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Challenges of manufacturing site in batch certification and release in European Union

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Abstract

A comprehensively designed Pharmaceutical Quality System (PQS) incorporating Good Manufacturing Practice and Quality Risk Management implemented, maintained and continuously improved, allows a consistent delivery of products with appropriate quality attributes. The manufacturer in the third country and the batch certification and release site in EU belong to the same organization operating under a corporate Pharmaceutical Quality System. A signed Quality Agreement between both parties provides improvement of the Pharmaceutical Quality System and continual maintenance of the quality of the medicinal product throughout its shelf life. This paper outlines the role and the challenges of the manufacturing site in third country within the process of batch certification and release in EU (by EU QP) and also highlights the importance of the technically justified approach including Quality Risk Management process regarding sampling in third country. Through a Technical justification for sampling including Quality Risk Assessment, it is considered that the samples taken from the manufacturing site in third country ensure representation of the whole batch. Technical justification is performed periodically to identify and manage any risks associated with this approach, thus ensuring the quality, safety and efficacy according Marketing Authorization.

Keywords: batch release in EU, third country, Pharmaceutical Quality System, QP

Background

Pharmaceutical Quality System

Pharmaceutical Quality System, *PQS* incorporating Good Manufacturing Practice, *GMP* (Eudralex, Vol.4, Chapter 1) and Quality Risk Management, *QRM* (ICH Q9) is the basic concept for implementing consistent quality of pharmaceutical products. The goal of the quality system is to assure that manufacturing site continuously provides products with the highest standards for quality, safety and efficacy, fit for their intended use and fulfill the requirements of the patients, all relevant regulatory requirements and the requirements of the international standards (Directive 2001/83/EC; Directive 2003/94/EC). It is in fact complex system, represented as the sum of all processes that are responsible for assuring quality of product.

Monitoring of Pharmaceutical Quality System has the main role in assuring the quality of the product. Regular Reviews are the basis of maintaining the PQS. They can

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be *Internal Reviews* (through the process of Management review and Self-inspection/internal audits) - in order to determine the effectiveness and compliance of the PQS with regulatory and internally set requirements and procedures, and *External Reviews* (regular GMP inspection by National Competent Authority, other regulatory agencies, partners, International certification body for compliance with ISO/other international standards).

Pharmaceutical Quality System should be fully documented and its effectiveness monitored. It might be *product oriented* (supply, manufacturing, testing, certifying, batch release) and *process oriented* (deviations, change control, Corrective actions/preventive actions, out of specifications results, out of trend results).

One of the most important documents, as part of PQS, that is product oriented and provides complete image of the quality of specified products is Product Quality Review, *PQR*.

Product Quality Review

Regular Product Quality Reviews of all authorized medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished products, to highlight trends and to identify product and process improvements. Such reviews should be conducted and documented annually.

The results of this review should be evaluated to determine whether actions are required, including corrective or preventive actions, validation or re-validation, as well as other site or process changes.

The aim of PQR is to maintain quality of product through process improvements. This should also facilitate the batch certification and release process.

Batch certification and release in EU

For medicinal products manufactured outside the EU, physical importation and certification are the final stages of manufacturing which precede the transfer to saleable stock of the batch. The main role of the manufacturing site in third country is to ensure all necessary data relevant for EU-batch release. Each batch of finished product must be certified by a QP in EU before being released for sale on the EU market or for export (Eudralex, Vol. 4, Annex 16).

Also, when it comes to production in third countries, the correlation between batch certification and release site / European QP and manufacturing site / QP is very important for batch release in EU. This is defined in Technical Agreement as per GMP (Eudralex, Vol. 4, Chapter 7).

The QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the Marketing Authorization (MA) and with GMP (Eudralex, Vol. 4, Annex 16).

Additional checks relevant for certification and batch release for EU QP are:

- Reviewing the transport conditions for the samples and the whole batch;
- Reviewing the results of quality control testing laboratory in EU, verified by analytical method transfer with manufacturer;
- Reviewing the certificate of a batch from a manufacturing site that is issued with a statement of GMP compliance, if applicable according to Quality Agreement.

The responsibilities of both sides are presented in Table 1.

Testing of the samples is performed in a quality control testing laboratory (within EU) which has valid authorization in accordance with local laws and EU legal requirements. Quality Agreement with defined responsibilities must be in place between manufacturing site, batch certification and release site and EU quality control testing laboratory.

Number of samples to be tested should be enough to carry out one complete analyses of the medicinal product. Number of reference samples should be enough to carry out at least two complete analyses according to the specifications on the Marketing Authorization (Eudralex, Vol. 4, Annex 19).

Batch certification and release site keeps these reference samples into warehouse facilities. The retention sample is kept on the location of designated European QP. Manufacturing site keeps reference and retention samples at its manufacturing location.

Sampling of imported product should be fully representative of the batch. Samples may either be taken after arrival in the EU, or be taken at the manufacturing site in the third country in accordance with a technically justified approach that is documented within the company's quality system. This technical justification should include formal QRM process in order to identify and manage any risks associated with this approach (Eudralex, Vol. 4, Annex 16).

The aim of this paper is to outline the role and the challenges of the manufacturing site in third country within the process of batch certification and release in EU. Furthermore, this paper highlights the importance of the technically justified approach including Quality Risk Management process regarding sampling in third country.

Overview of a technical justification for sampling including quality risk management

The Technical justification for sampling should be prepared to conclude that procedure of sampling at the manufacturing site in the third country is acceptable. Thus, it encompasses all possible risks, their mitigation, and acceptance criteria for continually ensuring the quality of the product during shelf life.

Table 1. Roles and responsibilities of the third country manufacturer and EU certification and batch release site related to certification and batch release in EU

Responsibilities of third country manufacturer	*Responsibilities of EU certification and batch release site*
1. Activitites associated with manufacture and testing of the product before import to EU	
Whole process	NA
1.1. API (active pharmaceutical ingredient), excipient, starting materials and packaging materials requirements	
Whole process	Assuring GMP manufacturing for API and distribution in accordance with Good distribution practice for Active substances
1.2. Packaging	
Whole process except responsibilities of other party mentioned	- design of printed packaging material specifications - final approval of artwork for labelling instructions and product specification
1.3. Finished product	
Whole process except responsibility of other party mentioned	Whole process plus Certification and release of finished product by EU QP
1.4. Stability testing	
Whole process	NA
1.5. Product Quality Review and Product update	
Whole process except responsibility of other party mentioned	- Review of Product Quality Review
2. Storage	
Whole process, except storage of the finished products within EU	- compliance with given storage instructions - storage of finished products within EU
3. Changes and Change controls	
Whole process except submitting change notification/applications to authorities	Whole process except - Evaluation of impact of changes related to manufacturing or testing of the product - Implementation of changes related to product specification or manufacturing process including packaging and sourcing of any active substances and excipients upon approval by Regulatory Authorities

4. Complaints and Product recalls	
4.1. Complaints Whole process except responsibilities of other party mentioned	- collection of complaints - responding to complaints
4.2. Product Recalls Responsible for investigating Product recall	Whole process
5. Deviations	
Whole process	Whole process except providing Report regarding deviations during manufacture, testing, packaging, storage conditions or stability
6. Documentation and records used in a manufacture, testing and packaging	
Whole process	NA
7. Regulatory responsibilities	
Whole process except liaison with regulatory Authorities for approval, maintenance and updating of Product Marketing authorization	Whole process
8. EU-batch certification	
Assuring that review of all batch records and analytical results for compliance shall be done by appropriate personnel	Whole process, except responsibilities of other party mentioned

Note: The Table represents critical activities related to batch certification and release and it is not comprehensive overview of the responsibilities as required by Technical Agreement

SWOT analysis

As part of this approach, SWOT analysis for sampling in third country should be made. Basic principles of this analysis regarding sampling in third country are presented below:

- *Strength* - The samples should be taken during production processes and represent the whole batch. Sampling should be performed by trained personnel, dedicated for this activity, belonging to QC department.
- *Weakness* - No weakness should be detected as for each product the number of samples are predefined for in- house samples, in- house-retained samples and samples for EU.
- *Opportunity* - Samples should be tested prior batch delivery in order to obtain results from quality control testing laboratory in EU in the time when batch is ready for Certification after importation.
- *Threat* - Possible damage during the transport of either samples or batch which is easy to detect.

Risk assessment

Risk assessment should be performed due to the need to prove that the samples taken at the manufacturing site in the third country are acceptable.

Risk assessment steps are defined below:

1. Risk identification - Samples taken in third country are not representative for the whole imported batch.
2. Risk Analysis

2.1. Review of an audit on site - during audit of the manufacturer by EU QP, it should be concluded that sampling procedures are in place; samples are taken during production processes and represent the whole batch; sampling method is clearly defined and assures that samples are fully representative of the whole batch; the amount of samples are predefined for each different product; samples size provides the performance of the full analysis that is required by the approved Marketing Authorization; sampling is performed by continuously trained staff, dedicated for this activity and belonging to QC department; adequate records for all sampling activities are in place.

2.2. Review of transport of samples - the samples should be shipped according to predefined standard schedule and standard route, for not more than 72 hours. They can be shipped either by plane (if there is urgent need of the batch to the market) or by qualified vehicles. Samples shipped by plane should be shipped in specially designed temperature control packaging systems that are maintaining the temperature between 15-25ºC for up to 72 hours. Samples shipped by vehicle, should be shipped under the same controlled temperature conditions in the vehicle.

2.3. Review of arrival of samples - each arrived sample should be inspected to ensure that it remained undamaged. Temperature from data logger (electronic device that records temperature over time) should be checked and approved. In case of temperature deviation or significant delay of shipment or any other potential reason which may impact the quality of the samples should be treated as deviation.

2.4. Consideration of time interval between sampling and importation of batch in EU - The time interval between EU analyses and importation should be relatively short, less than a month. The transport conditions of samples and batches should be considered as equivalent; the temperatures during transport should be in accordance with Marketing Authorization. Duration of transportation of samples and batches should be comparable.

2.5. Review of transport of batch - All vehicles for transport of batches should be suitable for their use and appropriately equipped to prevent exposure of the product to conditions that could affect their quality or packaging integrity. Each vehicle should have temperature monitoring and the temperature records should be checked, approved and archived.

2.6. Review of responsibilities according to Quality Agreements - Quality Agreements (QA) between manufacturer in third country and batch certification and release site in EU should be in place; QA with delivery services for samples and for transportation services for batches should also be in place; QA with warehouse by local wholesaler for storage of batches of finished product as well as QA with quality control testing laboratory in EU should also be in place.

2.7. Review comparative analysis of samples taken in the third country and samples taken after importation - Plan for random periodic comparative analysis of samples taken after importation to justify on going reliance on samples taken in a third country should be in place.

Before the comparative analysis is done, the preconditions have to be completed:

- Analytical Method Transfer (AMT) should be successfully done. Manufacturing site and Batch certification and release site shall be responsible for transfer of testing method, using transfer protocols prepared by manufacturing site, approved by both parties. The results from both sides are given in Analytical Method Transfer Report and must be reviewed and approved prior to the commencement of routine testing (Eudralex, Vol. 4, Chapter 6).
- Both analyses should be performed according to the same and approved Analytical method defined in Marketing Authorization
- The Protocol for comparative analysis should be prepared, checked and approved before the analysis. The purpose of the Protocol for comparative analysis of samples is to define, describe and approve actions to provide high degree of confidence that samples taken by manufacturer in third country and samples taken after importation in EU are both providing comparable results by using approved and already successfully transferred analytical method as defined in Marketing Authorization. The protocol must define number of samples to be tested, results to be reported, acceptance criteria and other details as required. The approved protocol and acceptance criteria for comparative analysis should be provided to the laboratory before the analysis.
- The results of comparative analysis should be given in parallel Analysis Report. Report for parallel analysis of samples is in fact comparison of the results between samples taken in the third country and samples taken after importation in EU. It is issued by quality control testing laboratory in EU. The report should be reviewed, checked and approved. Both documents should be approved by the EU QP.

3. Risk evaluation

Process of sampling and distribution of samples from the third country should be well established, managed and monitored. Conclusions stated in parallel Analysis Report should prove that the analytical results are highly comparable.

If any unexpected result or conformed out of specification result is reported, the investigation should be done to identify the root cause. The Competent authorities should be informed.

4. Risk acceptance and proposed further actions

The risk should be accepted if the following conditions are met:

- No risk for the product quality nor for the patient is found nor expected.
- Regular audit at the manufacturing site, reviews and updates of all relevant Quality Agreements should be provided.
- Continual monitoring of the process by batch certification and release site should be performed.
- Imported product will be comparatively tested according to the risk-based approach to justify ongoing reliance on samples taken in third country
- Plan for random periodic analysis of samples

taken after importation to justify on going reliance on samples taken in a third country should be in place.

Conclusion

A signed Quality Agreement between manufacturing site, batch certification and release site and EU quality control testing laboratory provides improvement of the Pharmaceutical Quality System and continual maintenance of the quality of the medicinal product throughout its shelf life.

The main role of the manufacturing site in third country is to ensure all necessary data relevant for EU-batch release. Moreover, it should be highlighted that huge impact in the process of certification and batch release in EU has the Technical justification regarding sampling, which encompasses all possible risks, their mitigation, and acceptance criteria for continually ensuring the quality of the product during shelf-life. This approach including Quality Risk Assessment should be conducted on random basis in order to prove that samples taken in third country are representative of the whole imported batch. Comparative analysis of samples taken after importation is performed periodically to justify on going reliance on samples taken in third country.

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Резиме

Предизвици на производител од трета земја во сертификација и пуштање на серија на лек во промет во Европската Унија

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Клучни зборови: пуштање на серија на лек во промет во ЕУ, трета земја, Фармацевтски систем за квалитет, Одговорно лице

Сéопфатно дизајнираниот Фармацевтски систем за квалитет во кој е инкорпорирана Добрата производна пракса, како и имплементиран, одржуван и континуирано подобруван Системот за управување со ризик, овозможува постојана испорака на производи со соодветен квалитет. Производителот од трета земја и локацијата каде се врши сертификација и пуштање на серијата на лек во промет во Европска Унија, припаѓаат на иста организација под корпоративен Фармацевтски систем за квалитет. Помеѓу производителот од трета земја и локацијата каде што се врши сертификација и пуштање на серијата во промет во Европска Унија, мора да има потпишан т.н. Договор за квалитет, со кој се обезбедува подобрување на Фармацевтскиот систем за квалитет, како и одржување на квалитетот на лекот за време на рокот на употреба. Овој труд ја нагласува улогата и предизвиците на производителот од трета земја во рамките на процесот на сертификација и пуштање на серијата на лек во промет во ЕУ (за кој е задолжено Одговорното лице во ЕУ), како и важноста на т.н Технички оправдан пристап во однос на земањето мостри во трета земја, вклучувајќи го процесот за управување со ризик. Овој пристап обезбедува доказ дека мострите земени од производна локација надвор од ЕУ се репрезентативни на целата серија. Се изведува периодично за да се идентификуваат и контролираат ризиците што се јавуваат при узорцирањето на серијата во земјата на производителот. На овој начин се обезбедува квалитет, безбедност и ефикасност согласно одобрението за ставање на лекот во промет.