1. Introduction

Active Pharmaceuticals Ingredients (API's) must always comply with authorized specifications requirements for release and retest dates. Assurance with which these products can be accepted for release depends on many aspects of the manufacturing process and supply chain, and the sampling and testing may be reduced without compromising the quality of the API.
It is recognized that a manufacturer may obtain sufficient assurance that a product meets all stipulated quality specifications through "A system of release that gives the assurance that a product is of the intended quality based on the review of information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release." (ref. 3)

A comprehensive set of process measurements and controls will provide greater quality consistency of the product meeting the specifications than traditional QC testing. A toolbox would be or could be utilised containing more tools than before (on-line, in-line, at-line and off-line measurements).

Parametric release is such a system, which is based on evidence of successful process validation of the API manufacturing process in qualified and correctly maintained production equipment and facilities, and review of the documentation on process monitoring and in-process data performed to provide the desired assurance of the specified quality of the product. Parametric release is therefore an operational alternative to routine release testing of samples taken from every finished batch to be tested according to release specifications.
Implementation is in line with the text in the Ph. Eur.(ref.1).

2. Scope

This document is intended to give guidance for applications that propose parametric release for Active Pharmaceutical Ingredients and isolated intermediates that are intended for commercial use.
The guideline highlights the different requirements that have to be fulfilled in the application.

The principle of parametric release may be applied during the manufacture of different products resulting in the elimination of specific or ultimately all tests of the Active Pharmaceutical Ingredients or isolated intermediates.

Parametric release is not applicable for time zero testing of samples for stability testing.

3. Parametric Release

3.1. Parametric release of Active Pharmaceutical Ingredients and isolated intermediates

Parametric release is referred to in the General Notices of the Eur. Pharm. , where it states: "The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived for example, from validation studies of the manufacturing process and from in-process controls. Parametric release deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia." (1) and in the USP as "Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. " (2)

Parametric release can be applied to both Active Pharmaceutical Ingredients and isolated intermediates.
Approval for parametric release eliminates the requirement for some or all final testing as a condition for batch release. The release of each batch is dependent on the successful demonstration that predetermined validated conditions have been achieved.

3.2. Process monitoring

Process monitoring is routinely applied to all production processes for API's and intermediates.
Critical process parameters (parameters that have an impact on the quality attributes of the product) are usually defined during process development and are confirmed during validation.
During the continued manufacturing, data are collected and analysed to verify that the process remains in control and guarantees the product to meet predetermined specifications. Useful tools for analysing data are the use of statistical process control (SPC) and process capability indices (e.g Cpk's).
It is good practice to calculate and report Cpk-values in Annual Product Reviews (when applicable).

Process monitoring can either be by direct measurements (e.g. temperature, pressure, time etc.) and/or through in-process controls by analytical means (e.g. pH, density, viscosity), spectroscopic techniques (e.g. NIR, FTIR, Raman, MS) and chromatographic techniques (such as GC and HPLC). Techniques can be combined. All can be either on- or off-line.

Spectroscopic techniques can be used directly or in combination with multivariate analysis. Spectral data monitored on-line may be useful in controlling e.g. water content, blending homogeneity, powder properties as particle size and in well defined, isolated cases, product purity and could thereby replace traditional end-product testing.

When parametric release, including acceptance criteria, is applied, it should be mentioned in the registration dossier. A scientifically sound justification establishing a clear relation between end-product quality attributes and process monitoring data, should be provided.

4. Regulatory aspects

Prior Regulatory Approval is required before parametric release can be used to substitute for end-product testing, and this requires submission to relevant competent authorities.

The information may be submitted as part of the dosage form sponsor's documentation, as part of a DMF or an application for a Certificate of Suitability. For a DMF or a Certificate of Suitability it may be necessary for the manufacturer to wait for approvals to be received from all current sponsors before implementation.

In general the documentation submitted for a new market authorisation or a variation should contain only the elements of the quality assurance that are specific for the API or intermediate. The quality assurance of elements not specific to the product falls within the field of GMP.

Before considering parametric release the manufacturer should contact the sponsor, if applicable, about the concept and approach of parametric release and give an outline how this would be achieved (appropriate validation, running in parallel etc)

5. Manufacturing Processes

5.1. General

An API or intermediate can be produced by a batch process a continuous process or a combination of both.
In batch processes the sampling usually will be discrete thus allowing sampling at critical parts of distinct stages of the process, whereas in a continuous process a more integrated process monitoring will be applied, usually sampling at critical parts will occur at predetermined time intervals.
It is therefore not possible to specify in a guideline, specific details of how parametric release can be applied.

The application that proposes parametric release should be based on sufficient experience with the process, full adherence to current GMP-requirements. The documentation should include the following evidence:

- that all critical process parameters have been established and operational ranges defined
- that all critical steps of the manufacturing process are validated
- that the process is reliably controlled
- that the relationship between a critical process parameter and a specific quality attribute is well established, e.g. an excessive drying temperature or residence time at elevated temperature may have a detrimental effect on the impurity profile (degradation products)
- the relationship between end-product testing and process monitoring, including justification of acceptance criteria is understood
- that in process requirements chosen for approval/rejection are decided on the basis of acceptance criteria generally defined through process development research and verified during validation
- that clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection
- that historical process data is regularly reviewed (e.g. Annual Product Reviews)
- that a structured technique, e.g. failure mode effect analysis has been applied to both the manufacturing process and the controls

5.2. In-process controls/Data collection/Tool box

5.2.1 In-process controls

During the development the in-process tests of the process for the API, synthetic routes, conditions etc are established in a way that a robust process is obtained and in-process testing will enable parametric release.
There are two types of in-process tests:

- process related, e.g. temperature, pH, pressure, time etc.
- product related, e.g. purity, morphology, solvent residue

For parametric release both types can be applied, depending on the nature of the process.

5.2.2 Data Collection

By collecting data during routine production, especially of the critical parameters from the reactions and unit operations, the product attributes may be discovered much earlier than when relying on end product testing only.
Typical data which may be of interest are:

Reactions:	amounts of chemicals charged, their impurity profile, concentration, pH, temperature, pressure, stirring rate, conversion, contamination control and/or time. For heterogeneous systems, the morphology of the solid form may also be of importance
Extractions	amounts of chemicals, including solvents charged, concentration, pH, temperature, time, stirring rate
Distillation	temperature, pressure, stirring rate, initial and final concentrations, reflux ratio, refractive index of fractions
Crystallisation	seeding (amount and timing), super saturation generation rate (i.e. cooling rate/profile and or charging rate and/or evaporation rate), temperature, concentration, solvent composition, stirring rate
Centrifugation/Filtration/	amount of washing liquid, pressure drop, temperature, applied pressure/vacuum, rotational speed in centrifugation
Drying	temperature, pressure, relative humidity, stirring, time

By being able to monitor and control these parameters within their pre-established limits, the product attributes like purity, assay, morphology etc. will be assured.

5.2.3 Tool Box

Apart from traditional in-process tests tools like thermometers, pH-meters etc. (process related) there now are newer tools that can be used for in-process testing (product related) like on-line measurements as UV/VIS, ATR (Attenuated Total Reflectance) probes or mid IR, Raman, and NIR

A typical Process for Manufacturing of the API consists of a reaction (or a couple) followed by a few unit operations for purification, such as extraction, distillation, crystallisation and isolation (filtration/centrifugation, drying and de-lumping). The number of stages needed to produce the API, will differ depending on the complexity of the process.

Use can be made of the data collected at various stages of the process (see above under “Data collection”)

5.3. Statistical approach/Interpretation of data/Trend analysis

5.3.1 Statistical process control

SPC is utilised to measure and monitor the changes of critical process parameters that could vary between batches. From a set of data the upper and lower limits within which the process normally works, can be determined. From these a control strategy and proper action and/or alarm limits can be derived. Using these tools it is possible to identify when a result is to be considered significantly different from the expected value. Actions can be taken before values deviate too much from the expected values.

Statistical techniques can be applied to both process and product parameters.

Other statistical techniques like CUSUM may have their value as well.

5.3.2. Multi Variate Analysis

With MVA one seeks the interrelationship between several process parameters. It is possible to deal with large amounts of results and parameters thus to achieve statistically how relevant these interrelationships are. MVA is utilised both in trouble shooting to investigate deviations and also proactively to increase process know how and therefore optimising and stabilising the process.

5.3.3 Process capability indices

The process capability index is calculated from the following equation:

$$Cpk = \frac{(\text{limit} - \text{mean value})}{3 \text{ sigma}}$$

The calculation of process capability indices (Cpk's) is a common practice in the chemical industry. These process capability indices allow to judge whether a process is under control and to calculate the probability of making batches that meet predefined specifications.
Low process capability indices are indicative that a process is not yet amenable to parametric release because of the intrinsic variability of the process.

5.3.4 Kinetic data

In some cases, companies have determined all thermodynamic data and kinetic data (enthalpy, entropy, order of reaction etc) for both the main reaction and the by-products. In this case, it is possible to accurately predict/ control the level of impurities in the reaction mass. Based on such profound knowledge a control strategy should be developed that will allow for parametric release of the product.

5.4 Release decision

The release decision should be based on the batch history and the applicable process control parameters. The level of confidence should be at least the same as under the conventional release process.

In case a control parameter is out of control, GMP-measures like deviation investigations should be performed and documented and the result taken into account at the release process.

For reprocessed materials, parametric release is applicable only if part of the validated and risk assessed scheme.

5.5 Quality Agreement

It will be necessary to have a Quality Agreement to define the responsibilities of the API-manufacturer and the customer when parametric release will be applied for the API. It is especially important in respect of the customer's need to demonstrate regulatory compliance.

5.6 Certificate of Analysis (Certificate of Quality/ Certificate of Specification Compliance(based on parametric release))

A conventional CoA is not appropriate for products where Parametric Release is applied.

The basic legal requirements should be included, such as:

- name of product
- batch number
- manufacturing date
- expiry*/retest* date
- specification limits for all parameters
- signature of an accountable person who is responsible for the release decision

It will also be necessary to include a statement such as:
"This batch of product has been manufactured according the requirements of the parametric release scheme"

5.7 Change Control

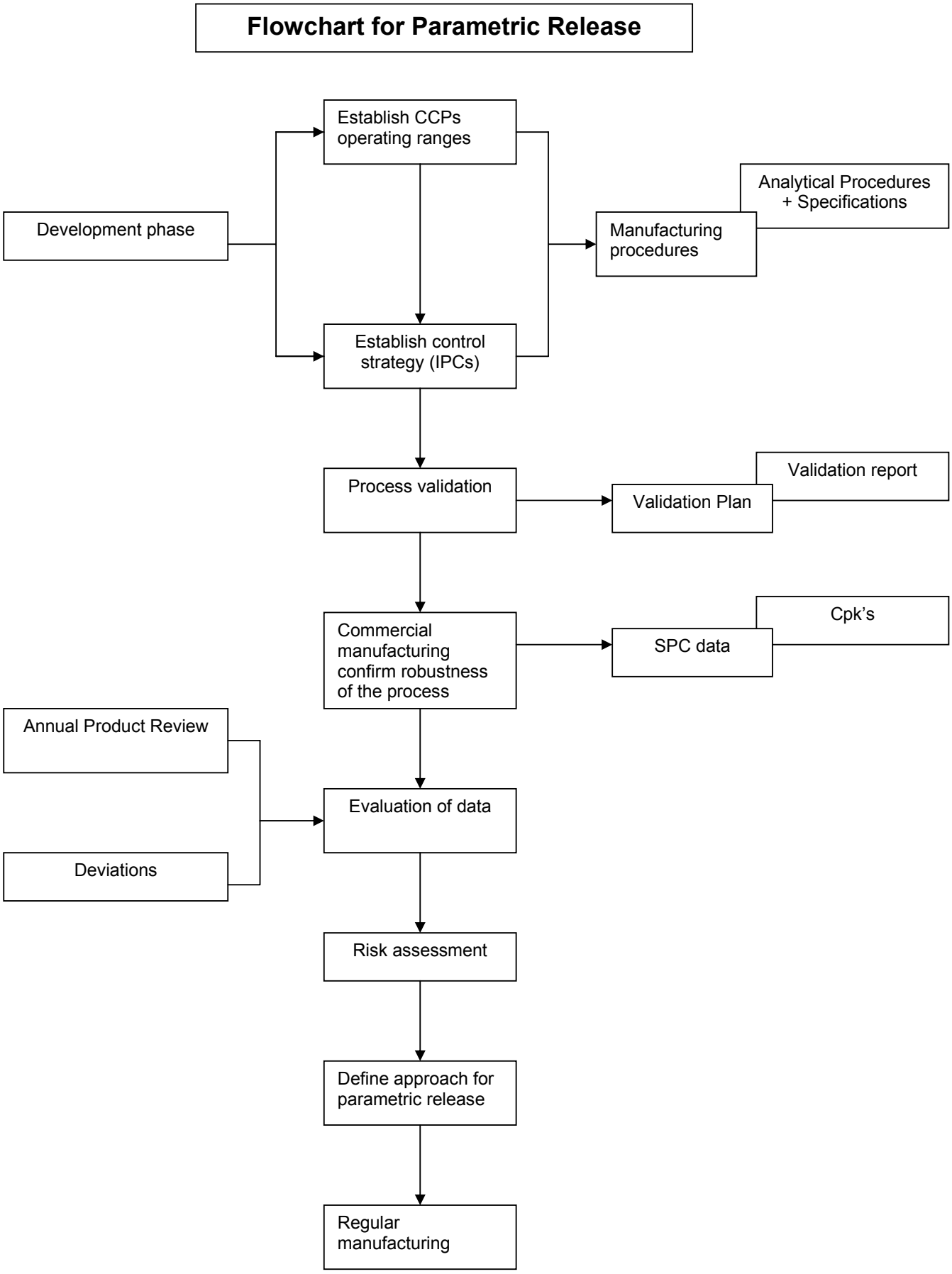
Any change that is proposed should be assessed for the potential impact on the justification of parametric release and the need for revalidation and risk assessment should be reconsidered (4).
Elements of change control include, but is not limited to:

- Changes in the process itself
- Changes in equipment
- Changes in measuring devices and analytical methods
- Changes in manufacturing sites
- Upgrading of software
- Changes in the maintenance and calibration schedules
- Notification of customer
- etc

6. References

1. Ph. Eur. 4th edition, 1.1 General Notices
2. USP25, General Notices
3. Annex 17 to the EU guide to Good Manufacturing Practice (ENTR/6270/00)
4. CEFIC/APIC guide on “How to do” ICH Q7a (September 2002); www.cefic.apic.org

ANNEX 1


Flowchart for Parametric Release
Establish CCPs operating ranges
Development phase
Analytical Procedures + Specifications
Manufacturing procedures
Establish control strategy (IPCs)
Process validation
Validation report
Validation Plan
Commercial manufacturing confirm robustness of the process
Cpk's
SPC data
Annual Product Review
Evaluation of data
Deviations
Risk assessment
Define approach for parametric release
Regular manufacturing