CoA check includes a check against the specification in the IMPD.
  - **Certificate of Analysis (CoA)** for bulk product
  - **Stability documentation** to support shelf life and storage conditions of bulk product (not required for marketed/commercial products.) or equivalent documentation that provides a shelf life and/or storage conditions of the product or a manufacturing date to determine shelf life based on an approved CoC, CoR of CoA)
  - **Manufacturing schematics for:**
    - Formulation manufacturing process
    - Primary packaging process
    - **Note :** Manufacturing schematics are not required when the complete set of manufacturing batch records have been provided.

QP Certification and Release

- **Deviation/Non-Conformance Reports,** if any (for the manufacture of the bulk product only)
- **Investigations,** if any (for the manufacture of the bulk product only)
- **Temporary Change Requests,** if any {for the manufacture of the product only)
- **Assay Results for Viral contamination (TSE/BSE)**
  - **Note 1:** These results are required for biological/ fermentation products on the end formulated in formulated bulk product, if these results are not reported on the CoA.
  - **Note 2:** These results are not required when no animal or human drug materials are used in the manufacturing process.
- **Assay Results for nitrosoamines** (IMP/MP containing chemically synthesised active substance)
- **Bioburden Test Results**
  - **Note:** These results are required for biological/ fermentation products on the end formulated in formulated bulk product, if these results are not reported on the CoA.
- **Sterility and endotoxin test results**
  - **Note:** For-sterile products only, and are not required if reported on CoA.

QP Certification and Release

- **Disposition Notice Record Review Statement**
  - **Note:** The statement must be signed by a Site Quality Management Representative stating that all records of the above mentioned lot of product have been reviewed and approved according to the current approved manufacturing method and relevant SOP‘s.
    - in-process and final product testing meet all compliance requirements for this material
    - the lot of product has been manufactured in accordance with current GMP guidelines.
- **Date of Manufacture** (not required if stated on the COA)
  - Bulk Active and Placebo Product (previously QP released)
  - Where an Investigational Product has been QP released, the following documents are required.
- **Certificate of Analysis**. For EU GMP, the CoA check includes a check against the specification in the IMPD.
- **Certificate of Conformance (COC) or Certificate of Release** (COR) - a statement saying that product has been manufactured in accordance with GMPs.

QP Certification and Release

- When receiving a second or subsequent shipment(s) of the same lot of material, the following documents are required:
  - **COA**
  - **Incoming Receipt Form**
    - **Finished Product**
  - For finished product, not previously released by a QP, the following additional packaging documentation is required:
    - **Packaging Batch Record**
      - **Deviation/Non-Conformance Reports** - if any
    - **Investigations** - if any
    - **Temporary Change Requests** - if any
    - **Transport Temperature Records**

QP Certification and Release

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Appendix I

Content of the confirmation of the partial manufacturing of a medicinal product

[LETTER HEAD OF MANUFACTURER WHO CARRIED OUT THE MANUFACTURING ACTIVITY]

1. Name of the product and description of the manufacturing stage (e.g. paracetamol 500 mg tablets, primary packaging into blister packs).
2. Batch number.
3. Name and address of the site carrying out the partial manufacturing.
4. Reference to the Technical Quality Agreement (in accordance with Chapter 7 of the Guide).
5. Confirmation statement.

   I hereby confirm that the manufacturing stages referred to in the Technical Quality Agreement have been carried out in full compliance with the GMP requirements of the EU and the terms described in the Agreement for ensuring compliance with the requirements of the Marketing Authorisation(s) as provided by [Contract Giver/manufacturer certifying and releasing the batch].
6. Name of the Qualified Person confirming the partial manufacturing.
7. Signature of Qualified Person confirming the partial manufacturing.
8. Date of signature.

QP Certification and Release

Content of the Batch Certificate for Medicinal Products

[LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER]

1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package).
2. Batch number of the finished product.
3. Name of the destination country/countries of the batch, at least when within the EU.
4. Certification statement.

I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the EU and [when within the EU] with the requirements of the Marketing Authorisation(s) of the destination country/countries.

5. Name of the Qualified Person certifying the batch.
6. Signature of the Qualified Person certifying the batch.
7. Date of signature.

QP Certification and Release

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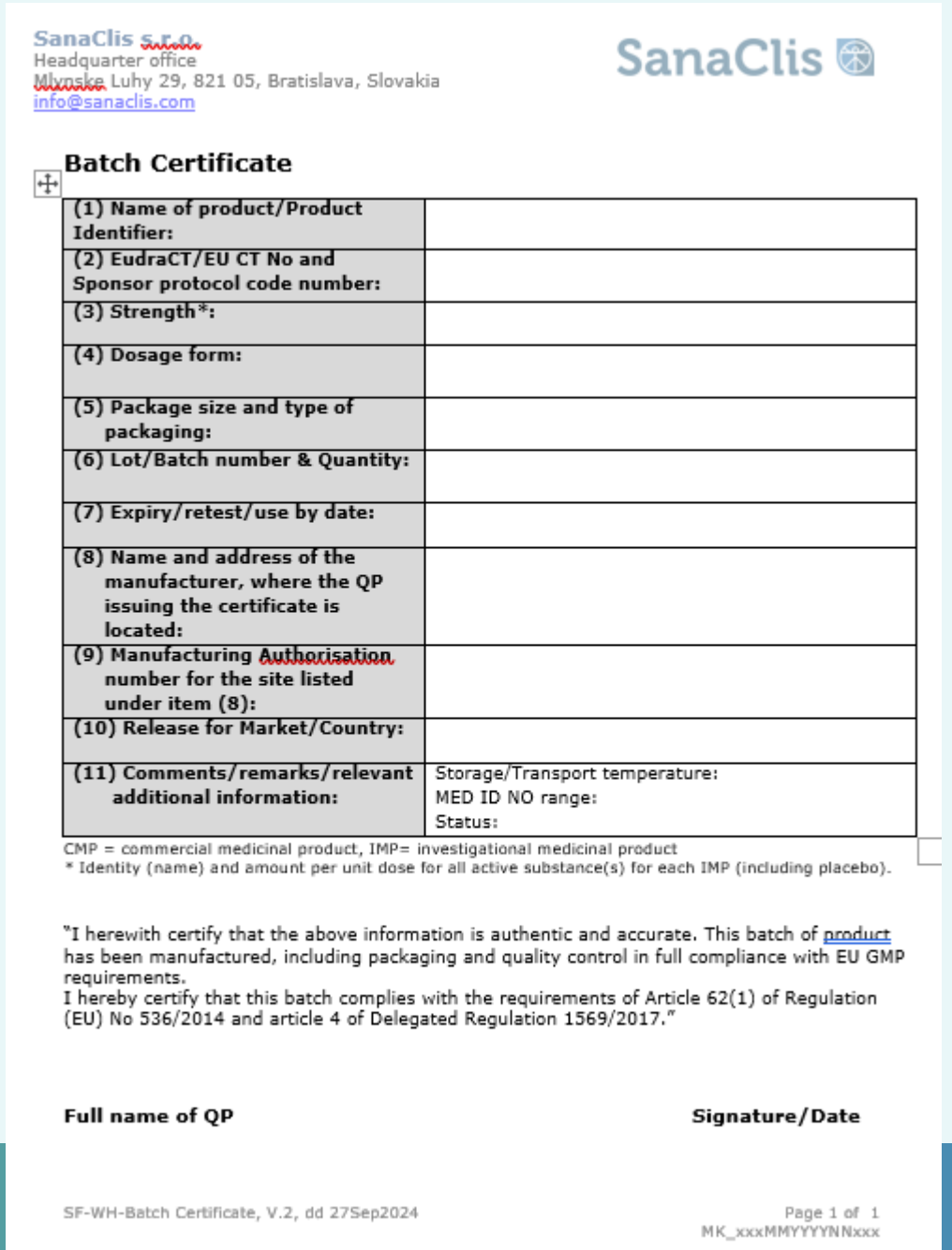

SanaClis s.r.o.
Headquarter office
Mlynske Luhy 29, 821 05, Bratislava, Slovakia
info@sanaclis.com

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Batch Certificate

(1) Name of product/Product Identifier:	
(2) EudraCT/EU CT No and Sponsor protocol code number:	
(3) Strength*:	
(4) Dosage form:	
(5) Package size and type of packaging:	
(6) Lot/Batch number & Quantity:	
(7) Expiry/retest/use by date:	
(8) Name and address of the manufacturer, where the QP issuing the certificate is located:	
(9) Manufacturing Authorisation number for the site listed under item (8):	
(10) Release for Market/Country:	
(11) Comments/remarks/relevant additional information:	Storage/Transport temperature: MED ID NO range: Status:

CMP = commercial medicinal product, IMP= investigational medicinal product
* Identity (name) and amount per unit dose for all active substance(s) for each IMP (including placebo).

"I herewith certify that the above information is authentic and accurate. This batch of product has been manufactured, including packaging and quality control in full compliance with EU GMP requirements.
I hereby certify that this batch complies with the requirements of Article 62(1) of Regulation (EU) No 536/2014 and article 4 of Delegated Regulation 1569/2017."

Full name of QP **Signature/Date**

SF-WH-Batch Certificate, V.2, dd 27Sep2024

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QP - Role, Tasks, Responsibilities and EU procedures

QP to QP

- the legal "handshake" that allows one Qualified Person to rely on the work of another without re-testing the product.
- It is most common when **Site A** (the CMO) manufactures a bulk product and **Site B** (the Sponsor or Packager) performs the final certification for release to the market or clinical site
    - Scope of activities
    - Deviationj reporting
    - Audit access
    - Sample retention
- The QP Confirmation vs QP final Batch Certificate
    - QP1: *"I confirm that the manufacturing stages listed were performed in accordance with GMP and the Technical Agreement."*

QP - documents issued/involved - summary

- Audit reports
- QP declaration (Active Substance declaration, IMP QP Declaration)
- QP Supply Chain confirmation
- Batch Certificate, Certificate of Conformance
- TQA
- QP to QP

EU vs UK – post Brexit

Direction	Primary QP Location	Oversight Requirement
EU → GB	EU/EEA (Original Certification)	UK QP provides **Import Oversight**
GB → EU	EU/EEA (New Certification)	EU QP performs **Full Re-certification**
EU → NI	EU/EEA (Original Certification)	No additional UK check required

CASE study I.

QP and Deviations:

- **Release:** If the investigation proves the quality is unaffected (e.g., a "stability-supported" temperature excursion), the QP certifies the batch.
- **Reprocess/Rework:** If allowed by the Product Specification File (PSF), the QP can oversee a fix (like relabeling) and then certify.
- **Reject:** If the risk to the patient or the trial's data is too high, the QP **must** reject the batch. Their personal liability means they cannot be "forced" by a Sponsor to release a suspect batch.

Deviation	QP Action
Temp. Excursion	Review stability data to see if the drug survived the heat/cold.
Labeling Error	Assess if the "blind" was broken. If so, the batch is usually destroyed.
Broken Seal	High risk of contamination; usually results in immediate rejection.

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CASE study II.

The "Euro-IMP" Journey

Stage	Origin	QP Document Issued
API	Italy	QP Declaration
Finished IMP	Germany	**Final Batch Certificate**
Non-EU Import	UK	UK QP Oversight Confirmation

CASE study III.

Third country (USA) origin

Feature	CT IMP: API + DP from USA (Third Country)
Audit Requirement	**EU QP** must verify/organize the audit
Import Testing	**IMP exemption**
QP Declaration	Issued by the EU **QP**
Regulatory Risk	Higher (QP is personally liable for the US site)

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SanaClis Contact

Sascha Sonnenberg

VP Global Business Development

Sascha.Sonnenberg@Sanaclis.com

CASE study IV.

Global Study: US manufactures DP/DS, Asia handles packaging + blinding, EU imports IMP for distribution

- QP must verify GMP equivalence, audits, PSF completeness
- Risks: labeling errors, cold-chain issues, inconsistent documentation
  - Verify GMP across all sites
  - Review audit/inspection evidence
  - Assess deviations/change controls
  - Check blinding + labeling validation
  - Certify only if fully compliant