Guidance Number: 84

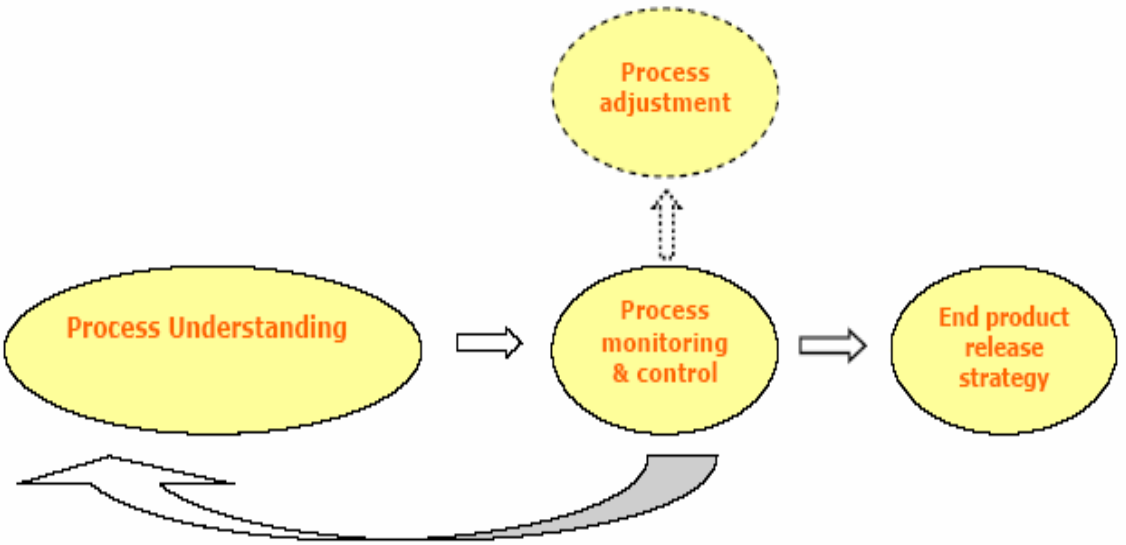

Figure 1: Key elements of any RTR strategy

	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.

Table 1: 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*

Table 2: Batch Process

	Conventional testing	RTR	Rationale
Appearance	Visual	Visual	No change
Identity 1	HPLC	Identity by NIR on API charged to process	NIR ID of tablets can be inferred from ID testing of raw materials. API remains within a closed manufacturing system and quality system ensures material control. Discrimination of measurement allows switch from 2 ID tests to 1.
Identity 2	TLC		
Potency	HPLC	In line assay NIR on tablet cores during compression	In-line NIR will deliver real time information on potency over a wider portion of the batch than that covered by off line testing.
Uniformity of dosage units	HPLC	Must comply if tested' & In line assay NIR on tablet cores during compression with large N specification	In-line NIR coupled with in line weight control will deliver real time information on content uniformity over a wider portion of the batch than that covered by off line testing.
Impurities	HPLC	None - Testing only at stability.	Test removed based on high capability (Ppk), parameter control and understanding of formation conditions for DP impurities.
Disintegration	Disintegration tester	Disintegration tester	No change
Water determination	At line NIR	At line NIR	No change
Microbial purity	Ph Eur (skip lot)	Ph Eur (skip lot)	No change
Dissolution	Not tested	Not tested	Disintegration used in lieu of dissolution based on high solubility compound class

NOTE: *Shelf life testing as per conventional specification*