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Product Quality Review: Overview and Feedback from Inspection

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Scope of Presentation

- Overview of the PQR and requirements
- The importance of the PQR
- Feedback from the IMB Inspection Programme 2006-2008
 - Overview of common deficiencies
 - Examples of Practice



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Overview of the PQR & Requirements

Finished Product

- EU GMP requirement implemented from Jan 06.
- Requirement of Part 1 of EU GMP Chapter 1: Quality Management
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2005_10_gmp_part1_chap1.pdf.
- PQR is required to be completed annually and incorporates a review of multiple aspects impacting on the quality of the finished product.



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Overview of the PQR & Requirements

API Manufacture

- EU Guide to GMP Part II Covering Basic Requirements for Active Substances used as starting materials: Section 2.5 includes the conduct of AQRs for APIs.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2005_10_gmp_part1_chap1.pdf.



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Overview of the PQR & Requirements

PQR is a regular rolling annual review of all products including the following components:-

- Starting materials & packaging materials.
- Critical in-process controls & results.
- Batches failing to meet specification & investigation of these.
- Significant deviations/non-conformances & associated investigation including evaluation of the effectiveness of CAPAs implemented.

Overview of the PQR & Requirements

PQR components continued:-

- Changes to processes or analytical methods.
- Variations to MAs submitted/granted/refused including those relevant to 3rd country markets.
- Results of the on-going stability programme including adverse trends.
- Quality related returns, complaints and recalls including associated investigations.



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Overview of the PQR & Requirements

PQR components continued:-

- Adequacy of implemented CAPAs relating to product process or equipment.
- Post marketing commitments relating to new MAs and MA variations.
- Qualification status of relevant equipment & utilities.
- Technical Agreements to ensure that these are up to date and reflective of current activities.



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Overview of the PQR & Requirements

Similar requirements for APRs for API focussing on:-

- Critical in-process control and test results.
- Batches failing to meet specification.
- Critical deviations/non-conformances & associated investigations.
- Changes to processes or analytical methods.
- On-going stability programme.
- Quality related returns, recall, complaints.
- Adequacy of CAPAs implemented.



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Overview of the PQR & Requirements

Other Important Requirements

- Joint Responsibility for evaluation of the PQR by the Manufacturer and the Marketing Authorisation Holder (MAH).
- Technical agreement between the Manufacturer and MAH.
- Qualified Person responsible for batch release should ensure the accuracy of the review and for its timely performance.



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Overview of the PQR & Requirements

PQRs

- Should not be a meaningless listing of data.
- Should review of all required components including: appropriate summary; evaluation and interpretation of the information available on the manufacturing process.
- Should have the capability of detecting long term trends.
- Should not be considered in isolation and should be linked to the findings of previous reviews.



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The Importance of the PQR

- Controlling and improving processes and quality.
- Highlighting areas for focusing resource thereby:-
 - Decreasing risk of out-of specification results.
 - Decreasing downtime and increasing productivity.
 - Decreasing the risk of product recall.
 - Enhancing regulatory compliance.
 - Improving communication across all areas including production, engineering, quality and regulatory functions.
- Enhancement of visibility where aspects of the manufacturing operation are contracted out (production, distribution, testing etc).
- Improvement of product quality thereby contributing to the protection of public and animal health.



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Feedback from Inspection

- IMB commenced review of PQRs during finished product manufacture inspections in 2006.
- From 2006-2008

No specific critical deficiencies have been issued relating to PQRs.

Major Deficiencies have been issued.

Majority of deficiencies classified as “Others”.



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Feedback from Inspection

Major Deficiencies

Relate to the absence of an adequate system for performing PQRs and/or significant non-compliance with requirements:-

- PQRs have not been prepared.
- PQRs not completed for all products.
- No interpretation, evaluation or trending of data.
- Inappropriate grouping of reviews.
- MAH responsibilities not adhered to.
- In-appropriate devolution of PQR responsibilities to 3rd country manufacturers.
- Contracted manufacturing operations not (adequately) involved.



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Feedback from Inspection

Other Deficiencies

Relate to less significant non-adherence with EU GMP requirements which include administrative & technical issues.

Administrative

- No SOPs describing the process for preparing PQRs or process not adequately described.
- Timelines for completion of the review not met.
- Review and approval of PQR not documented.



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Feedback from Inspection

Other Deficiencies continued

Technical

- PQRs not including all of EU GMP requirements.
- Individual aspects of the review not adequately evaluated, reviewed and/or trended.
- PQR incomplete with respect to detail available from other GMP systems e.g. complaints, deviations etc.
- MAH review & approval of PQRs not apparent.
- Technical Agreements not describing responsibilities relating to completion of PQRs.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
Critical In Process Controls & Results	<ul style="list-style-type: none">• Statement that process validated & considered to remain in control	<ul style="list-style-type: none">• Full discussion of in-process results over the review period.• Evaluation of process in consistently achieving required results.• Statistical evaluation of this consistency.• Trending in comparison to previous reviews.• Conclusions relating to re-validation requirements.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
Batches Failing to Meet Specification	<ul style="list-style-type: none">•List of batches failing to meet specification	<ul style="list-style-type: none">•Full review of batches not meeting specification in review period.•Evaluation of underlying causes.•Statistical evaluation of significance.•Comparison with previous reviews.•Conclusions/ CAPAs.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
Critical non-conformance/ deviations	<ul style="list-style-type: none">•List of deviations	<ul style="list-style-type: none">•Listing of deviations considered to be significant over review period.•Overview of assigned cause.•Information on trending and CAPAs.•Assessment of effectiveness of CAPAs.•Comparison of deviation with previous reviews.•Discussion of trends.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
Changes to Processes & Analytical Methods	<ul style="list-style-type: none">• List of changes	<ul style="list-style-type: none">• Overview of all changes to processes & analytical methods.• Details of associated change controls.• Details of the assessment of any regulatory impact.• Details of the status of the implementation of change.• Discussion of benefits & improvements.• Recommendations.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
On-going stability programme	<ul style="list-style-type: none">• General Statement about the compliance of the on-going stability programme	<ul style="list-style-type: none">• Overview of the stability data collected over the review period.• Discussion of deviations in collated data, including OOS & resultant actions.• Evaluation of stability trends or shifts, taking into account evaluation from previous reviews.• Conclusions including assessment of the impact of stability trends.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
Quality Related Returns, Recall, Complaints	<ul style="list-style-type: none"> •List of returned batches •List of Recall batches. •List of complaint numbers 	<ul style="list-style-type: none"> •Overview of product returned due to quality concerns: Discussion of underlying causes, implications & CAPAs •Overview of product recalls: Discussion of underlying causes, implications & CAPAs •Overview of quality related complaints; Full discussion of trends, problem batches & CAPAs; Trending with previous reviews.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
Assessment of CAPAs	<ul style="list-style-type: none">• Process validated & considered to remain in control	<ul style="list-style-type: none">• Focus on CAPAs relating to process & equipment.• Focus is on previous review periods but may cover the current review period.• Focus on evaluation of the impact of CAPAs and benefits in improving product quality.• Recommendations for further CAPAs.• May be considered within individual sections of the review.

Feedback from Inspection

Requirement	Practice Examples	
	Minimal	More Comprehensive
Inclusion of a summary	<ul style="list-style-type: none">• No summary of review findings	<ul style="list-style-type: none">• Include an over-riding summary• Overview key observations made.• Highlight unexpected results.• Highlight recommendations arising from the review.• Conclusions with respect to evaluation of the review.

Conclusions

In summary the PQR should include sufficient discussion and evaluation to allow realisation of the objectives of the review which are

- Verification of the consistency of the process.
- Verification of the appropriateness of the specifications for starting materials & finished product.
- Highlight trends.
- Identify Improvements.
- Contribute further to protection of public & animal health.



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