GMP Inspection of Pharmaceutical Plants: Case Studies

“Getting prepared for FDA or PIC inspections”

APV/IKEV Seminar on Good Manufacturing Practice: Compliance and Inspection, Istanbul, June 10/11, 2004

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  - of a plant which produces sterile products
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Inspection Management

- Preparation: **before** the inspection
- Escort: **during** the inspection
- “Close-out meeting”: **after** the inspection

Preparation: **externally**

- when will the inspection take place (period/timeframe) ?
- how many inspectors will be present ?
- Inspectors' competence
  - generalist or
  - specialist ?
- will the inspectors
  - work together or
  - will they split up?
- what regulatory principles apply?
- agree upon a common agenda in advance (if possible)
- notification of sub-suppliers and third-party contractors during the preliminary stages of the inspection

In-house preparation

- Preparation team: audit co-ordinator, escort (main escort, note taker, “runner”)
- Discussion of the results of previous inspection(s) (has all corrective action agreed upon been implemented)
- What documents will be sent to the auditors beforehand?
- Working out an inspection “strategy“ for
  - Product audit: which batches have been produced, have there been deviations in the produced batches, OOS, have all deviations been implemented according to the relevant SOP ?
  - System audit: are all systems, change control, validation, training, etc. in order?

Remark: Most audits will be a “mix” of product/system audit !

In-house preparation (cont'd)

- Reservation of meeting rooms
- Booking/providing hotels/means of transportation
  - organisation of arrival and departure times
  - catering during the inspection
  - "socialising"
- Providing person/subgroup involved with information
  - compiling a list with the phone numbers of necessary participants
- Possibly pre-inspections at the audited units
- training behaviour:
  - to determine who is to answer (how to proceed with foreign-language auditors?)

Presentations to foreign-language inspectors

slides

language

	mother tongue (e.g. German)	foreign language (e.g. English)
mother tongue (e.g. German)	 *	
foreign language (e.g. English)	./.	

*interpreter to be provided

Function: main escort

- ensures a pleasant inspection atmosphere and co-ordinates the general audit procedure (duty to supply information!)
- makes sure that the interviewee responds (correctly) to a question
- negotiates GMP interpretations (where appropriate)
- lists what documents have to be provided during the absence of the notetakers and compiles a “shopping list” of the relevant topics/documents
- arranges organisational matters with other escort(s)
- summons meetings at short notice if required (“crisis meeting”)
- informs affected areas about the topics on the shopping list

Function: notetaker

- makes a note of the items inspected and covered
- stamps the documents handed out with a “confidential” stamp
- records which documents have been looked at/handed out
- includes outstanding items/documents in the “shopping list”
- informs a fixed person sub-group*, if required, and, at least once a day, writes a **concise report** about how the inspection is proceeding (“notetaker’s report”):
  - areas inspected and items discussed
  - observations and other distinctive aspects

* sub-group of relevant persons for the notetaker’s report: environment and persons (in)directly affected who will be covered on the next days’ agenda, management

Function: runner

- provides necessary documents
- makes sure that the correct documents are handed out
- if necessary, looks at the documents with the interviewee before handing them out
- initiates the inclusion of outstanding documents in the “shopping list”

During the inspection

- first impressions count !!
- think first ……. then answer
- if something was misunderstood: **do** ask again !!
- only respond to those questions that have been asked
- present only those documents required
- only one person at a time should reply
- “endure” silence
- present only facts, not assumptions
- check documents again before finally handing them out (... are all signatures available ...?)
- if an interpreter is available: give him/her the opportunity/time to translate

What should be avoided?

- departments/areas are not prepared
- production processes have to be interrupted
- involved persons are difficult or impossible to get a hold of
  (no deputy/deputies has/have been organised)
- it takes some time (> 30') to provide the required documents
- frequent correction of wrong information
- ….

Between two inspection days

- An “inquest”
  - what was audited?
  - who was audited?
  - what were our observations? What were the inspectors’ (a comparison) ?
  - what was positive, what was negative?
- can single observations still be corrected during the inspection?
- how may the observations of the past day influence the rest of the inspection?
- who is to be informed that evening?
- …

After the inspection

- All personnel involved should attend the final wrap-up (= close out) meeting (including management)
- are the observations of the inspector(s) correct (compare with own records)
- may observations still be clarified / eliminated on the day of the final wrap-up?
- by when must replies to the observations be given? (give a realistic timeframe !!)
- who is responsible for the corrective action agreed upon ?
- what went well and what didn't during the inspection (inquest) ?

Keep in mind: After the inspection is before the inspection !

Typical focal points during an inspection of a sterile product plant (non-exhaustive list)

- Is there a coherent zone concept?
- Results of the personnel and production hygiene tests
- Water
  - have alert and action limits been determined?
  - were gram-negative germs found?
  - what happens if an alert/action limit has been exceeded (if an alert limit is exceeded for the third time is it considered equivalent to the action limit being exceeded once)?
- Media fills (if products are manufactured aseptically)
  - change procedure
  - training of personnel for the particular requirements of aseptic production

Typical focal points during an inspection of a sterile product plant (cont'd)

- are 3 successive media fills o.k. ?
- are monitoring data relevant to release during aseptic filling?
- has the "worst case" been considered during validation of aseptic filling ?
- has an attempt been made to find out the reasons for the specific non-sterility even if the number of non-sterile containers during validation of aseptic filling met the 95% confidence interval?

- Qualification/validation of sterilisation
  - has an SAL of 10^{-6} been proved ?

Inspection focus in a “solids plant”

- Stability tests
- Cleaning validation for “non-dedicated equipment”
- Packaging: avoidance of mix-ups
- Avoidance of “cross contamination” during the manufacture of products which can develop dust
- marking the status of rooms: “cleaned”, “cleaned/disinfected”, “released for production” …
- Compliance of the “master batch record” with the “batch record”
- General impression of the production rooms
- Results of room monitoring