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**Reflection Paper:
Chemical, pharmaceutical and biological information to be included in dossiers when Process
Analytical Technology (PAT) is employed.**

[Please note that this is a working document and remains under development]

Introduction

The EMEA PAT team has published this reflection paper to provide preliminary recommendations on how PAT related information should be presented in applications or variations to Marketing Authorisations. Work on this topic is under continuing development and as a flexible regulatory approach is important to avoid unnecessary barriers to improved product quality, it is not appropriate to publish formal guidance at this time. Nevertheless, the paper is intended to assist companies already planning to file PAT-based submissions. Feedback from the industry on the contents of the paper is welcome and should be sent to David.Cockburn@emea.eu.int

When an application for, or variation to, a marketing authorisation is submitted supporting documentation should be provided in accordance with CTD requirements (Module 3). This document identifies specific information that should be provided where relevant when aspects of Process Analytical Technology are employed in the manufacture or control of the medicinal product or active substance.

In addition, the Expert Report provided in Module 2 (Quality Overall Summary) should include a PAT critique highlighting the positive and negative aspects of the technology.

Prior to submission, applicants intending to include PAT elements in an application or variation are recommended to engage in early discussion with the relevant regulatory authority.

Quality Risk Management

Quality Risk Management sections should be provided at the beginning of each part of the dossier where the principles of Quality Risk Management have been applied so that the relevant part of the dossier can be read together with the basis on which the conclusions were reached.

Where Quality Risk Management principles have been applied a summary should be provided of the methodology indicating how the conclusions were reached. Where relevant, a literature reference should be provided for the chosen Quality Risk Management tool.

A tabulated summary should be provided of the conclusions reached with headings such as parameter studied, consequence of failure, the level of risk and any mitigation measures. The data itself should be retained and made available for inspection.

An overview should be provided of the identified critical points and how these points have been dealt with or are controlled.

Public

Raw Data

Some raw data is necessary to support the conclusions reached but it is difficult to be precise about how much should be presented in the dossier. In principle sufficient and representative data should be provided to enable an independent assessment to be made of the conclusions reached by the applicant. All data generated by the company during development should be archived in such a way so as to be available during any inspection associated with the application or variation.

The validation and calibration data used to establish the model should be made available to the assessor on request

Recommendations for particular sections of the dossier:

3.2.P.2 and 3.2.S.2.6 Pharmaceutical development/Manufacturing Process Development

Introductions to these sections of the dossier should be provided that give an overview of the PAT approach and strategy.

3.2.P.2.2.1 Formulation development

The principles of Quality Risk Management, Design of Experiments and Design Space can be applied to both formulation development and manufacturing process development. A Design Space for composition of the drug product may also be acceptable provided the composition is as described in section 3.2.P.1 and in module 1 (e.g. factorisation of an ingredient and respective balancing in weight with an excipient, adjustment of excipient concentration based on performance properties etc.)

Design of Experiments

When applicable the design of experiments (DoE) should be described and the results shown graphically together with a narrative interpretation. The applicant should provide an adequate level of information for the assessor to understand which factors and responses were studied and why, as well the conclusions of each study. The following list of documents is indicative of the information that could be provided. A critically based approach to the list should take account of the relevance of the DoE study performed to the description of the design space, e.g. less information is needed for studies performed in early development compared to a study used for the development of a model to predict quality attributes of the finished product.

- Type of experimental design used e.g. full/ fractional factorial.
- Justification of the selection of factors and responses (including reasons for non-inclusion of factors). A fishbone diagram or similar where all factors and steps of the process are presented could be useful for this.
- Number and levels of factors under study (both in coded and uncoded values, preferably in a tabulated format as an appendix).
- The experimental matrix with the values of the responses for each combination of factors, as an appendix.
- Graphical representation e.g. coefficient plot of the relative significance of the factors under study as well as of the interactions between them.
- Statistical evaluation of the model derived from DoE (e.g. ANOVA table).
- Graphical representation of the relationship of the significant factors under study with the responses (e.g. response surface and contour plots) providing a clear overview of the conclusions.
- The Design Space (based on real test results and/or on the model) as defined in ICH Q8 should be described.
- Verification of the model derived from DoE.

Data acquisition and chemometrics approach to establish the Design Space

The methods and their validations should be described. The chemometric techniques should be discussed and described, preferably with a literature reference.

The following basic information relating to Multivariate Data Analysis/statistical methods should be presented including:

- pre-treatment of data (e.g. scaling, centring, transformation, derivation, smoothing, normalisation, baseline correction, multi-scatter correction)
- name of the computerised program used and justification for the use of different programs (if applicable)
- justification for omission of data, if applicable (e.g. strong outliers, dependent variables).
- validation and calibration data should be presented (e.g. score plot, loading plot, leverage plot, comparison of prediction and calibration data)

3.2.P.2.3 and 3.2.S.2.6 Manufacturing Process Development

The Design Space for each affected manufacturing step should be described. Any intended flexibility in the manufacturing process, e.g. the use of different sites, scales or equipment, should be covered by the Design Space description.

Process Capability

The results of any process capability analyses should be presented

3.2.P.3.3 and 3.2.S.2.2 Description of Manufacturing Process and Process controls

The applied design space in the manufacturing process, as justified by the experimental/development studies, should be clearly indicated.

Where relevant, methods and requirements for Real-Time-Release (RTR) should be described. These should be calibrated and validated to the same extent as methods and validations described in section 3.2.P.5 or 3.2.S.4 as appropriate. The RTR methods should also be described in section 3.2.P.5 or 3.2.S.4 as appropriate.

The relationship between PAT/RTR measurements and the conventional release specification should be described.

Apparatus, measuring devices, probes

Brief details should be provided on in-line, on-line and at-line equipment used to monitor and/or control the process and/or product quality attributes and to demonstrate operation within the Design Space. The suitability of these tools, and where relevant, their positioning, should be commented upon.

Handling of outlying results

It is to be expected that enhanced process monitoring will detect an increased level of process outliers. A description of, and justification for, the handling of such process outliers should be included.

3.2.P. 3.4 and 3.2.S.2.4 Control of Critical Steps and Intermediates

The frequency of testing and calibration of the analytical methods applied (on-line, in-line or at-line) should be stated. The approach to validation of these methods should be described and justified. Reference can be made to the conclusions described in section 3.2.P.2.3 (Manufacturing Process Development).

3.2.S.2.3 Control of Materials and 3.2.P.4 Control of Excipients

In addition to the established requirements, e.g. the European Pharmacopoeia, all chemical and physical characteristics shown to have an influence on the manufacturing process or the analytical methods (e.g. particle size distribution, modifications etc.) should be specified.

3.2.P.5 and 3.2.S.4 Control of drug product/drug substance

In the case of RTR, the list of drug product specifications and test methods should also include a reference to the RTR methods, where applicable. For information on these methods cross-reference should be made to the Pharmaceutical Development part (section 3.2.P.2) (or section 3.2.S.2.6 where applicable).

References

Notice to Applicants, Volume 2B, incorporating the Common Technical Document (CTD) (Eudralex Volume 2)

ICH Q8- Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068/2004)

ICH Q9- Quality Risk Management

Note for Guidance on Parametric Release (CPMP/QWP/3015/99)

EC GMP Guide Annex 17 Parametric Release (Eudralex Volume 4).