



European Regulations for Excipients and the application of EXCiPACT

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EXCiPACT Certification Workshop

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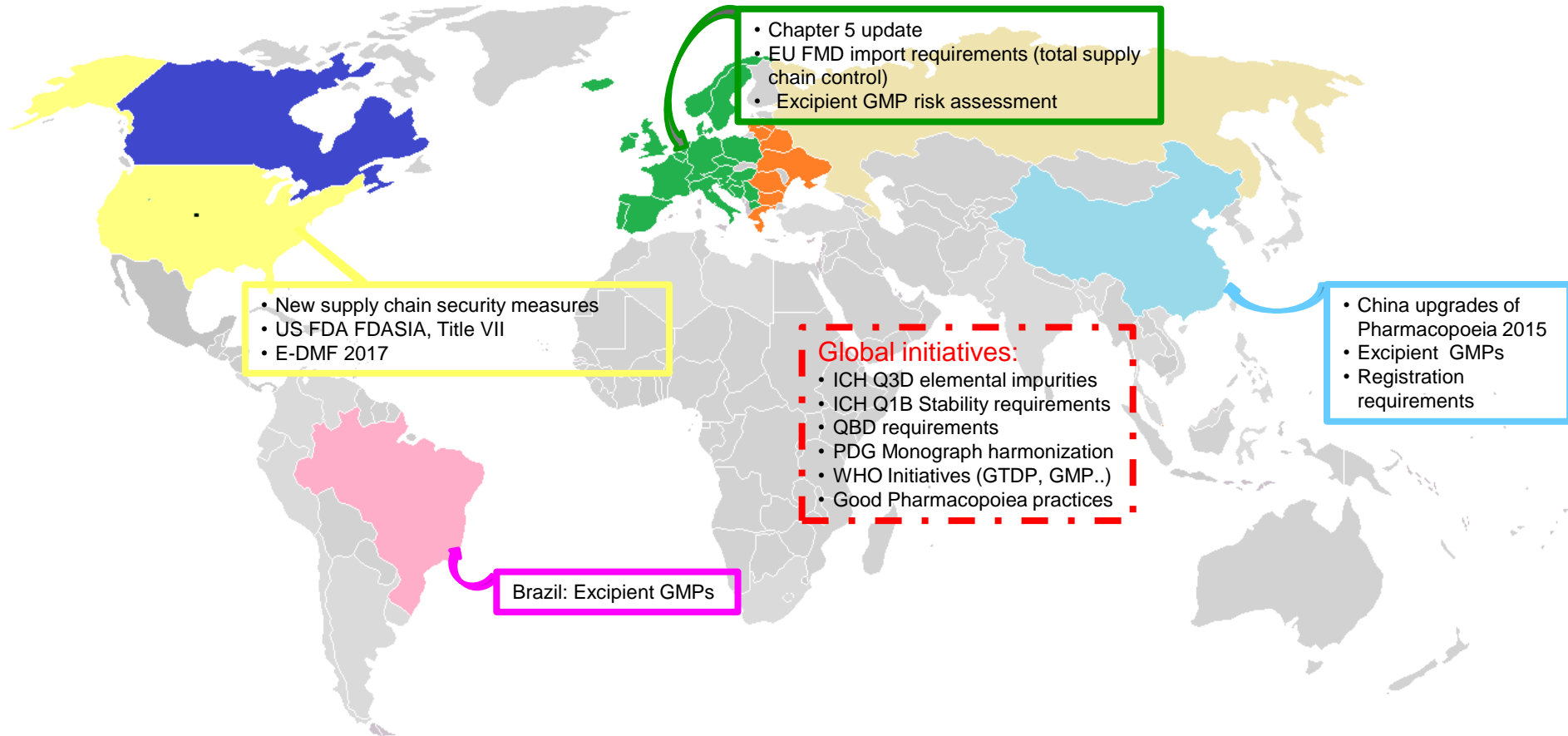


Agenda

- Pharmaceutical Excipients - EU Regulatory Position and The Risk Assessment Guidance
- Fulfilment of the requirements by Pharmaceutical Companies (Excipient Users)
- The GMP/GDP Verification Process
- The EXCiPACT Certification Scheme



Emerging Global Regulatory Trends





Pharmaceutical Excipients EU Regulatory Position

Eudralex Volume 4 Chapter 5

Production – starting materials, 5.29 excipients

5.29 For the approval and maintenance of suppliers of ... excipients, the following is required:

*Excipients and excipient suppliers should be controlled appropriately based on the results of a **formalised quality risk assessment** in accordance with the European Commission 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use'.*



Pharmaceutical Excipients EU Regulatory Position

C 95/10	EN	Official Journal of the European Union	21.3.2015
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Guidelines
of 19 March 2015
on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use
(Text with EEA relevance)
(2015/C 95/02)

Introduction

These guidelines are based on the fifth paragraph of Article 47 of Directive 2001/83/EC (1).

- Manufacturing Authorisation Holders (MAH) have to determine the GMP needed for every excipient they use in each dosage form
- Deadline for compliance was 21st March 2016



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 1 — SCOPE

1.1. These guidelines apply to the risk assessment for ascertaining the appropriate GMP for excipients for **medicinal products for human use**. According to Article 1(3b) of Directive 2001/83/EC, an **excipient is any constituent of a medicinal product other than the active substance and the packaging material**.

1.2. These guidelines do not cover substances added to stabilise active substances that cannot exist on their own.



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 2 — DETERMINATION OF APPROPRIATE GMP BASED ON TYPE AND USE OF EXCIPIENT

2.1. In EudraLex Volume 4, Guidelines for Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part III: GMP related documents, ICH guideline Q9 on Quality Risk Management (ICH Q9), principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, including excipients, can be found.

2.2. These quality risk management principles should be used to assess the **risks presented to the quality, safety and function of each excipient and to classify the excipient in question, e.g. as low risk, medium risk or high risk**. Quality risk management tools such as those listed in EudraLex Volume 4, Part III, ICH Q9 (e.g. hazard analysis and critical control points — HACCP) should be used for this purpose.



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 2 — DETERMINATION OF APPROPRIATE GMP BASED ON TYPE AND USE OF EXCIPIENT

2.3. For each excipient from each manufacturer used, the manufacturing authorisation holder should identify the risks presented to the quality, safety and function of each excipient from its source — be that animal, mineral, vegetable, synthetic, etc. — through to its incorporation in the finished pharmaceutical dose form. Areas for consideration should include, but are not limited to:

- (i) transmissible spongiform encephalopathy;
- (ii) potential for viral contamination;
- (iii) potential for microbiological or endotoxin/pyrogen contamination;
- (iv) potential, in general, for any impurity originating from the raw materials, e.g. aflatoxins or pesticides, or generated as part of the process and carried over, e.g. residual solvents and catalysts;



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 2 — DETERMINATION OF APPROPRIATE GMP BASED ON TYPE AND USE OF EXCIPIENT

- (v) sterility assurance for excipients claimed to be sterile;
- (vi) potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;
- (vii) environmental control and storage/transportation conditions including cold chain management, if appropriate;
- (viii) **supply chain complexity**;
- (ix) stability of excipient;
- (x) packaging integrity evidence.



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 2 — DETERMINATION OF APPROPRIATE GMP BASED ON TYPE AND USE OF EXCIPIENT

2.4. Additionally, with respect to the use and function of each excipient, the manufacturing authorisation holder should consider:

- (i) the pharmaceutical form and use of the medicinal product containing the excipient;
- (ii) the function of the excipient in the formulation, e.g. lubricant in a tablet product or preservative material in a liquid formulation, etc.;
- (iii) the proportion of the excipient in the medicinal product composition;
- (iv) daily patient intake of the excipient;



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 2 — DETERMINATION OF APPROPRIATE GMP BASED ON TYPE AND USE OF EXCIPIENT

- (v) any known quality defects/fraudulent adulterations, both globally and at a local company level related to the excipient;
- (vi) whether the excipient is a composite;
- (vii) known or potential impact on the critical quality attributes of the medicinal product;
- (viii) other factors as identified or known to be relevant to assuring patient safety.



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 3 — DETERMINATION OF EXCIPIENT MANUFACTURER'S RISK PROFILE

- 3.1. After determination of the appropriate GMP, a gap analysis of the required GMP against the activities and capabilities of the excipient manufacturer should be performed.
- 3.2. Data/evidence to support the gap analysis should be obtained through audit or from information received from the excipient manufacturer.
- 3.3. **Certification of quality systems and/or GMP held by the excipient manufacturer and the standards against which these have been granted should be considered as such certification may fulfil the requirements.**



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 3 — DETERMINATION OF EXCIPIENT MANUFACTURER'S RISK PROFILE

3.4. Any gaps identified between the required GMP and the activities and capabilities of the excipient manufacturer should be documented. Furthermore, **the manufacturing authorisation holder should perform a further risk assessment to determine the risk profile, e.g. low risk, medium risk or high risk, for that excipient manufacturer.** EudraLex Volume 4, Part III, ICH Q9 should be used for that purpose. Quality risk management tools such as those listed there — HACCP etc. — should be used for this.

3.5. The manufacturing authorisation holder should have a series of strategies ranging from acceptance through control to unacceptable for the different risk profiles and based on these a control strategy, e.g. audit, document retrieval and testing, should be established.



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 4 — CONFIRMATION OF APPLICATION OF APPROPRIATE GMP

Once the appropriate GMP for the excipient and the risk profile of the excipient manufacturer have been defined, **ongoing risk review** should be performed through mechanisms such as:

- (i) number of defects connected to batches of excipient received;
- (ii) type/severity of such defects;
- (iii) monitoring and trend analysis of excipient quality;
- (iv) loss of relevant quality system and/or GMP certification by excipient manufacturer;



Pharmaceutical Excipients The Risk Assessment Guidance

CHAPTER 4 — CONFIRMATION OF APPLICATION OF APPROPRIATE GMP

(v) observation of trends in drug product quality attributes; this will depend on the nature and role of excipient;

(vi) observed organisational, procedural or technical/process changes at the excipient manufacturer;

(vii) audit/re-audit of excipient manufacturer;

(viii) questionnaires.

Based on the outcome of the risk review, the established control strategy should be reviewed and revised if needed.

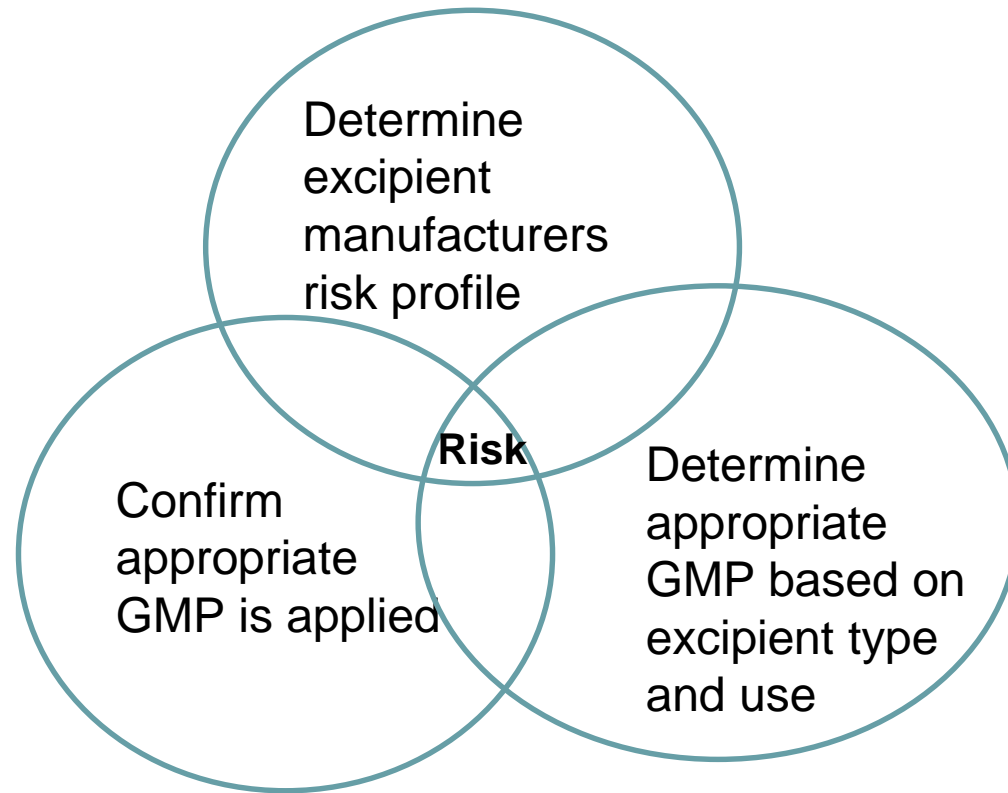


Fulfilment of the requirements by Pharmaceutical Companies (Excipient Users)



Risk Assessment

- The risk assessment is comprised of three distinct phases:





Appropriate GMP

- **Determination of appropriate GMP based on type and use of excipient**
 - *The excipient itself*
 - *how it is used*
- From these two factors it is necessary to determine which elements of GMP need to be in place to control and maintain quality
- References include Annex 1 or/and Annex 2: Part II Basic Requirements for Active Substances used as Starting Materials



- **Determination of excipient manufacturer's risk profile**
 - Perform a gap analysis between the determined appropriate level of GMP against the capability of the manufacturer
 - Use data from an audit or information from the manufacturer
 - Take into account any certification against appropriate standards
 - Any gaps identified should be documented and a mitigation strategy implemented



Risk Profile

- **Internal**
 - ✓ Supplier quality records
 - ✓ Supplier performance
 - ✓ History of supply
 - ✓ Audits
- **External**
 - ✓ Excipient Information Package (EIP)
 - ✓ Certifications
 - ✓ Supply Chain information



Determination of Risk Level

- Identify and evaluate the potential risk factors
- Ensure the risk factors clearly characterise severity, probability & detectability, and their likely impact on product quality / performance
- Risk scoring, some possible examples:
 - ✓ Linear: 1, 2, 3, 4
 - ✓ Exponential: 1, 2, 4, 8
 - ✓ Logarithmic: 1, 10, 100, 1000
 - ✓ 'Self made': 1, 3, 7, 10
- The identified risks should be correlated with GMP principles that mitigate or control the risks



Determination of Risk Level

Material & Usage Risk Level				
		Low	Medium	High
Supplier risk category	High	Medium	High	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium



Confirmation of Supplier's GMP

- **Confirmation of application of appropriate GMP**
 - After the appropriate level of GMP and the risk profile of the manufacturer have been defined then an ongoing risk review needs to be performed
 - Using for example monitoring and trend analysis of excipient quality, type and severity of defects, changes control at the manufacturer



The IPEC Europe 'How To' Document



The International Pharmaceutical Excipients Council Europe
"Helping To Shape The Future Of Excipients"

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Supporting the interests of pharmaceutical excipient developers, producers, distributors and users.

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Guidelines

IPEC Guidelines

The IPEC guidelines can be downloaded here:

2016 The IPEC Europe 'How-To' Document on EU Guidelines on Risk Assessment for Excipients
> [Download PDF Format](#)

2014 The IPEC Glossary of Terms
> [Download PDF Format](#)



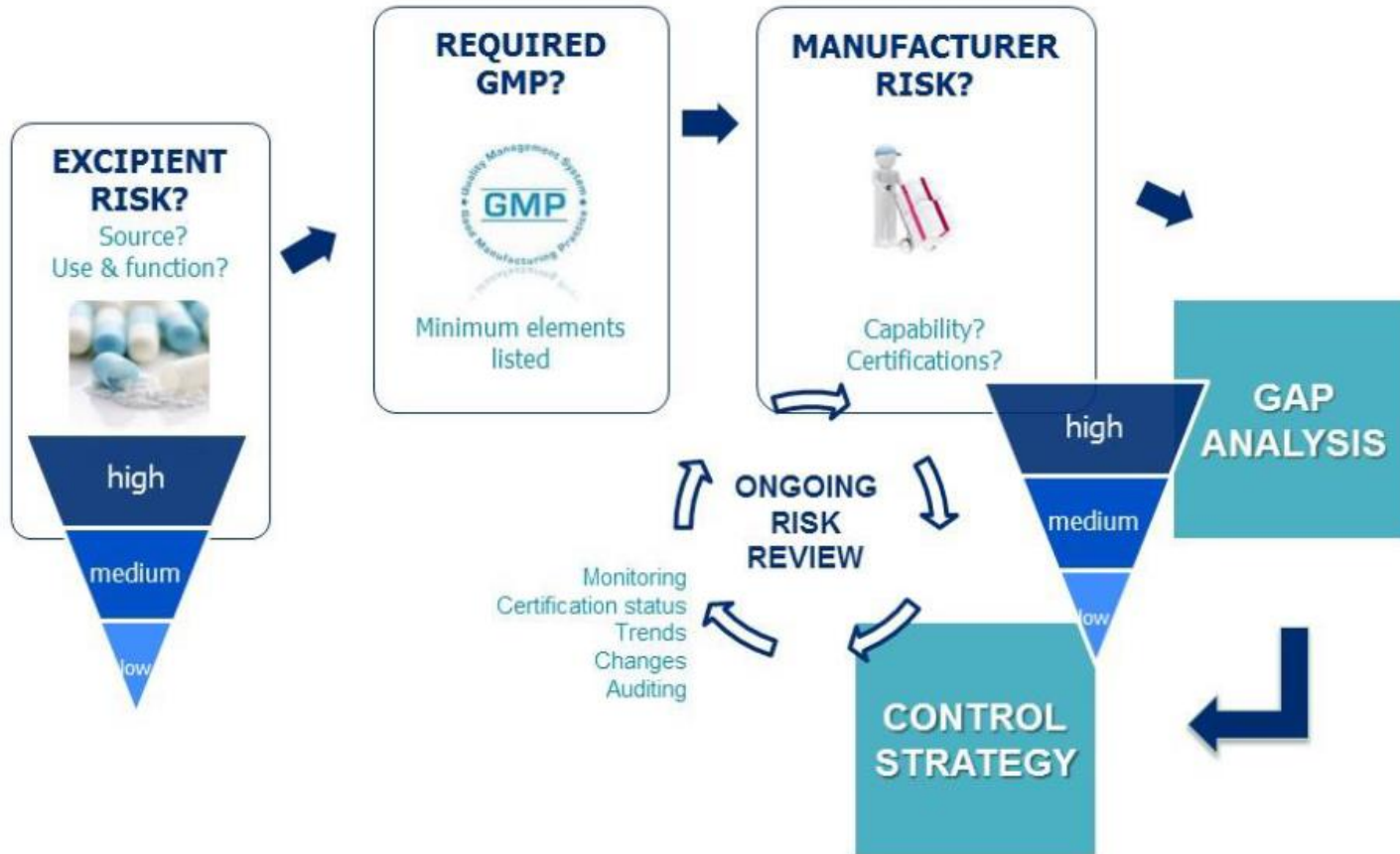
The IPEC Europe 'How To' Document

- 1. Introduction*
- 2. Preamble*
- 3. The Risk Assessment process*
- 4. Risk mitigation activity including communication with suppliers*
- 5. Residual risks resolution (e.g. Excipient risk classification)*
- 6. Triggers for risk review*



The IPEC Europe 'How To' Document

The Process





The GMP/GDP verification process



Who's Who Amongst Excipient Suppliers

Supplier Type	Key Characteristics
Manufacturer	<ul style="list-style-type: none">• “Realises” excipient (performs first of processing steps where product is designated for excipient use)
Distributor	<ul style="list-style-type: none">• Reseller of excipient• Takes possession of and title to excipient
Broker/Agent	<ul style="list-style-type: none">• Connects buyer and seller• Takes neither possession of nor title to excipient
Trader	<ul style="list-style-type: none">• Connects buyer and seller• Usually sells before buying• Takes title to but not possession of excipient
Supplier	<ul style="list-style-type: none">• Supplies excipients – broadest, most general term; includes manufacturer
Reseller	<ul style="list-style-type: none">• Resells excipients – broadest, most unspecific term for seller who doesn't make excipient



GMP/GDP Verification Process

- Once the GMP and GDP have been defined for the excipient and supplier a gap analysis has to be conducted against the GMP/GDP implemented by the supplier
- This is usually based on **an audit or from information received** from each supplier
- This could potentially increase the audit burden substantially for both suppliers and users



Issues With Physical Audits

- Excipient users have to qualify their suppliers
- Past expectations are that there should be a physical audit at the manufacturing site to confirm GMP is implemented
- But more and more physical audits cannot be accommodated either by suppliers or users
 - ✓ *not enough auditors or days in the year to audit all of the suppliers*
 - ✓ *dilutes resources from assessing higher risks*
 - ✓ *suppliers could face 100s of audit requests a year – many will be refused – what happens then?*



GMP/GDP Verification Process

- The Guideline also states (3.3)
 - *Certification of quality systems and/or GMP held by the excipient manufacturer and the standards against which these have been granted should be considered **as such certification may fulfil the requirements**.*
- An independently assessed GMP Certificate held by a manufacturer or a GDP Certificate held by a Distributor, against recognised standards, would therefore be suitable for the MAH to demonstrate that the risk assessed requirements have been met
- An independent, high quality third party audit scheme is the solution... EXCiPACT Certification



The EXCiPACT Certification Scheme



The EXCiPACT Certification Scheme

- ✓ EXCiPACT is an independent, voluntary Certification Scheme for excipient suppliers
- ✓ Scheme was developed by suppliers and users of excipients
- ✓ Scheme Comprises the following:
 - *GMP Standard for excipients*
 - *GDP Standard for excipients*
 - *Auditor Competency definition, training course, exam, and registration process*
 - *Certification Body quality system definition and qualification process*



**Certification Standards for Pharmaceutical
Excipient Suppliers:**

Good Manufacturing Practices
Good Distribution Practices

Requirements for Auditor Competency and Third
Party Organisations Providing Certification of the
Management System

2017





The EXCiPACT Certification Scheme

- Use of Third Party Audit Organisations requires that the auditor is visibly competent to assess excipient suppliers
- An Annex to ISO 19011:2002 *Guidelines for quality and/or environmental management systems auditing* was developed which sets out the auditor requirements
 - ✓ *Knowledge of excipient manufacture and supply*
 - ✓ *Knowledge of the pharmaceutical industry, regulations and GMP, GDP*
 - ✓ *Experience in both industries*
 - ✓ *Experience of auditing*



The EXCiPACT Certification Scheme

- We also require the Third Party Audit Organisations to have a quality management system suitable for delivering the EXCiPACT Certification
- An Annex to ISO/IEC 17021-1:2015 “*Conformity assessment - Requirements for bodies providing audit and certification of management systems - Part 1: Requirements*” is used as the basis of this element
- EXCiPACT checks the implementation of these requirements, thereby effectively taking on the duties of an accreditation body



The EXCiPACT Certification Scheme

- The Annex to ISO/IEC 17021-1:2015 requires that an *independent review panel* in the Certification Body determines if an excipient supplier meets the requirements for Certification *not the auditor*
- The review panel has to meet the requirements for auditor competency
- EXCiPACT Association will audit the Certification Bodies against ISO 17021 and the corresponding EXCiPACT™ Annex



The EXCiPACT Certification Scheme

1. Excipient supplier selects:

- *EXCiPACT™ Registered Certification Body from www.excipact.org*
- *GMP and/or GDP Standard to be audited against*
 - ✓ *Supplier must have ISO 9001 certification to use EXCiPACT™ GMP and/or GDP Standards as basis of audit*



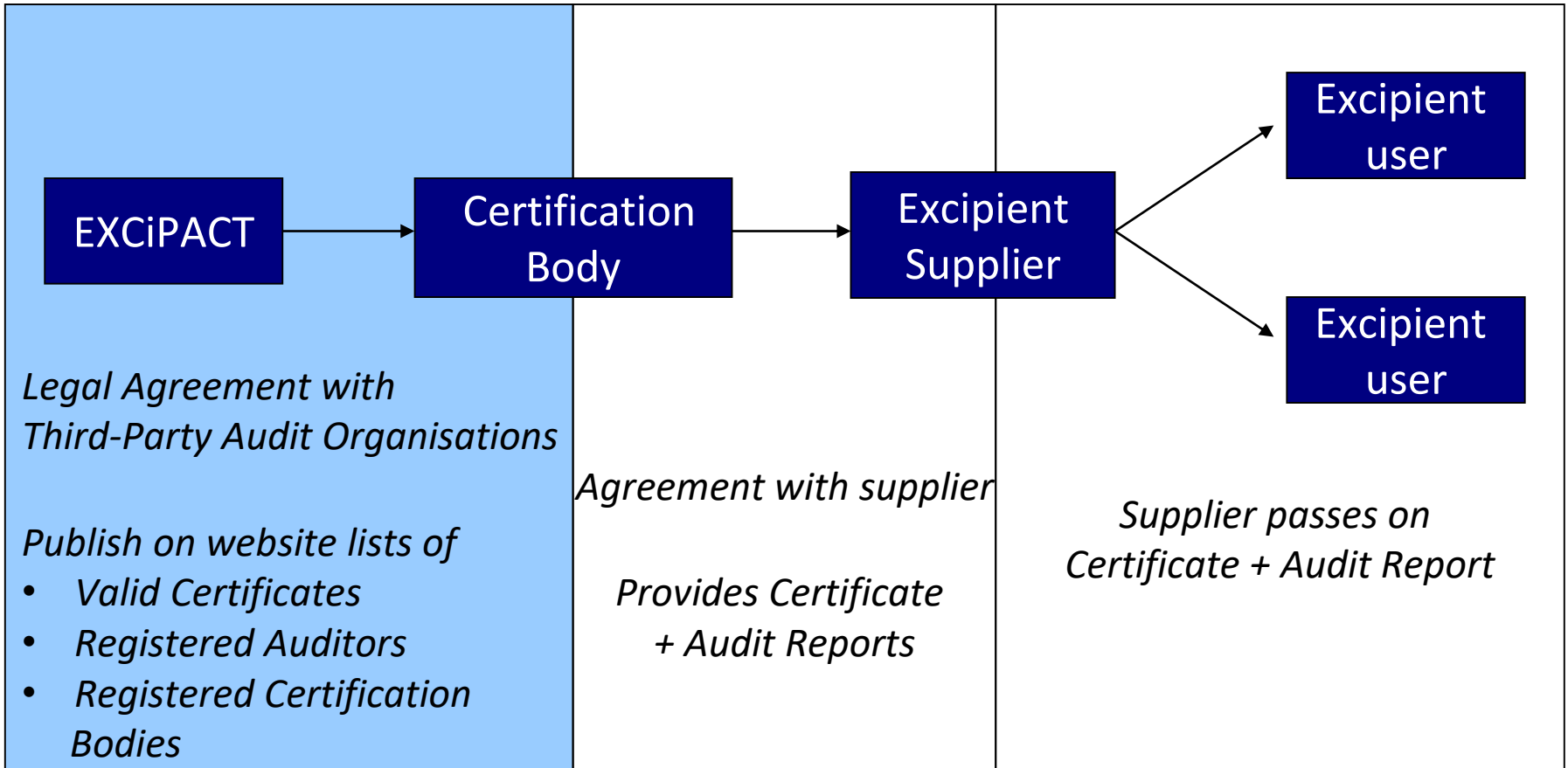
The EXCiPACT Certification Scheme

2. EXCiPACT Registered Certification Body conducts audit using EXCiPACT™ Registered auditors

- *Auditors submit report, but DO NOT make certification decision*
- *Independent Certification Board in the Certification Body reviews audit and makes certification decision*
 - ✓ *based on audit report and if needed, an interview with the auditor*



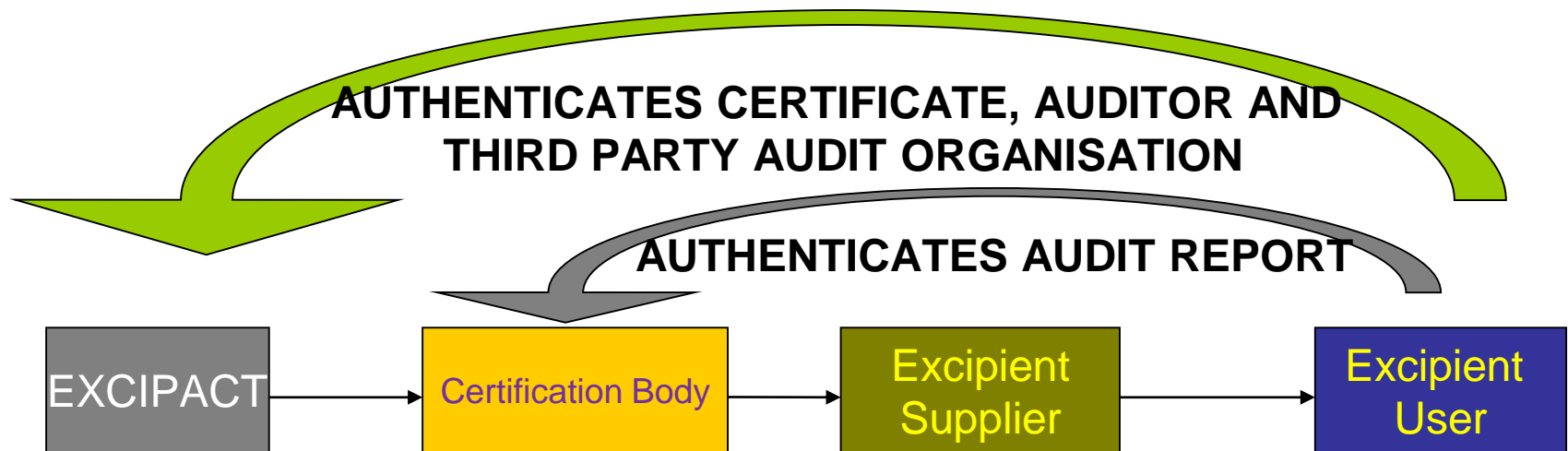
The EXCiPACT Certification Scheme Process and Relationships





Using the Certificates and Audit Reports

- Supplier issues the Certificates and Audit Reports to their Pharmaceutical Customers (Users) including any CAPA (corrective and preventive action) correspondence
- Excipient User verifies that the Certification Body, Auditor(s) and Certificate are legitimate by checking the EXCiPACT website





EXCiPACT Certification

More than a Certificate....

- Certification Body issues Certificate + Audit Report to the supplier
- Excipient supplier makes available Certificate and Audit Reports to their pharmaceutical excipient customers/user(s)
- Scheme requires at least an annual EXCiPACT Audit, so the assessment of compliance status of a supplier has more depth than any 1st party audit programme
- Entire information about level of GMP/GDP of the supplier available to the pharmaceutical company for evaluation





EXCiPACT Certification

EXCiPACT™ Certification Scheme will not replace ALL pharmaceutical company audits BUT...

- Significant and growing interest in the Scheme in many countries
- Both Users and Suppliers of Excipients making more and more use of the Scheme for mutual benefit without compromising regulatory compliance or patient safety
- Fully satisfies the EU Guidelines on ascertaining GMP/GDP for excipients
- Helps reduce costs for both suppliers and users by reducing the audit burden



Is a Supplier Initiated Process a Concern for Users?

- As the Supplier contracts with the Certification Body there could be a concern that the Supplier will have undue influence over the audit process
- Yes, in theory that is a potential hazard – BUT the oversight applied by EXCiPACT asbl mitigates the risks by independent auditor registration and re-registration, witnessed audits and regular audits of the Certification Body



Regulators view of EXCiPACT

- Regulators indicated that third-party auditing may be acceptable subject to certain conditions; these are.....
 - ✓ The use of credible Certification Bodies who employ qualified auditors, and issue the Certificates and Audit reports, and
 - ✓ Auditors who are demonstrably competent in these standards and the needs of the pharmaceutical industry
- To manage this, an independent, high quality, third-party audit and certification scheme is the solution, e.g., *EXCiPACT*



Regulators view of EXCiPACT: MHRA 2012

At the European EXCiPACT launch in Barcelona on 25 January, 2012, Richard Andrews from the UK's MHRA stated:

“Third Party certification schemes can assist medicinal product manufacturers in achieving compliance with GMP at reduced cost and impact on time and resource”.

“Such schemes will also benefit excipient manufacturers as they should reduce the number of audits they are required to host with the consequential reduction in time and cost”.

“Overall patient safety should be enhanced”



Pharma Companies view of EXCiPACT

- ✓ We are obtaining and evaluating EXCiPACT certification audit reports during the excipient supplier audit planning and preparation process – these are fed into the supplier audit risk assessment process”.
- ✓ “The EXCiPACT Certificate and Audit Report allowed us to decrease audit frequency and spend half a day on site rather than a full audit”
- ✓ “Helps avoid *duplication of effort*since each element of the excipient GMP standard is already periodically assessed”
- ✓ “If an audit is deemed necessary, its scope could then be focused on specific topics that are not already addressed by the certification standard”
- ✓ “EXCiPACT audit reports provide an expedient and cost effective means for excipient users to assess GMP/GDP conformance of suppliers, which is needed to demonstrate ongoing supplier qualification”.



Suppliers view of EXCiPACT

- ✓ We got major non-conformities raised at the first EXCiPACT audits because we did not do a thorough gap analysis – the requirements for documented risk assessments are “new” GMPs for excipients”
- ✓ “The audit was very thorough – at least as good as a regulatory inspection and at the same level as the best customer audits”
- ✓ “The EXCiPACT certificate and the audit report are well accepted by the customers”
- ✓ The investment has paid off, customer feedback is very positive!



The EXCiPACT Initiative

EXCiPACT asbl is a not-for-profit organization and was established in Belgium at the start of 2014.

It has the following Full Members:



The Pharmaceutical Quality Group



As an association of associations, impartiality is assured