Quality Assessment & GMP

Similarities & Differences

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Content

• Overview of commonalities & differences
• A brief insight into GMP and the inspection process
• Overview of specific topics
  • QP release
  • Variations – when assessment ends & inspections begin
  • Reduced (skip) testing of materials
  • Ongoing stability programme
  • Technical transfer
  • Technical agreements
• Virtual tour of an API manufacturing site
• Questions
Separate activities for both groups

- **Quality Assessment**
  - Product specific issues which are an integral part of the dossier
  - Guidance on content provided by NtA, Volume 2B, CTD - Module 3 (& many references therein)

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**The Grey Area**

- **GMP Inspection**
  - An assessment of the level of compliance of a facility with Good Manufacturing Practices (GMP)
  - **Legal** basis for GMP is EU Directive 2003/94/EC (human) & 91/412/EEC (veterinary)
  - Reference guideline document is the EU Guide to GMP
Common activities for both groups

- **Both assessors & inspectors require information**
  - Any information can be requested. The question to consider is:
    - (a) what is the basis for requesting the information?
    - (b) what will you do with the information received?
  - The mechanism of communication is generally different
    - Written word (quality assessment)
    - Face-to-face (inspection) followed by written word
Inspections & the EU Guide to GMP

- The Rules Governing Medicinal Products in the European Union, Volume IV, (or the EU GMPs)
  - Part I - Basic Requirements for Medicinal Products
  - Part II - Basic Requirements for Active Substances used as Starting Materials (same as ICH Q7)
  - Annexes – specialised topics
EU Guide to GMP – Part I and II

- **Part I** comprised of 9 chapters

  1. Quality Management (e.g. SOPs)
  2. Personnel (e.g. training)
  3. Premise and Equipment (e.g. facility & tablet press)
  4. Documentation (e.g. records)
  5. Production (where product is made)
  6. Quality Control (where product is tested)
  7. Contract Manufacture & Analysis (e.g. technical agreements)
  8. Complaints and Product Recall (e.g. market complaints)
  9. Self Inspection (e.g. internal audits)

- **Part II** - detailed consolidated guide for API manufacturing sites

- These guides provide the **basis** for inspector queries
The process of QP batch release

- Each batch is required to undergo certification by a QP within the European Union.

- A statement that the batch has been manufactured in accordance with:
  - GMP
  - Marketing Authorisation

- **This requires that the inspector reviews sections of the quality module of the dossier during the inspection**

- Important when there are changes to the dossier i.e. variations

- **Note** – if data/information is registered in the dossier, it is not reassessed by the inspector!
Examples of boundaries with variation applications

- **Type 1 – # 7: new site of manufacture**

- **Quality Assessment**
  - Documentation Requirement No. 4
    - *Batch numbers or validation protocol for process validation*

- **Inspection Review**
  - Validation Master Plan *(Annex 15)*
  - Process validation protocol & study report
    - especially any deviations to the protocol, changes etc.

- **Additional inspection review**
  - Was any equipment cleaning validation study performed
  - Was product placed on stability – review stability report
  - Verification that batch numbers submitted to Competent Authority were the same batches employed in validation exercises.
• Type 1 – # 7: new site of manufacture

• Quality Assessment
  • Documentation No. 9, QP declaration re: API site

• Inspection Review
  • Is there an audit schedule for all API sites (Chapter 1)
  • Is there an audit report of actual API site involved (Chapter 5)
  • How was training provided to auditors (Chapter 2)
  • Was the auditing contracted out to third party (Chapter 7)
  • Is there a Technical Agreement in place where one QP (e.g. batch release) declaration is based upon another QP declaration (e.g. manufacturer) as specified in the variation regulations (Chapter 7)
Type 1 – Number 33

- **Type 1 – # 33: change to manufacturing process**

- **Quality Assessment**
  - Documentation No. 8 = Stability
    *Batch numbers of batches placed upon stability*

- **Inspection Review**
  - Review stability report – see later slides on stability

- **Additional inspection review**
  - How was the change control process managed
  - Was there any consideration for any validation studies
  - Were any new equipment qualification studies performed
• Type 1 – # 38: change in test procedure

• **Quality Assessment**
  • Documentation No. 2 – *Test Method Validation*
  • Note – validation data is not reviewed by inspector as it was already submitted & approved by quality assessor

• **Inspection Review**
  • What was the origins of the test method – another site?
  • Was there a Technical Transfer process? If so, review protocol and report.
  • What analytical technology was employed – GMP requirements for calibration, maintenance & validation of all equipment.
Technical Transfer to Contract Site

- Common practice between sites reviewed during inspection
- Applies to analytical test method transfer (or stability studies)

**Technical transfer protocol**
- define what testing is required
- define what samples will be tested ~ same batches ideally
- define specification limits
- pre-defined acceptance criteria e.g. % RSD
- contact personnel & protocol signed by both parties

**Technical transfer report**
- outcome of the technical transfer – success?
- any deviations from the original protocol
Note on skip testing of finished product

- ICH Q6A describes concept of periodic/skip testing performed at release
- Example that is referenced is microbiological testing
- For example, company proposes to perform the test on every 10th batch
- This typically requires pre-approval by Competent Authority
- This is a quality assessment issue—approved by variation application
- Inspectors commonly encounter skip testing on raw materials (excipients & APIs)
Note on reduced & skip testing of materials

• GMP Guide makes reference to sampling & testing

• Quality Control - EU GMP, Part I, Chapter 6.11-6.14
  • The physical method of sampling containers

• Sampling of Starting & Packaging Materials - EU GMP, Annex 8
  • Identity testing requirements & reduced testing
  • Vendor verification and reduced testing

• Sampling and Testing of Incoming Production Materials (for API production) - EU GMP, Part II (7.3)
  • Identity testing requirements & skip testing

• Skip testing & associated controls performed on raw materials is reviewed during inspection
Skip testing on raw materials

- Aspects that companies should consider, which initiating ‘skip testing’ on raw materials
  - Appropriate Standard Operating Procedures covering approval of API manufacturers, criteria for implementing skip testing and re-instigation of full testing for the received lots of API
  - The number of batches received per year
  - Critical Quality Attributes e.g. particle size, polymorphism etc.
  - Analytical batch data used by the finished product manufacturer to support reduced testing frequency
  - Vendor approval, including the report from an audit conducted at the API site
  - Complaints & deviations associated with the vendor’s material
  - Details of the supply chain for the API
  - Technical agreements with the API manufacturer
  - Checks performed on incoming goods at warehouse
Note on on-going stability studies

• One batch of finished product per year: EU GMP, Chapter 6.29
• One batch of API per year: EU GMP, Part II, 11.5
• Storage conditions & testing frequency (i.e. various time-points) as per ICH recommendations
• There should be procedures in place for selecting batches:
  • for routine purposes (per annum)
  • for non-routine studies
    ▪ from validation studies
    ▪ from process deviations e.g. API reworking
• If the company are using Bracketing or Matrixing, this must be justified
The On-going Stability Study – How many samples?

- GMP requirements for stability samples *(EU GMP, Part I, Chapter 6.29)*

- The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis

- Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year)

- The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol
The On-going Stability Study – API samples

- Similar GMP requirements for stability samples of API samples
  - 1. Stability program in place.
  - 2. Validated, stability indicating test methods employed.
  - 3. Containers that simulate the market container.
  - 4. First three commercial batches included on stability.
  - 5. One batch per year thereafter.
  - 6. ICH conditions applied.
  - EU GMP, Part II (11.5)
Variations to MA requiring stability studies (but the data is **not assessed** with the variation)

- Type 1B (18): replacement of excipient with comparable excipient
- Type 1A/1B (29): change in composition of immediate packaging
- Type 1A/1B (32): change in batch size of finished product (FP)
- Type 1A/1B (33): change in manufacturing process of FP
- Type 1A/1B (34): change in colouring/flavouring system of FP
- Type 1A/1B (35): change in tablet coating weight or capsule shell
- Type 1A/1B (36): change in shape/dimensions of container closure system
- Type 1A/1B (41): change in pack size of FP
Reviewing On-going Stability Data

- This is a routine part of the inspection process

- Key features inspectors look out for:
  - Why are the company conducting the stability study?
  - Routine stability studies conducted (annual GMP commitment)
  - Significant ‘change controls’ initiating stability studies
  - ICH requirements fulfilled (long term stability conditions)
    - temperature, humidity & testing frequency
    - is the product destined for many markets?
Reviewing On-going Stability Data (cont’d)

• Additional features inspectors look out for:
  
  • Justification for skip-testing of timepoints – trend data required
  
  • The important process of trending of data
    ▪ should be performed at every timepoint
    ▪ any **significant changes (as per ICH Q1A(R2) definition)**
    ▪ testing against specification limits or ‘for information only’
  
  • Final stability report conducted & reported (to QP) in timely manner
  
  • Out-of-specification results investigated and reported to Competent Authorities
When MA holder and Manufacturer are different

- Very common scenario, across different countries

- Technical Agreement in place which outlines responsibilities for:
  - generating Product Quality Reviews (Chapter 1)
  - batch release (Annex 16)
  - complaint investigations & recalls (Chapter 8)
  - stability studies & evaluation (Chapter 6)
  - vendor verification, especially API supply chain (Chapter 5)
  - regulatory changes (Chapter 1)

- Technical Agreement requirements are outlined in Chapter 7 of Guide
A note on APIs

• Approval of dossier / DMF (or ASMF) by quality assessment

• National approval or EDQM approval (Certificate of Suitability)

• Key part of the dossier which inspectors review is:
  - Reprocessing & Reworking sections
    - Any ideas why?

• Part II of the GMP Guide (or ICH Q7) is very detailed and inspections are performed against that guideline

• Example of an API inspection follows

• Note – these images are atypical and are not representative of API manufacturing sites either within the EEA or outside the EEA!
An ‘atypical’ manufacturer of an API

- Company website message
  - "Its all a part of our commitment to provide a better quality of life for all."
- Holder of Certificate of Suitability
Extract from the EDQM Application

- Certificates of Analysis – as part of EDQM Application
- Demonstrates compliance with the Marketing Authorisation
A virtual trip to an ‘atypical’ API site
Typically ‘industrial’ with lots of pipe-work
Example of a well designed & maintained facility
Manufacturing Area
API Production Facility?
Processing vessels, labelled as clean
Processing vessels, labelled as clean
Water source & the use of water in API process

Water treatment in local area

Vapi Waste & Effluent Management Co. Ltd.
India's Largest Composite Effluent Treatment Plant

Pilot Anaerobic Reactor
R & D Project in Technical Collaboration With
IIT-KANPUR & IIT-MUMBAI
Water purification – feed water
Example of water purification unit
Water purification system
Water purification loop
Water Purification storage (no recirculation)
Appropriate Containment ?
Inspection outcome

- CEP suspended following inspection
- No export of API to Europe had occurred
- Inspectors examined records of API sales & distribution
- API ~ Propofol Ph. Eur.
- Employed in a sterile parenteral finished product
Company website message (as of today)

- **Propofol**
  - Certificate of Suitability available – advertised on website
  - eDMF is available in CTD format

- Company advertises many other APIs in DMF CTD format

- ‘*We have been able to make a remarkable impression globally in our strengths to supply world class API's to regulated and non regulated markets*’.
Final words

• Both groups want information and in general, obtain it by different means.

• There needs to be a basis for requesting & reviewing information
  • why do I require this information?
  • what will I do with the information?

• Inspectors look at aspects of the quality dossier, to assess compliance with the MA at the manufacturing site, yet do not routinely comment on the detail therein.

• Issues identified by inspectors that impact on the dossier are often forwarded to quality assessor.

• Inspectors can follow up assessment observations / queries during any inspection.
Effective regulation requires cooperation between assessors & inspectors at a local and international level.

Many future challenges lie ahead:
- Changes to variation regulations
- Concept of ‘QP discretion’
- Quality by Design / PAT applications
- Possible joint inspector / assessor inspections

It is good (and very important) for both groups to talk!!

Thank you for listening today.