October 2007

The QP and Product Quality Assurance, including contracts for external Manufacturing and Laboratories

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QP must confirm API-Related Notification of Changes

- In June 2006 the EC Commission published the revised "Guideline on dossier requirements for type 1A and 1B notifications
  - The QP of the marketing authorisation holder must confirm that each API supplier indicated in the marketing dossier has manufactured the API in compliance with ICH Q7A.
  - The QP who has overall responsibility for the batch must certify the batch

EMEA Statment on QPs Discretion in Batch Certification.

- Based on article 51 of Directive 2001/83/EC and article 13.1 of Directive 2003/94/EC the ad hoc GMP Inspection Services decided:-

If a batch does not fully meet the requirements defined in the MA....

"....The QP should perform a risk assessment of the impact on qualty,safety and efficacy but affected batches should not be released without first consulting the Supervisory Authority.."

"In some Member States....it is necessary to submit a formal variation application on a batch specific or temporary basis.

Given the Proposal, then a Batch can be considered to meet the M.A. When :-

1. The deviation is minor, one-off and unplanned …and relates only to the manufacturing process and/or the analytical control methods of either the starting materal or medicinal productas described in the M.A.
2. The Active substance/antigen and finished product specifications as described in the M.A. Are complied with.

Given the Proposal, then a Batch can be considered to meet the M.A. When :-

3. An assessment is performed..using ICHQ9..to support a conclusion that the occurence is a minor quality deviation and does not affect the Safety or Efficay of the batch.
4. The risk assessment should assess the need for inclusion of the affected batches in the ongoing stability program.....

Given the Proposal, then a Batch can be considered to meet the M.A. When :-

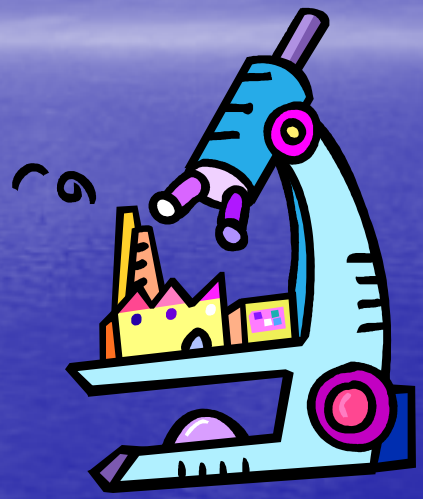
5. The Quality Risk Management process is integrated into the manufacturers QA system.....and records are available for inspection.....
6. All such deviations must be reviewed as part of the annual product review as required by Chapter 1 of the GMP guide.

Conclusion of EMEA Proposal

- Trends or recurrences and other deviations from the detailed M.A. must be flagged as problems that require resolution with the Competent Authorities, including, if necessary, the submission of variations.

QA of Contract Manufacturers.

- GMP Audits



  - Carried out to assess the contractor and to maintain the level of GMP compliance.

Supplier Qualification

- Most companies have different categories for each of their suppliers. The category should be material specific. The way a supplier can become more qualified will depend on a number of factors including the history they have with that supplier and the frequency they receive the material and how critical it is.

Approved Supplier

- A supplier that has sent back an acceptable quality questionnaire, or if deemed necessary by QA has had a successful quality audit . Samples of up to three lots of the material would have been sent and tested against the purchasing specification. If the material is deemed critical then it would also be advisable to have carried out pilot-scale manufacture using a lot to check for user acceptability.
  - A C.o.A and full testing would be required on receipt of each batch received. A composite sample may be made from samples from every container form the same batch.

Certified Supplier

- As an approved supplier plus:-
  - Have a good history of supplying material which meets specification and has had an acceptable Quality Audit in the last two years.
  - This would allow approval of the material on receipt with a C.o.A and some partial reduction of in-house testing. Full testing would be required on at least one batch each year.

Qualified Supplier

- As Certified Supplier plus:-
  - Longer history of no quality problems plus a reliable service and a good relationship with the supplier. Change-Control communications proactively demonstrated . No adverse comments from any regulatory inspections and a continuing acceptable audit report from QA.
  - Material can be received on a C.o.A plus and ID test. One batch per year to be fully tested to re-confirm Qualified status.

Can you add a second supplier, or change suppliers for a common component ?

- Yes, BUT, if it is for a key material such as the API or key excipients
  - There may be regulatory implications.
  - There may need to be comparability studies or even bioavailability studies.
  - A QA audit of the new supplier may be required first.

Check with your regulatory and QA functions first.

The use of Brokers ?

- Some raw materials are only available at reasonable costs if purchased through an intermediary, i.e. a Broker. If the material is critical to the process, e.g. an API or a key excipient this can give an added complexity to the process and this must be fully investigated with the Quality and Regulatory units being involved, before any orders are placed.

Process Validation

- Any new process or move to different production facility, or a major change to equipment used requires the process to be re-validated. The QP must be aware of any changes to the validated status of the process

Cleaning Validation Expectations the QP must be aware of-1

- Validation Protocols should be written before the studies are performed.
- Protocols should address sampling procedures, analytical methods (including the sensitivity of those methods) and the acceptance criteria to be used.
- Validation studies should be conducted in accordance with the protocols and the results documented

Cleaning Validation Expectations the QP must be aware of-2

- The protocol should address the “Worst Case” conditions.
- The validation procedure and specification should match that of the routine cleaning schedule.
- Analytical methods should be validated.
- A final validation report should be approved by QA and management to confirm the validity of the cleaning validation study.

Cleaning Validation Summary

- Plan ahead and write and approve protocols before starting.
- Agree acceptance criteria based on maximum allowable carryover calculations (MAC) .
- Carryout DQ/IQ where appropriate for all equipment.
- Carryout OQ/PQ every time.
- Develop scientific rationales for what you are doing.
- Validate everything !!
- Ensure there is sufficient resources and time to carry out the cleaning validation properly.

- Cleaning Validation requires a team approach.

Registration

- Any change to Manufacturing Authorisation /Product Licence has to be notified to the authorities with supporting data for the change.

  E.g. Validation.

Pre-Contract

- Before signing any contract arrange a due-diligence visit before final selection
- Assemble a “project team” to include personnel from QA/TS/H&S/Labs/Commercial
- Ensure any gaps identified by the due-diligence visit have been closed
- Get the proposed supplier to fill in a questionnaire which covers basic GMP issues.

Contracts

- There must be a written Technical/Quality Contract with the supplier which in addition to the financial aspects should also include:
  - To be open to QA audits on an agreed frequency.
  - The purchasing specification which must be met.
  - Who the actual manufacturer/supplier is (very important if dealing with a broker)
  - Requirement to notify any changes before they are made
  - A documented frequency of updates

EU. Chapter 7. Contract Manufacture and Analysis

- 7.1 There should be a written contract covering the manufacture and/or analysis……
- 7.2 All arrangement for contract manufacture and analysis……..should be in accordance with the marketing authorization…..
- 7.3 ……..ensuring by means of the contract that the principles and Guidelines of GMP as interpreted in the Guide are followed.

Documentation

- **Procedures / Work-tickets / Specifications / Control documents)-** The contract giver should ensure that all documentation and control systems are in place to ensure products are manufactured in accordance with licence agreements

Technical / QC support

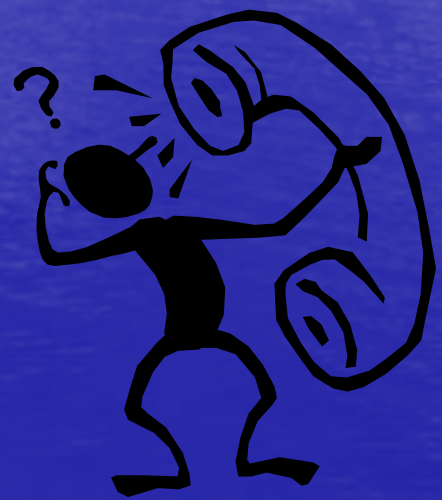
- To ensure the details of Manufacture and QC controls are in place and maintained with respect to the licence agreements

QC/ QP Release

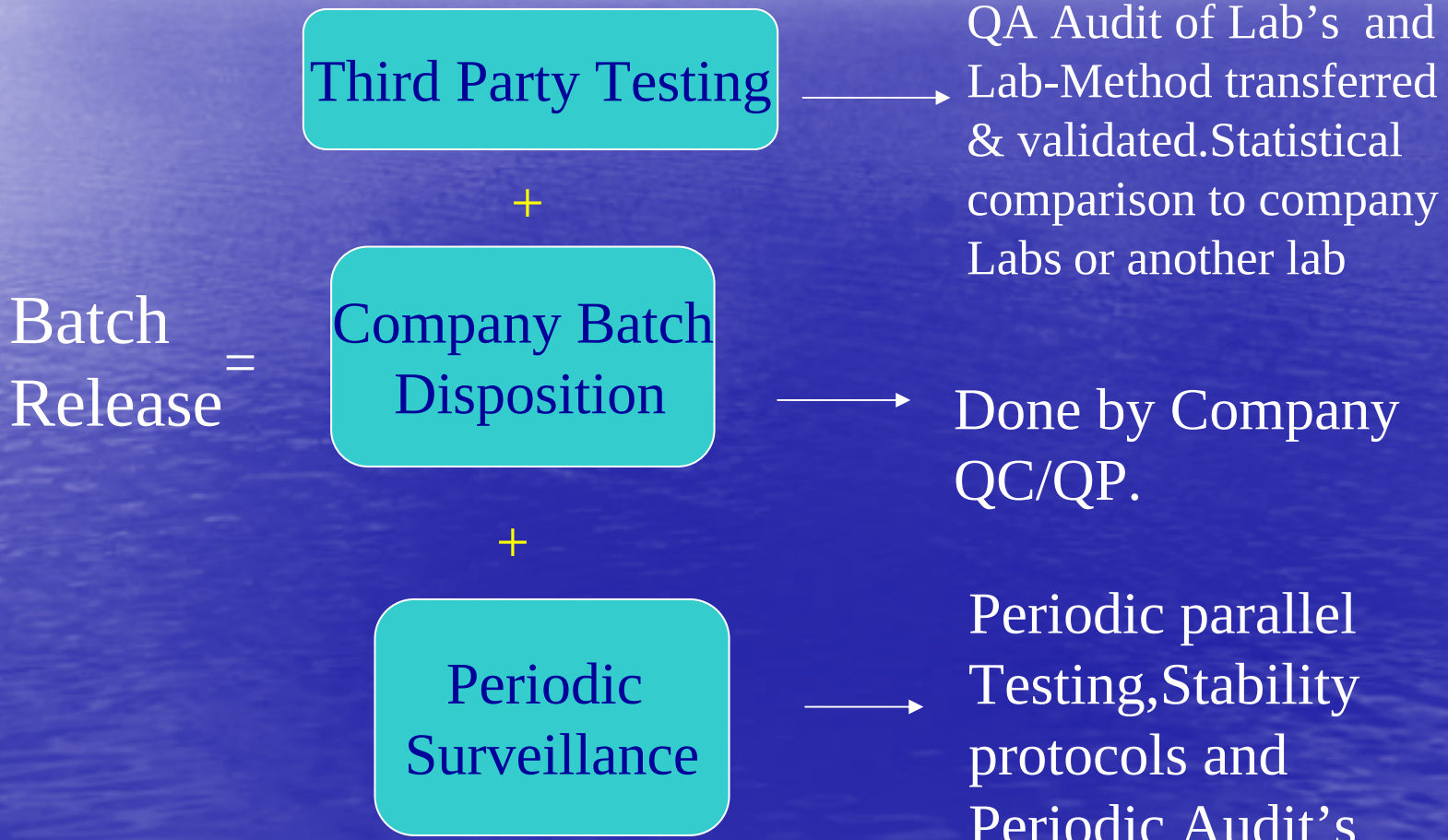
- The requirement in the EU is that medicinal products are released to the market place by a Qualified Person. Part of this role is to ensure that the Product and Manufacturers licence requirements for the medicinal product have been met for each batch of material manufactured.

Complaints/Defects

- The contract giver is still responsible for all product sold to the market place and any complaints or faults associated with such product.

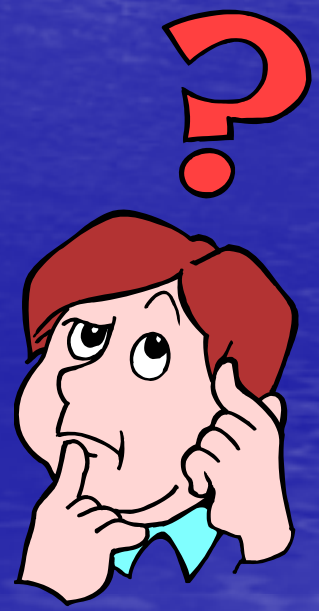


Release from Contractor's



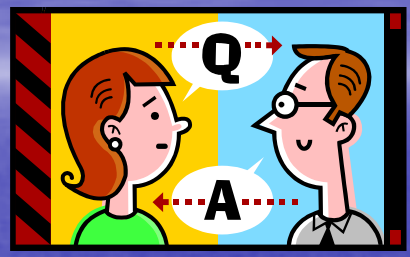
Multiple Products from one Supplier

- What if one supplier makes 5 different products for you and 3 are produced routinely with no issues and 2 seem to always have multiple deviations and re-tests.
- Can you certify the 3 “good “ products only ?



Multiple Products from one Supplier

- The answer is :-



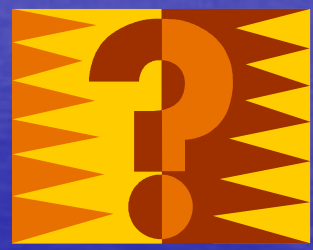
Yes, if the issues are product specific for the 2 problematic products

BUT

No if the issues are Quality Systems problems.

Availability of material.

- Is material availability a GMP Issue ?
- The answer is .....Maybe



- If supply of a critical component for a life-saving product is not available the consequences could be dire. In this scenario I would say availability is a GMP issue which , if there is a supply problem, may require notification to the relevant regulatory authorities.

Trademarked- Products

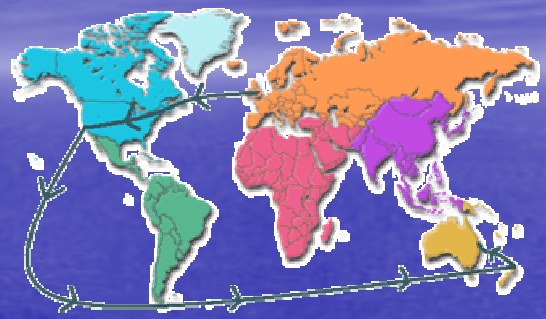
- Any Product Marketed MUST comply with all the Quality Systems. This applies to:-
  - Supply Agreements
  - Manufacturing Agreements
  - Distribution Agreements
  - Co-Marketing and Co-Promotional Agreements
  - “Piggy-Back” submissions.

QP and BATCH DISPOSITION.
Check-List Summary-1

1. GMP activities carried out in other area's have been completed. (e.g. Work tickets,analytical data etc)
2. Batch produced by a validated approved process.
3. The batch is in regulatory compliance.
4. Analytical Testing is completed including review of any OOS or OOT results.

QP and BATCH DISPOSITION.

Check-List -2



5. All country specific registrations and specifications have been met.
6. CoAs are accurate.
7. Purchased and manufactured components have been approved.
8. Lot number, manufacturing/expiry and/or re-evaluation dates are correct.
9. Reference samples and stability samples (if required) have been submitted.

QP and BATCH DISPOSITION.

Check-List Summary-3

10. All batch related deviations have been approved.
11. All change controls have been approved.
12. Actual yield is within expected limits.
13. Other specific items complete (e.g. random pack checks, water reviews etc)
14. Annual Product Review up to date and approved. (See next slides) How does the QP know this ?

Product Quality Review.1

Chapter 1 Requirements

- (i) A review of starting materials and packaging materials used for the product, especially those from new sources.
- (ii) A review of critical in-process controls and finished product results.
- (iii) A review of all batches that failed to meet established specification(s) and their investigation.

Product Quality Review.2

- (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

- (v) A review of all changes carried out to the processes or analytical methods.

- (vi) A review of Marketing Authorisation variations submitted/granted/refused,
  - including those for third country (export only) dossiers.

Product Quality Review.3

- (vii) A review of the results of the stability monitoring programme and any adverse trends.
- (viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
- (ix) A review of adequacy of any other previous product process or equipment corrective actions.

Product Quality Review.4

- (x) For new marketing authorisations and variations to marketing authorisations, a review of post marketing commitments.
- (xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.
- (xii) A review of Technical Agreements to ensure that they are up to date.

Summary

- The accountability of the QP and the responsibility of certifying batches for release may not be delegated
- A QP may delegate tests and checks to appropriately trained and experienced staff
- It remains the QPs responsibility to ensure that these tests and checks have been carried out in accordance with the requirements

Question Time >???