markets and whether CQV will be considered in conjunction. The scope should be defined before progressing through the key elements of the RTR testing strategy to ensure that the resulting RTR testing strategy fully addresses the desired RTR scope.

**Recommendations and Rationale**
This guidance sets out to recommend a number of practical steps that should be considered in the development of any RTR testing strategy.

**Step 1: Compile process understanding**
Process understanding is the foundation of any process control strategy to enable RTR. Process understanding should be based on sound science and quality risk management. CQAs should be defined and sources of variability (input material attributes and process parameters) that can impact product quality should be identified and appropriately understood.

Understanding of the functional relationship between CQAs, material attributes and process parameters may be based on experimental studies, knowledge of similar processes and/or historical manufacturing data. It is also important that the boundaries of the process are well understood.

**Step 2: Define process monitoring and control requirements**
A control strategy incorporating RTR testing should enable a move from an approach reliant exclusively on end product testing and offline assessment of product quality to an approach that facilitates release based on process controls and/or real time monitoring and control of attributes and parameters that are critical to quality.

*" ICH Q10 and Q8 (R1) Control Strategy: A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."*

*"ICH Q8(R1): Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimise the need for end product testing."*

The process control strategy, which is predicated on the functional relationships between input material attributes, process parameters and quality attributes, will demonstrate that the process produces product complying with predefined acceptance criteria.

Based on process understanding, the outlined process boundaries and the use of a quality risk management approach, it should be possible to develop an effective control strategy that supports the product specification. This control strategy should ensure that final product quality is acceptable by control of raw material attributes, CPPs and CQAs.

Rationale should be provided to support the proposed control strategy and any amendments to the analytical procedures and acceptance criteria in the specification. Process understanding can also be used to provide rationale for exclusion of parameters or tests previously applied. When real time / near real time monitoring is employed, careful consideration should be applied to the sampling location and frequency to ensure adequate control of the CQA's and CPP's. The sampling strategy will differ for different operations particularly with regards to continuous versus batch processes.

A typical RTR control strategy could include (but is not limited to) any of the following elements:

- Control of raw material attributes.

 

effective deviation investigation, change management and validation.
Assessment of current quality systems and documentation (Policies, Master Plans, SOPs) should be part of the scope of the implementation of new RTR approaches.

**Examples**

Two examples of RTR projects are presented in this section. One example is included for a continuous process and one example for a batch process. In each case the appropriate work was completed to develop process understanding based on risk assessment, define process boundaries and develop effective process control strategies. The tables below show the output of the RTR strategies by highlighting the difference in conventional vs RTR testing requirements.

**Table 2: Example of Continuous Process**

| | Conventional Testing | RTR | Rational |
|---|---|---|---|
| Blend Appearance | Visual | Visual | No change |
| Blend Potency & Content Uniformity | HPLC | On-line fast NIR measurement | Blend released based on CoA based on overall Potency and C.U. calculation for the entire continuous run |
| Moisture | KF | Remove or replace with in-process blend NIR measurement | Based on historical data analysis and lack of blend water uptake Moisture will remain part of stability testing |
| Impurities | HPLC | Remove, replace with the API impurity result | The formulation conditions do not create any further degradation path and risk |
| Capsules Potency & Content Uniformity | HPLC | Replace with Blend Potency & statistical weight control of capsules using NETT system | The API concentration above that needed to allow C.U. based on weight control. NETT system provides in-process weight measurement & control. The NIR system provides in-process measurement & control of blend C.U. |
| Dissolution | Dissolution Testing | Under evaluation | The dissolution has been found to be dependant on the continuous blending and compaction conditions |

*NOTE: Shelf life testing as per conventional specification*

 