therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8R1).

Critical Quality Attribute (CQA):
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8R1)

Continuous Quality Verification (CQV):
An approach to process validation where manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted as necessary. It is a science-based approach to verify that a process is capable and will consistently produce product meeting its pre-determined critical quality attributes. (ASTM E2537)

Design space:
The multidimensional combinations and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8 and ICH Q8R1) [NOTE: Q10 definition is limited to the first sentence above]

PAT
A system for designing, analyzing and controlling manufacturing through timely measurements(i.e during processing) of critical quality and performance attributes of raw materials and in-process materials and processes with the goal of ensuring final product quality (ICH Q8 R1/FDA definition)

Quality by Design (QBD):
A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Q8 R1).

General Guidance
Real Time Release encompasses more than just end product test replacement. It considers building a level of understanding of the manufacturing process that allows definition of the important parameters and attributes that need to be monitored and controlled to ensure quality. Real time release is a product of this requisite process understanding and an effective process control strategy.

The following graphic shows the key elements of any RTR 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.
- Control of process parameters.
- On line or at-line monitoring (close to the source of variability) to control key unit operations that have an impact on downstream processing or product quality.
- Process capability based test elimination
- Rapid on-line/ at-line testing of finished product
- Surrogate testing (e.g. replacement of dissolution with disintegration when correlation has been demonstrated)

	Process step 1	Process step 2	Process step 3	Process step 4	Change to conventional finished product test	Rationale	Example
Attribute 1					End product test 1 required	CQA tested off line as normal	
Attribute 2			On line monitoring and control of CQA		End product test 2 removed	Control implemented and end product test removed based on on line monitoring and control of CQA(s)	*NIR used on line to stop drying once product reaches specification*
Attribute 3		Critical Process parameter control		Critical Process parameter control	End product test 3 removed	Control implemented and end product test removed based on control of CPP(s)	*Particle size controlled by control of granulation parameters and milling parameters*
Attribute 4			On line monitoring of CQA	Critical Process parameter control	End product test 4 removed	Control implemented and end product test removed based on on line monitoring and control of CQA and control of CPP	*NIR used on line during blending to monitor blend uniformity; On line weight monitoring with feedback to press used to control weight variation*
Attribute 5	Raw material input control				End product test 5 removed	Control implemented and end product test removed based on control of raw material input	*Identification carried out on raw materials with effective material control allowing replacement of end product ID test*
Attribute 6					End product test 6 removed	End product test removed based on high PbCpk	*Impurities test in drug product (degradants) removed based on high process capability and process knowledge/control*
Attribute 7					End product test 7 substituted for test 8	Measurement of one attribute based on known correlation with another attribute allowing test elimination	*Use of disintegration in lieu of dissolution based on known correlation*
Attribute 8							
Attribute 9				End product test carried out in-line	End product test 9 moved on line	Off line end product test replaced with in-line monitoring	*In line monitoring of CU of tablets post compression*

Table 1: Optional approaches to demonstrate product quality as part of an RTR testing strategy.

Incorporating RTR into existing quality systems

RTR will be implemented on a product basis while other products manufactured at the manufacturing facility will remain released based on traditional approaches. Quality systems at a manufacturing site such as SOP's, Deviations, Change control, Process Validation, personnel roles and approval workflows, which cover, traditional approaches to GMP compliance and product release may need modification to facilitate parallel RTR and traditional release approaches operating at the manufacturing facilities. Careful consideration should be given to change control for RTR processes.

It is likely that the greater process understanding, mechanistic knowledge of process boundaries and presence of monitoring and control systems will allow more efficient and 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.

