A variety of GMPs exist

- ICH Q7 – GMP Guidance Active Pharmaceutical Ingredients
- 21CFR211 – US GMP Drug Products
- 21CFR111 – US GMP Dietary Supplements
- 21CFR110 – US GMP Foods
- General Principles of Food Hygiene, Composition and Labeling; Code of Practice (GPFHCL)
- Codex Alimentarius – FAO/WHO Food GMP
- EFfCI – EU GMP Cosmetic
- IPEC PQG GMP Excipients

Which applies and where.............?
Basic Concept

- **Food GMP**
  Product Safety - control of microbiological, chemical or physical hazards and prevention of spoilage and contamination with filth

- **Drug Product GMP**
  Product Safety, Identity, Strength, Quality, and Purity – must be safe and provide the intended benefit to the patient

- **Excipient GMP**
  Product Safety and quality of products sold to finished drug product manufactures

Differences in GMP

- **Food & Food Additives have different GMPs**
  - Focused on presenting no hazards to the person eating the material
  - No quality requirements for function (safety only)
  - Failure of a food additive or ingredient results in poor taste or rejection by the consumer

- **API manufacturing have different GMPs**
  - Full GMPs start earlier in the process
  - Degree of documentation & oversight greater
  - Control at every step to ensure the identity, strength, quality, and purity of the drug
  - Failure of API functionality has direct impact on drug performance
Excipient GMP focus on both Safety (like in food) and Consistent quality (like in API)

- Specifications, Process Capability (validation for Excipient), and Change Control with customer notification form the basis of difference between food and excipient GMP
- Starting point of full GMPs, degree of documentation & oversight form the basis of difference between API and excipient GMP
- Raw materials for excipient manufacturing are consumed by the process as compared to ingredients (excipients) for drug products that are consumed by the patient
- Failure of an excipient may result in rejection of a drug batch or decrease in effectiveness or stability of a drug product

Goal is to Manage Risk
Risk to Drug Maker & Risk to Patient

Adulterated excipient causes failure of drug batch during manufacturing

Adulterated excipient causes failure of drug in use or results in hazardous product
Implementing GMP procedures without understanding product and manufacturing risks is like driving blindfolded.

The justification for controls and absence of such are a critical part of effective GMPs.

GMP principles always apply

• GMPs are not like “Tax Laws” in which to find “loop holes”
• GMPs don’t tell “how to do” but provide guidance as to what must be done
• GMPs are a set of principles to address risk
• GMPs can not be effectively implemented without understanding both the principle concept and the risk that needs to be controlled
• GMPs can not be blindly copied
• The best GMP implementation is the one that works
Evaluating Excipient Manufacturers

- Basic Quality Management Systems principles plus key processes necessary to ensure production of safe consistent products
- Emphasizes communication between manufacture and user
  - Significant Change
  - Certificate of Analysis
  - Stability
- International in scope
- Useful and acceptable to Suppliers, Users and regulators

How do you know your excipients were made following GMPs?

- Receipt testing?
  - Not practical to test for everything
  - Sampling is still just a sample
  - Testing tells you about this lot not the next
- Ask the supplier?
  - Good start but who are you asking?
  - Are the answers the whole story?
- Ask the Government?
  - Good start but absence of information is not conformation that all is well
- Audit the supplier?
Trust but Verify

- Understanding the suppliers processes for GMP and managing risk is key
- On site audits allow a better assessment of risk
- CoAs should be periodically cross checked by testing samples
- Customer reported data should be traced back to the actual lab note books

Challenges to a global audit program

- Suppliers will not agree to an audit
  - Not enough days in the year for an audit from every customer
- Travel cost continue to rise
- Language barriers
- Employees don’t want to travel
- There are a lot of locations to audit
- In house auditors are not familiar with chemical processing resulting in less effect audits
Certification & 3rd Party Audits

• Provides information on Supplier’s GMP practices from experienced auditors with knowledge of excipient manufacturing & GMPs
• Allow companies to focus resources on excipients with highest risk
• Reduces audit load for suppliers
• Can allow a level playing field for all
  – Help small companies with limited budgets
  – Provide a consistent standard for suppliers
• Make 100% audit verification of suppliers practical

Nothing in FDA regulations prevents using 3rd party auditors to evaluate suppliers

Sec. 211.34 Consultants.
• Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.
Aim of certification is to replace low risk excipient. User audits but not stop user audits altogether.

**Goal is to Manage Risk**

**Risk to Drug Maker & Risk to Patient**

Adulterated excipient causes failure of drug batch during manufacturing. Adulterated excipient causes failure of drug in use or results in hazardous product.

**Internal policies may need updating**

- Procedures should be reviewed on a regular basis.
- Policies are made to protect the patient and should be changed to improve the system.
- Using a knowledgeable auditor with experience in excipient manufacturing provides better information on true risk.
- Qualification of third party auditors and the use of third party audits/certifications will improve a company’s supplier qualification program.

www.ipec-americas.org
International Pharmaceutical Excipients Auditing (IPEA)

- **Incorporated in 2001** (subsidiary of IPEC-Americas)
- **Mission**: Facilitate Site Assessment for Qualification of Excipient Suppliers
- **Objective**: Reduce Costs for Both Makers & Users
- **How**: Sharing of Excipient Audit Reports
- **Standard**: Excipient GMP Guideline
  - Reports document how site meets GMP expectations
  - GMP Certification
  - Final stages of ANSI Accreditation to ISO 65

Slides in this format are adapted from presentations by Dr. Irwin Silverstein, Ph.D. (VP and COO, IPEA).

www.ipeainc.com
Irwin.s@verizon.net
Report Sharing (2001 – Present)

- Audit Sponsor: Either Maker or User
- Audit Report: Available for Sale to other Users
  - With Maker Approval
- Confidentiality: Strictly Enforced
- Audit Sponsor Credited for Sale
  - 10 Report Sales=Free Sponsorship
  - 2 Report Sales=Free Report Purchase

2010 - Certification

- Procedures written to document certification process
- Expectation criteria developed for assessment to IPEC PQG Excipient GMP Guidelines
- Sponsor: Excipient Maker
- Report: Available at low cost
- IPEA Audited by ANSI for ISO 65 Accreditation
- Certification performed and GMP Certificate Issued
Auditor Qualification

- Education and Experience
- Training by IPEA
  - 3-Day Workshop, or
  - 1-Day Excipient GMP Expectations

  - Supervised Qualification Audit
    - On-site Performance
    - Audit Report
  - Continuing Oversight
  - 10 global auditors currently qualified

Excipient GMP Certification Board

- Certification Board: 2-Members each from Maker and User Community
- Review Application, Audit Report, and Findings
- Interview Auditor
- Assess Adequacy of Quality System
- Recommendation
  - Certification or
  - Correction of Deficiencies
Excipient GMP Certification

- Conflict of Interest
  - Disclosure of:
    - Employment by Applicant
    - Consulting for Applicant
    - Significant Financial Interest

Excipient GMP Certification

- Certification Criteria
  1. No Items Rated “Critical Failure”
  2. No Items Rated “Does Not Meet” Unless Interim Action or Implemented CAPA
  3. No Section with Sufficient “Partially Meets” to Cumulatively Indicate Failure to Comply
  4. Report does not convey a significant risk that the quality system will not assure the safety and quality of the excipient.
**Excipient Certification**

- Assess Conformance of Site Quality System to Excipient GMP Expectations
- Comprehensive Site Audit to Excipient GMPs
- Certify Conformance
  - Issue Certificate
  - Post to Website
  - Make audit report available

For more info:  [http://www.ipeainc.com](http://www.ipeainc.com)

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**Rx-360**

- Mission: Create and monitor a global quality system that meets the expectations of industry and regulators that assures patient safety by enhancing product quality and authenticity throughout the supply chain
- Developing a process for sharing supplier audits

www.rx-360.org
GMP Certification Standards by 2011
2 standards from 1 GMP (2006 IPEC PQG)

- **EXCIPACT**
  - GMP/GDP certification as an Annex to ISO 9001:2008 Quality System Standard
  - Joint effort of IPEC Europe, European Fine Chemicals Group, IPEC Americas, Pharmaceutical Quality Group, and European Association of Chemical Distributors

- **ANSI NSF 363** – Good Manufacturing Practices for Pharmaceutical Excipients
  - National Standard for certification of effective implementation of excipient GMPs by a manufacturing facility
  - For use by companies without ISO 9001 registration
  - Team of Makers, Users, and Regulatory/Academic/public

ISO 9001 – Integration & Independence

- Most Eu food and specialty chemical companies that sell products into the excipient market have third party ISO 9001 certification
  - EXCIPACT builds on this and so avoids duplication of management system requirements
  - ANSI NSF 363 is stand alone and includes quality systems elements that support GMP

- Most EU pharmaceutical companies require facilities producing excipients to be certified to ISO 9001 or at least to be very familiar with it while US pharmaceutical companies do not

- U.S. auditors with experience in Pharmaceutical Manufacturing and GMP are not typically ISO 9001 Lead Auditors

- US Companies do not associate ISO 9001 Certification with product quality or product safety while opposite is true in EU
  - Deceptive practices with scope of certification
  - Product failures from ISO 9001 Certified Companies
  - Inconsistency among auditing companies offering certification
Benefit of ANSI Standard

OMB Circular A-119

• The circular directs government agencies to use voluntary, consensus standards in lieu of government-unique standards

ANSI NSF 363 - Good Manufacturing Practices for Pharmaceutical Excipients

• NSF PINS filing for NSF 363 Good Manufacturing Practices for Pharmaceutical Excipients published September 11, 2009 in ANSI Standards Action
• Also published call for consensus body members who wish to participate on standards committee
• First meeting of consensus body, February 25, 2010
• Monthly meetings follow
• Target Publication of Draft for public comment Fall 2010
• Target Publication of Standard December 2010
Scope published in ANSI Bulletin

- Baseline quality system based GMP for Excipients (higher risk excipients will require controls in addition and beyond the scope of this certification standard)
- Include all principles of IPEC PQG GMP Guideline for Pharmaceutical Excipients
- Intended to assist in the determination of adequate facilities and controls for excipient manufacture and whether the excipients are manufactured with consistent quality and purity as declared by the manufacturer.

Development Team

- Iain Moore - Croda
- Katherine Ulman - Dow Corning
- Dale Carter – JM Huber
- Ann Van Meter - Dow Chemical
- Chris Moreton - FinnBrit Consulting
- Irwin Silverstein - IPEA
- Bob MaGee – SGS
- Anne Gayot - University of Lille
- Dr. Larry Block - Duquesne University
- Jeffrey Brambora - Eli Lilly
- Stephen Moss – GSK
- Walter Joppy – J&J Consumer Products
- David Klug - Sanofi-Aventis
- Steve Wolfgang - FDA CDER
- Scott Clipper – NSF International
- Jane Wilson - NSF International
EXCIPACT

International Excipients Certification Project
Minimize Risks – Maximize Benefits

Slides in this format are adapted from the EXCIPACT communication team or from presentations presented by Dr. Iain Moore (GMP Certification ISO Annex Project Coordinator) during Steering committee updates or other meetings.

EXCIPACT

- EFCG and IPEC Europe signed a MOU in May 2008 to generate a global excipient certification scheme. Joint project includes:
  - EFCG – European Fine Chemicals Group
  - IPEC Europe
  - IPEC-Americas
  - PQG - Pharmaceutical Quality Group
  - FECC – European Association of Chemical Distributors
- Annex takes the IPEC-PGQ Guide and backs out the Quality Management Systems elements currently given in the ISO 9001 standard
- Essential processes necessary for GMP compliance remain

www.ipec-americas.org
Do you need this slide as it was already in the 1st presentation?

Iain.Moore, 10/1/2009
Steering Committee

- Dr Iain Moore – IPEC Europe
  - (Project Coordinator)
- Alexandra Brand – EFCG
  - (Steering Committee Chair)
- Patricia Rafidison – IPEC Europe
- Beam Suffolk – IPEC Europe
- Tony Scott – EFCG
- Norman Randall – PQG
- Steve Moss – PQG
- Janeen Skutnik – IPEC Americas
- Dale Carter – IPEC Americas
- Hendrik Abma - FECC

EXCIPACT principles: involvement of all stakeholders

- International: certificates accepted globally
- Inclusive: certification scheme provide quality standards and applicable to as many excipients as possible
- Accessible: certification assessable for as many accredited 3rd party organizations as possible
- Evolutionary: builds on existing guides and standards
- Simple: easy to understand and apply for all stakeholders
Excipient Certification Project Principles

Evolve existing best practices
- Base on the IPEC-PQG GMP Guide 2006
- Base on IPEC GDP Guide 2006 & SQAS Distributor ESAD Scheme
- Align to ISO 9001
  - Many excipient suppliers are already ISO certified or familiar with this quality management system standard

International in scope
- Excipients are a worldwide commodity
- Be valuable and acceptable to Suppliers, Users and regulators

Excipient Certification Project Principles

Include as many Excipients as possible
- Set standards that are achievable
- Set standards that are auditable

Address the definition of and policing of auditor competency
- Be accessible to existing 3rd party audit organisations
- Consult with all Stakeholders throughout the project
  - One session held in Europe in May 2009
  - Sessions held with FDA in July 2009 and February 2010
Excipient GMP

- Certification will be against the core requirements in the IPEC-PQG GMP Guide 2006 – as converted to “ISO speak”
- Suppliers with ISO 9001 will only require additional audit time to cover GMP
  - Excipact
- Suppliers without ISO 9001 will require an audit covering GMP and the Quality Management System
  - NSF-ANSI United States National Standard
- Two definitions of Excipient GMP containing the same requirements

GMP draft based on core principles

- Follows the ISO standard language where intent and purpose for control is given (what to do) versus the how to achieve the control
- Looked again at IPEC PQG Excipient GMP to extract the main concept from the “how to” guidance
- Checked ISO 9001 to see if the concept was already captured and explicit
- Added concepts that were not included in ISO or needed further emphasis/clarification
Core principles not in ISO 9001:2008

- An independent Quality Unit for oversight
- Change control and determination of customer notification/prior approval for significant changes or outsourcing of production
- Personnel Hygiene
- Defined batch or processing records for quality critical processing steps
- Demonstration of consistent manufacturing process
- Packaging and Labeling controls
- Laboratory Controls (Testing, Release, OOS investigation, Retained samples)

Excipient GDP

- Certification will be against the core requirements in the IPEC GDP Guide 2006 – as converted to “ISO speak”
- IPEC GDP Guide 2006
Excipient Classification

• EXCIPACT is developing a Guide for Users to identify when the Scheme would not be suitable as the only means of Excipient Qualification
• When these excipients are identified Users could still use EXCIPACT as the base qualification but would then know which areas and activities required additional knowledge
  – Supplier aware of additional activities to address risks
  – Focussed audits by user
• Equally true that some excipients could be supplied which do not meet the IPEC-PQG GMP Guide requirements
• In this case the User would need to use other methods to help qualify the supplier

Auditor competency & qualification

Principles adopted
- Quality of auditors is critical
- Competency framework defined using internationally accepted i.e. ISO 19011 (Auditing standard)
- Alternative starting routes to qualification possible i.e. experienced in ISO 9001, GMP or GDP
- Considered best practices e.g. IRCA, SQA and Qualified Person assessment processes
Certification Scheme

Program elements
- Program Owner: Legal Entity representing listed organizations
- Certification Body: Accredited to ISO 9001, ISO/IEC Guide 65, ISO 17021 or equivalent and assessed by Program Owner
  - Impartial
  - Competent
  - Resources, auditors and technical experts, to implement certification requirements
  - Operational conformance to ISO 19011 (Management System Auditing)
- Excipient suppliers to be Certified on a 3 year cycle
  - Annual site surveillance audit
  - Triennial recertification audit

Audit Documentation
- Audit Report lists observations and the rates findings as critical, major or minor
- Technical Experts review audit report and findings, recommend certification if
  - No critical, no major without CAPA, no minors that indicate failure of quality system element
- Audit Report available to pharmaceutical customer with excipient maker approval
Certification Scheme

Public Access

- Website:
  - List of Third Party Certification Providers
  - Directory of certified excipients and their manufacturers
  - List of certifications suspended and withdrawn
  - Program Procedures
    - Appeals
    - Complaints
    - Requirements of Third Party Certification Providers
    - Study Guide for Excipient GMP Certification Auditors

EXCIPACT - International Excipients Certification Project – Minimize Risks, Maximize Benefits

Excipient GMP & GDP Certification Scheme

Current Project Status

- GMP Annexes
  - 1st Draft documented reviewed and revised
- GDP
  - 1st Draft documented and sent for review to membership of partner organisations & Selected stakeholders – undergoing review
- Auditor Competency
  - 1st Draft documented including a Study Guide
  - Ready for membership review
- Certification Scheme
  - Requirements defined and ready for review
  - Website being prepared
- Scheme Delivery?
Excipient Supplier?

Without ISO 9001?
Use NSF 363 Standard

With ISO 9001?
Use Excipact

Excipient User?

Use NSF 363 or Excipact Audit reports
Use Rx-360 Audit reports

All schemes aimed to be based on the same set of requirements for GMP and GDP for Excipients

EXCIPACT- International Excipients Certification Project – Minimize Risks, Maximize Benefits

THANK YOU!

Special thanks to:
Irwin Silverstein – IPEA
Iain Moore – Croda / IPEC Eu
Franco Ponquinette – JM Huber

dale.carter@huber.com
William Dale Carter
Director of Global Quality
JM Huber, Engineered Materials – Silica
1000 Parkwood Circle
Suite 1000
Atlanta, GA 30339
Phone 678-247-2735

www.ipec-americas.org