Pharmaceutical Excipients
Global business developments

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Today's Agenda

Changing global regulations:

- likely impact on pharmaceutical excipient manufacturers, suppliers and users

3rd Party Certification

- EXCiPACT, Rx-360 and ANSI NSF Standards
- The EXCiPACT Certification Scheme

Q&A session

Changing global regulations

- **Risks** in the pharmaceutical supply chain are not just API related, excipients may be impacted
- **Regulators expect** Marketing Authorization Holders to secure their supply chain
- **Physical audits** are an essential component in understanding supply chain risk and the controls needed to mitigate these risk.
- Implementing **risk management programs** to secure the supply chain will result in a substantial increase of periodical, physical audits
- The **economic burden** associated to these requirements are impacting both manufacturers and users

Changing global regulations

1. **EU - Falsified Medicines Directive 2012**
2. **EU - revisions to Drug Product GMPs 2012**
3. **USA - Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012**

- All require that the excipient user has to secure the supply chain and have physically audited their suppliers
- But can either Suppliers or Users of Excipients cope with more physical audits?

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

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. …
- Now elaborated in EU Part I GMP for pharmaceutical products, Chapter 5 = the qualification (approval) process for excipient suppliers

What about the new Chapter 5?

Chapter 5 Just Published:

Starting materials

5.29 …For the approval and maintenance of suppliers of active substances and 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'.

EU Risk Assessment for Excipient GMP

3. DETERMINATION OF EXCIPIENT MANUFACTURER´S RISK PROFILE

13. Data/evidence to support this should be obtained through audit or from information received from the excipient manufacturer

14. Quality system certification or accreditation held by the excipient manufacturer and the standards against which this has been granted should be considered as this may meet the required GMP

- Requirement for verifying the GMP has been applied = audits
- Overall the approach is fully compatible with a supplier using EXCIPACT™ Certification to demonstrate the implementation of a suitable GMP

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

Title	Authorization to FDA	Impact for Excipient Suppliers
VII Drug supply chain	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	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.

Changing global regulations - FDA

Quote: S Wolfgang, FDA, April 2013, US launch of EXCiPACT™

"**Excipient Standards Continue to Advance**

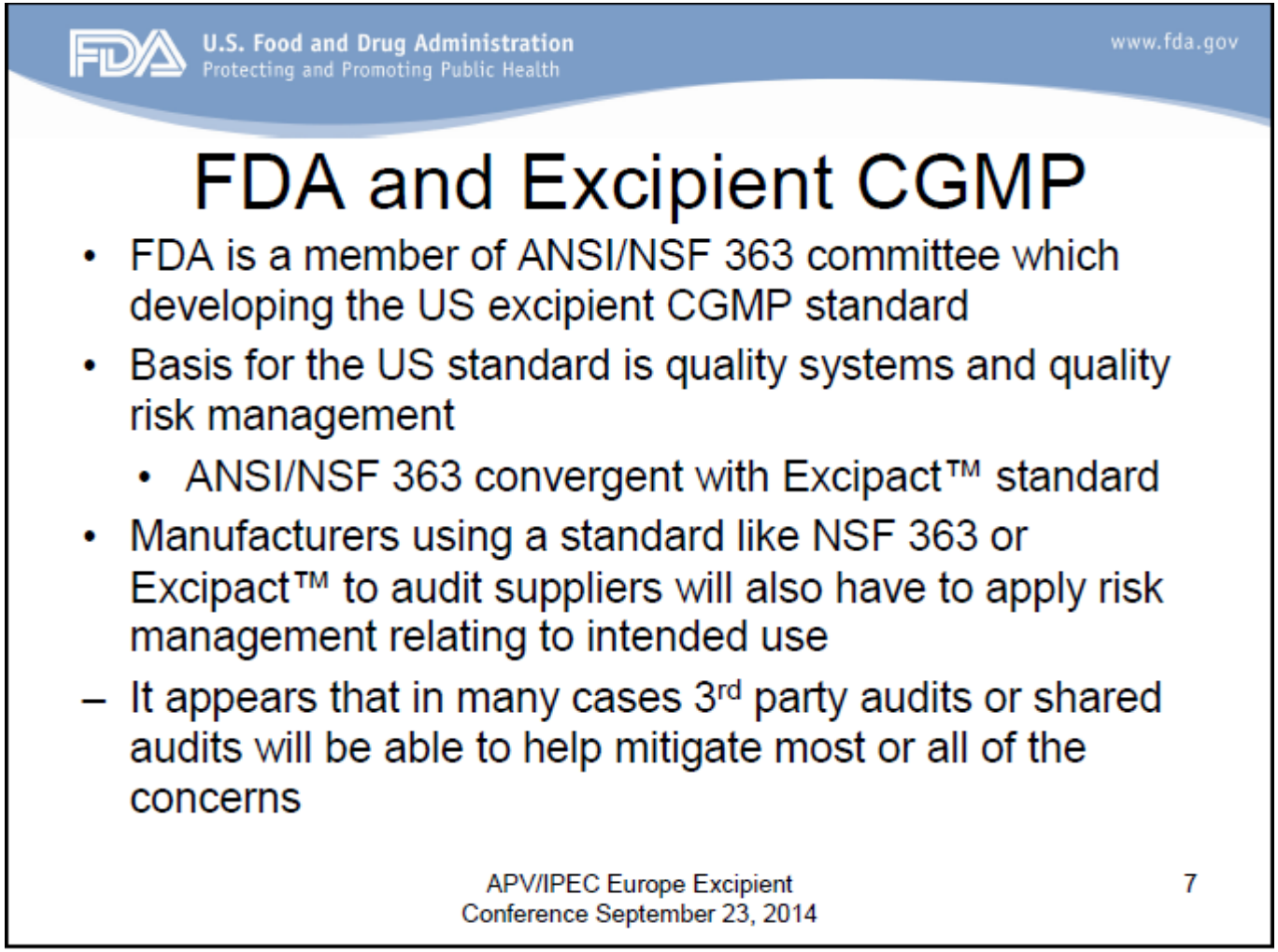
Evolutionary trends in global excipient regulation

- Approaching unanimous agreement that excipient GMP is necessary
- Approaching agreement between regulators and industry that a quality systems-based approach is the basis for all excipient GMP
- Broader GMP expectations are more clear
- Science-driven and based on understanding of end use
- In line with quality risk management approaches."

Changing global regulations - FDA

Dr Steve Wolfgang, FDA

APV Excipient Conference Dusseldorf Sept 23rd 2014



Changing global regulations -

- 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"

Changing global regulations

Summary

- The regulatory position in the US and Europe is very supportive of independent 3rd party auditing schemes if they meet two core principles;
  - **Auditor competency**
  - **Certifying Body independence and freedom from conflicts of interest**

- **The EXCiPACT™ Certification Scheme** has built these two principles into its core and meets these regulatory requirements

Likely impact on pharma excipient manufacturers, suppliers & users

- **What are the appropriate GMP & GDP for excipients?**
- **Push for on-site GMP & GDP audits of suppliers**
  - 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 audits requests a year – so will refuse to host many – what happens then?

3rd Party Audit & Certification Schemes

	EXCiPACT	NSF (IPEA)	Rx-360
GMP Standard*	Yes	No	Yes
IPEC-PQG Guide	No	Yes	Yes
Auditor Training/Qualif'n	Yes	Yes	No
Certification	Yes	No	No
Provider	Accredited 3rd parties	NSF (IPEA)	Sub-Contract/ BSI

EXCiPACT is the only available auditing standard for pharma grade excipients

EXCiPACT™ Certification

ISO 9001 certification

+

EXCiPACT™ GMP / GDP

=

EXCiPACT™ Certification

Successful EXCiPACT Certifying Body Audit

No ISO 9001 certification

+

ANSI NSF 363

=

EXCiPACT™ Certification

EXCiPACT™ Certification Scheme

- New independent 3rd party GMP/GDP audit service for suppliers of pharma grade excipients
- Provided by approved auditors from EXCiPACT-registered Certifying Bodies
- Offers big benefits to suppliers and especially users – QP/QA/QC/Purchasing
- Designed to help identify and to qualify suppliers
- Suppliers with EXCiPACT Certificates simplify MAHs responsibilities
- No loss of assurance of GMP/GDP compliance

EXCiPACT™ Certification Scheme

- 2013: Pilot audits validated the scheme rules and EXCiPACT™ Standards
- 2014: EXCiPACT asbl launched as a not-for-profit association in Brussels
- Unrestricted auditing by EXCiPACT™ Certifying Bodies using EXCiPACT™ Registered Auditors
- 4 Certifying Bodies approved – mdc, SGS, DQS and AJA
- 15 certificates awarded, most in EU + Canada and Saudi Arabia
  - more certifications expected in USA, India, China and Japan
- 5 auditor training courses completed – 3 more planned
  - 18/19th November 2014 and 17/18th March in Brussels + USA course 1Q15 TBA
- ANSI NSF 363 EXCiPACT-equivalent standard is pending

EXCiPACT™ Certification Scheme

- EXCiPACT-certified suppliers will provide users with

  Certificate + Audit Reports + any CAPA plans
- As surveillance audits are annual, also give a record of supplier compliance
- This audit frequency is greater than most users can perform, even for critical excipients
- Certification is not the auditor's decision - EXCiPACT requires it to be via an independent review board
- All EXCIPACT-Registered Certifying Bodies, Auditors and Suppliers are listed on the EXCiPACT website www.excipact.org to reassure users.

EXCiPACT™ Certification Scheme

May not replace ALL pharmaceutical company audits BUT…

- Scope, 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

Beneficiaries of EXCiPACT™ Certification

Everyone in the human medicines supply chain:-

- Patients
  - get higher quality medicines
- Excipient Users/Formulators
  - simplifies their responsibilities
- Excipient Suppliers
  - independent certification of their quality management system
- Auditors/Certifying Bodies

EXCiPACT™ Certification
Cost savings for stakeholders

Cost for EXCiPACT™ Audit	Excipient Supplier	Pharmaceutical Company
Audit fee ~ 10’000€ Certificate fee ~ 5’500€ Surveillance ~ 10’000€ Internal cost ~ 2’5 - 5’000€ Total cash-out ~ 28 - 30’000€	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	Reduction by one two-day audit a month, plus travel time/expenses and report preparation at total average cost of ~5’000€ to 6’500€ ~ minimum of 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€ + 180’000€ = 240’000€**

EFCG
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Thank You!

Questions?