Keynote Speaker

EXCiPACT™- GMP and GDP Certification, Progress and Use

Iain Moore

EXCiPACT™
EXCiPACT™ - GMP and GDP Certification, Progress and Use

ExcipientFest Europe
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Iain Moore
Chair Board of Directors
EXCiPACT asbl

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Amsterdam, The Netherlands
New Regulations affecting excipients

What is the EXCiPACT(TM) Certification Scheme and how does it work?

Core Features of a Credible Certification Scheme

EU Risk Assessment to ascertain the GMP required for excipients – use of EXCiPACT

Authorities‘ Comments

Conclusions
Art. 46 f

• The **holder of the manufacturing authorization** shall ensure that the **excipients** are suitable for use in medicinal products by ascertaining the **appropriate good manufacturing practice** on the basis of a formalized risk assessment. …

• The holder of the manufacturing authorisation shall ensure that **the appropriate good manufacturing practice** so ascertained, is applied.
  – How can this be achieved without an audit?
Risks in the pharmaceutical supply chain are not just API related, excipients may also have an impact

Regulators expect Manufacturing Authorization Holders to know and secure their supply chain

Expectation of periodical, physical audits of suppliers

Directive 2011/62/EU
(EU Falsified Medicines Directive)

EXCiPACT™ – minimize risks, maximize benefits
# US Food and Drug Administration Safety and Innovation Act 2012 (FDASIA)

**Title Authorization to FDA**  
**Impact for Excipient Suppliers**

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<th>Title</th>
<th>Authorization to FDA</th>
<th>Impact for Excipient Suppliers</th>
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<td>VII Drug supply chain</td>
<td>Registration and risk based inspection of domestic/foreign establishments and handlers of drug products/components. Includes supply chain security initiatives such as: importing drug product/components, sharing information with foreign reg. authorities, penalties for counterfeiting/adulteration</td>
<td>User have to list addresses of excipient manufacturing sites and they will have to register with FDA … Leading to FDA risk based inspections. Each site to have unique facility number. Final rules and implementation date for excipient site registration not yet set.</td>
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New regulations affecting pharmaceutical excipients

2. US Food and Drug Administration Safety and Innovation Act (FDASIA), 2012

- Both require the quality, safety and security of excipients are evaluated and controlled
- They clarify the responsibilities of drug manufacturers regarding the starting materials used
- Expectation that physical audits conducted for all excipient suppliers
  - No direction on use of 3rd parties for these audits – not prohibited!

EXCiPACT™ – minimize risks, maximize benefits
New Regulations affecting excipients

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What is EXCiPACT™?

- EXCiPACT™ is a voluntary certification Scheme for excipient suppliers
  - Developed by suppliers and users
  - Uses EXCiPACT GMP and/or GDP standards – based on well known IPEC-PQG and IPEC Guides
  - Emphasis is on auditor competency, and high quality audits
  - Focus is to give users and regulators confidence in the quality of the audit process
EXCiPACT™ Certification

- ISO 9001 certification
- EXCiPACT GMP / GDP
- ANSI NSF 363

SUCCESSFUL EXCiPACT CERTIFYING BODY AUDIT

- EXCiPACT™ Certification

EXCiPACT™ – minimize risks, maximize benefits
How does it Work?

- Excipient supplier selects EXCiPACT™ Registered Certifying Body from EXCiPACT™ Website
  - ideally the one that already provides them with ISO 9001
- Supplier identifies if GMP and/or GDP are needed
- Standard ISO certification audit process – pre audit, full audit, CAPA, Certification (ISO 17021)
- On first Certification Audit No Critical or Major non-conformities required for Certificate to be issued
  - Certification Board make Certification Decision not auditor
- Recertification every 3 years and annual surveillance audits at least every year
EXCiPACT™ – How does it work?

More than a Certificate…. 

• A Certificate is issued to the excipient supplier along with an audit report
• The excipient supplier will make the Audit Reports and Certificate available to the pharmaceutical excipient user(s)
• Entire information about level of GMP/GDP of the supplier with the pharmaceutical company for evaluation
Agenda

- New Regulations affecting excipients
- What is the EXCiPACT™ Certification Scheme and how does it work?
- Core Features of a Credible Certification Scheme
- EU Risk Assessment to ascertain the GMP required for excipients – use of EXCiPACT
- Authorities Comments
- Conclusions
A Credible Audit and Certification Scheme needs:

- Definition of what is a competent auditor and an evaluation process to qualify auditors
- Certifying Bodies with strong management systems for separating conflicts of interest and ensuring impartiality as well as implementing the specific rules of the Scheme
- Audit reports that meet best practices
On the “Questions and answers: Good manufacturing practice” webpage EMA added the following in May 2013:

10. How should active substance auditors be qualified?

- Need to have scientific, technical and other experience to allow them to perform the audit
- Trained in the product to be audited
- Trained on EU GMP and auditing techniques

EMA Q&A is on:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca
Auditor Competency

• How does EXCiPACT auditor requirements compare?
• EXCiPACT™ Registered auditors must have
  – Experience of auditing Quality Management Systems Experience of GMP and pharmaceutical regulations
  – Knowledge of how excipients are made & supplied
  – Attended a 2-day EXCiPACT™ Auditor Training Course
• And
  – Pass an EXCiPACT™ Training Course final exam
  – Be witnessed performing an EXCiPACT™ audit
  – Demonstrate continuous professional development and including EXCiPACT™ audits every 3 years

EXCiPACT™ – minimize risks, maximize benefits
EXCiPACT™ Training Courses

- Six 2 day training courses held in Europe and USA:
  - 19 auditors attended
  - 33 Excipient Suppliers
  - 15 Excipient Users
- Next course 18th 19th November 2014 in Brussels and one in the US being planned
- In-house customization available
- Currently there are 7 EXCiPACT™ Registered Auditors are listed on the website who have met all the registration criteria

EXCiPACT™ – minimize risks, maximize benefits
Certifying Bodies

• All 3rd Party Certifying Bodies sign an agreement with EXCiPACT asbl
  – Only use employed/contracted EXCiPACT™ Registered Auditors
  – Have an independent Certification Board that decides on Certification - not the Auditor
  – Perform audits in accordance with the EXCiPACT Annexes to ISO 19011 (Auditing principles) and ISO 17021 (Certifying Body Quality Management System) standards
• Are audited by EXCiPACT asbl to confirm these arrangements are in place and implemented and have an EXCiPACT™ audit witnessed
• Only then will they be Registered and entered on the website
• Have an EXCiPACT™ Audit witnessed once a year and full requalification every 3 years
Certifying Bodies

- Key principles in ISO 17021
  - Impartiality
  - Competence
  - Responsibility
  - Openness / Confidentiality
  - Responsiveness to Complaints

- Core within impartiality is that there is freedom from conflict of interest (no consulting)

- QMS rules including PDCA and management review

- EXCiPACT asbl added additional specific requirements to ensure the highest standards for the Scheme
3rd Party Certifying Bodies

- SGS and mdc
  - Signed up in 2012 and participated in Pilot Phase audits
  - mdc has issued 6 Certificates
  - SGS has issued 3 Certificates

- DQS
  - Signed up in late 2013
  - Has issued one certificate

- AJA Registrars
  - Have met all requirements except for a witnessed audit

EXCiPACT™ – minimize risks, maximize benefits
On the “Questions and answers: Good manufacturing practice” webpage EMA added the following in May 2013:

- Q9. *What expectations do Inspectors have for the content of reports of audits of active substance manufacturers carried out by the medicinal product manufacturer?*

- Only for APIs, but how do EXCiPACT audit reports compare?
EXCiPACT™ Audits Reports

• Guidance on the Minimum Content of an EXCiPACT™ GMP / GDP Assessment Audit Report
  – Audit reports are to be written in English.
  – Name and address equal to the scope on the Certificate
  – If separate audits, the ISO 9001 Certifying Body’s name
  – Date(s) of the Audit
  – Type of Audit
  – Name(s) of the Auditor(s) and their employer
  – Version of the EXCiPACT™ Standards
  – GMP and / or GDP assessment indication
  – Approval of the report by Auditors and certification board
  – Executive Summary including overall conclusion regarding conformity to the EXCiPACT™ GMP and or GDP Certification Standard

EXCiPACT™ – minimize risks, maximize benefits
EXCiPACT™ Audits Reports

• Guidance on the Minimum Content of an EXCiPACT™ GMP / GDP Assessment Audit Report
  – Classified Observations and non-conformities indexed to the clauses in EXCiPACT™ Standard(s)
  – List of Auditee personnel in attendance with job functions.
  – Scope of the audit
  – Status of previous audit non-conformities and observations
  – Details of any major changes
  – List of excipients audited
  – Identification of significant contract operations within the scope of the assessed activities, e.g., contract packager, warehouse

• Excellent Agreement – other differences are due to API vs excipients
New Regulations affecting excipients

What is the EXCiPACT™ Certification Scheme and how does it work?

Core Features of a Credible Certification Scheme

Excipient Users and Authorities

Conclusions
EXCiPACT™ how do Users use it?

• Suppliers issue the Certificates and Audit Reports to their customers (users) including any CAPA correspondence

• Excipient user check the Certifying Body, Auditor(s) and Certificate are listed on the EXCiPACT asbl Website
  • Users may verify the accuracy of the audit report by contacting the Certifying Body Directly
  • Users evaluate the report and findings against their needs for the excipients received from that supplier
  • Users take the information and plan the next steps – e.g. further dialogue with the supplier, a focussed audit etc.

• Ultimately the EXCiPACT™ Certificate and Audit report forms part of the overall supplier qualification

EXCiPACT™ – minimize risks, maximize benefits
EXCiPACT™ – What do suppliers say?

• We got major nonconformities raised at the first EXCiPACT audits because we did not do a thorough gap analysis – the requirements for documented risk assessments are “new” cGMPs for excipients

• We have saved 6 audits already

• The audit was very thorough – at least as good as a regulatory inspection and at the same level as the best customer audits

• A North American customer qualified us using EXCiPACT™ Certification and avoided transatlantic travel
EXCiPACT™ –
What do users say?

• We are obtaining and evaluating any existing 3rd party certification audit reports during the excipient supplier audit planning and preparation process – these are fed into the supplier audit risk assessment process.

• Helps avoid duplication of effort and can eliminate the need for an audit since each element of the excipient GMP standard is already periodically assessed as part of the 3rd party certification.

• 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™ Certification
Cost savings for stakeholders

**Cost for EXCiPACT™ Audit**
- Audit fee ~ 10'000€
- Certificate fee ~ 5'500€
- Surveillance ~ 10'000€
- Internal cost ~ 2'5 - 5'000€
- Total cash-out ~ 28 - 30'000€

**Excipient Supplier**
Reduction by one two-day audit a month, plus one day for preparation, at internal cost incl. of ~ 2'000€ each, plus ~ 5'000€ travel expenses per year
~ 30’000€ savings per year

**Pharmaceutical Company**
Reduction by one two-day audit a month, plus three days for travel and preparation of the report, plus travel expenses, at total cost of ~18’000€
~ 60’000€ savings per year

**Total cost in 3 years**
~ 30’000€

**Total Savings in 3 years**
~ 90’000€

**Total Savings in 3 years**
~ 180’000€

**Total Industry Benefit**
60’000€
240’000€

EXCiPACT™ – minimize risks, maximize benefits
EXCiPACT™ – What do Authorities say?

• FDA presentation by Dr. Steve Wolfgang during the EXCiPACT launch in Barcelona, January 25, 2012 stated:
  – “The scheme ticks the right boxes.”

• During Dr. Steve Wolfgang’s presentation at US launch of EXCiPACT in Baltimore/MD, April 29, 2013 he said:
  – “EXCiPACT can contribute towards fulfillment of expectations for drug quality and reliability.”
  – “EXCiPACT makes regulators more comfortable that a steady supply of high-quality excipients exists.”

EXCiPACT™ – minimize risks, maximize benefits
At the European EXCiPACT launch in Barcelona, January 25, 2012, Richard Andrews from the UK’s MHRA stated:

- “3rd 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”.

EXCiPACT™ – minimize risks, maximize benefits
EXCiPACT™ – What do Authorities say?

Risk assessment based on level of compliance with relevant non-EU or non-pharmaceutical quality system accreditations – Parenteral Product

- ISO 9001
  - May not be directly applicable to a pharmaceutical oriented product. Unlikely to reduce risk rating

- Local regulatory approval for food manufacture
  - Food accreditation not suitable for a parenteral product. Would not reduce risk rating

- Local regulatory GMP approval
  - Depending upon local authority GMP assessments / controls, may be suitable. May reduce risk rating.

- Accredited for EU API manufacture in the same facility
  - Relevant standard; provided excipient manufactured under same control systems. Would reduce risk rating

- Accredited to relevant EU standard for food safety
  - Not applicable to a parenteral product. Unlikely to reduce risk rating

- IPEC-PQG excipient GMP certification
  - Relevant standard, would reduce risk rating.
New Regulations affecting excipients
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EXCiPACT™ – Certification

- 10 Excipient suppliers have been granted Certificates within the past 12 months the scheme has been running
  - Many in Europe but one certificate in Saudi Arabia and one in Canada

- At least 10 more audits in progress or have been completed so far in 2014
EXCiPACT™ – Certification

• May not replace ALL pharmaceutical company audits BUT…
• Scope and duration and quality of the audit is greater than typical excipient supplier audits
• Frequency of audits is yearly - higher than the industry average
• Allows pharmaceutical companies to use EXCiPACT™ Certification and Audit Reports to support
  – initial qualification of the excipient supplier
  – qualification of suppliers of low and medium risk excipients
  – a risk assessment to justify no further action required
  – an aid to auditing those aspects of the supplier which are critical to higher risk excipients

EXCiPACT™ – minimize risks, maximize benefits
EXCiPACT asbl

- is a non-for profit organization established in Belgium, with the following full members

for further information visit

www.excipact.org

Thank You!