Title: Validation of Process Analytical Technology System					
Guidance Number: 99					
Prepared by:		Date:		Supersedes:	
Checked by:		Date:		Date Issued:	
Approved by:		Date:		Review Date:	

Introduction
This document provides guidance for validation of PAT systems to assure compliance for PAT applications which can be implemented at a GMP site. The scope of this guidance includes PAT systems used in both Drug Product and Active Pharmaceutical Ingredient (API) manufacturing.

This guidance provides quality risk-based recommendations for validating PAT systems and provides examples with a flow chart to assist in performing the impact assessment and determining validation requirements. The extent of validation required for a PAT system is determined by the potential risk to quality posed by its intended use.

It is recommended that an impact assessment of each PAT system be performed. Those systems that are determined by the impact assessment to have a potential impact on product quality are considered direct impact systems and shall be qualified. Others which are determined to be indirect or no impact are Commissioned.

Terminology
To enhance understanding of the content and recommendations in this guidance, terminology used in this document is defined below.

PAT Measurement System (or PAT system):
A measurement system can consist of several elements that generate analytical measurements which relate either to the identification, monitoring, or control of process parameters or product quality attributes. These elements may include one or more analyzers, instruments or sensors, either stand-alone or networked, including but not limited to those with software or firmware, as well as the interface of the system to the process or product being measured (sample interface), and interface of the measurement system to the process control system.

The PAT measurement system is typically comprised of some or all of the following:

- Field hardware (e.g. sample loop, supply piping, nitrogen feed).
- PAT instrument (e.g. NIR, HPLC, probe, fiber optics).
- PAT software (e.g. computer program and configuration).
- Data management (e.g. archival of results).
- Distributed Control System connectivity.

Appendices 1 through 4 provide some examples of PAT systems and how their boundaries may be defined. As defined, a PAT measurement system does not include the PAT-associated analytical measurement method.

PAT Application:
A PAT application is the use of a PAT measurement system for a particular purpose, for example, in-process reaction completion measurement in the manufacture of an API. A PAT application includes PAT measurement system elements and the analytical measurement method.

pieces of equipment, then the probe would typically be within the PAT "system" boundary. How the system boundaries are defined can have a significant impact on the validation strategy and can reduce or eliminate the need for validation of some systems.

System Level Impact Assessment
Some of the primary considerations when determining if a system is direct impact or not, are listed in the following questions. If one of the answers to any of the questions is yes, then the system is considered Direct Impact and is qualified. The questions that are most likely to apply to a PAT system are in bold font:

1- Does the system come in direct physical contact with the product?
Answer yes, if a system component makes direct physical contact with the product (including in-process materials, or intermediates subsequent to the API starting material) and the component's material of construction or the ability to clean the product contact surface will affect the product's safety, quality or purity.

For example, a measurement probe that makes direct product contact.

2- Is the system used in cleaning, sanitizing or sterilizing?
Answer yes if a system is used exclusively for cleaning verification (i.e. there is no other cleaning verification test performed).

3- Does the system create or maintain a cGMP environmental or process condition required to preserve product quality? And

4- Does the system produce, monitor, evaluate, store or report data used to accept or reject product or material, or data used to support Regulatory Compliance – Practices?
Answer yes, for PAT systems that monitor critical process parameters, used to support release decisions.

Answer yes, for PAT systems that perform exclusive verification of critical quality attributes or specification used to support cGMP decisions.

Answer yes, for PAT systems used to fulfil a regulatory commitment (e.g. registered in-process test result)
Answer no, for PAT systems that are used exclusively to gain knowledge, where data are not used to
support release decisions.

Answer no, when a PAT system is used for "processing forward" decisions where the decision is financial risk only and the product-quality attributes are verified by other means (e.g.: lab sample) at a later stage.

5- Does the system perform a function in the manufacturing, processing, packaging, labelling, testing, holding or distribution of a *product or material*, that is required to achieve a quality attribute or specification*?*
Answer yes, if the system controls a critical process parameter (CPP) (e.g feedback loop) or critical quality attribute (CQA). For definitions of CPPs and CQAs, refer to guidance 015. If a system is initially defined as an indirect impact system but it is known that the system will become a direct
impact system (e.g. data from the PAT system replaces final product testing), the system should be qualified.

As with the first example, one must also consider other aspects of this system, such as whether it has direct product contact, to determine if any components would require qualification. Because this case is a direct impact system, the PAT system will be qualified. The system components in direct contact with product can be included within the scope of the PAT system and qualified as a component of the PAT system, or they can be included within the scope of the reactor system itself and qualified as part of the reactor system.

For this Direct Impact System, a Component Level Impact Assessment was performed and is attached as an example in Appendix 4.

Example 3 (Appendix 3): No Impact: A PAT system that is used to measure the % of un-reacted starting material following a reaction for purposes of optimizing yield only. There is no impact on product quality if under-reaction or over-reaction takes place. The data are not used to release material and the test is not included within a regulatory filing.

As with the first example, one must also consider other aspects of this PAT system, such as whether it has direct product contact, to determine if any components would require qualification. In this example, the direct product contact surfaces of the PAT system are qualified as part of the reactor system. The boundary for the PAT system has therefore been drawn to exclude the product contact components from the PAT system, and include qualification of those components in the reactor system qualification. This PAT system would require commissioning only.

Conclusions

Quality risk-based, impact assessment of PAT systems and PAT applications is fundamental to establishing the validation strategy. By utilizing concepts presented in this GUIDANCE, validation resources can be targeted to those applications with direct impact on quality that require qualification, while still ensuring the robust operation of lower risk applications via commissioning.

Appendix 3: Example 3 – No Impact: System Level Impact Assessment

System No.	System Name/ Description	System Impact Assessment	Basis used for Impact Assessment ^					Commission	IQ	OQ	PQ	Notes
			1	2	3	4	5					
Example 3	PAT System Boundary: HPLC and data collection system, cables. Direct product contact surfaces (e.g. sample loop) are outside of the PAT system boundary. These components are included within the reactor system boundary.	No Impact	1	2	3	4	5	Y	N	N	N	Assumption: PAT is a system interfacing to another system (e.g. reactor system). The responses to the questions were based on: • Product contact surfaces (e.g. sample loop) are assumed to be outside boundary of PAT system. They are within the boundary of the reactor system: 'N' to Q1. • This is a test that is not included in a regulatory filing. • Data from this testing are used either to gather process knowledge (For Information Only) to optimize yield, to gain knowledge regarding feasibility of the PAT application, or to gain knowledge about the PAT system's capabilities. • There is no impact on product quality if under-reaction or over-reaction takes place.

^ If the answer is "yes" to any of the questions (page 3) **BOLD** the number(s) that correspond to the question.

Appendix 4: Example 2 – Direct Impact System: Component Level Impact Assessment

Component Tag / ID #	Component Description	Component Impact Assessment	Basis used for Impact Assessment ^		Commission	IQ	OQ	Existing IA on file?	Notes
XXX	Sample loop	Non-Critical	1	2	Y	Y	N		Materials of construction must be verified for qualified manufacturing systems
YYY	Cabling	Non-Critical	1	2	Y	Y	N		
ZZZ	HPLC Black-box (inc. computerized system and field device I/O calibration and testing	Critical	**1**	**2**	Y	Y	Y		
WWW	Waste handling components associated with on-line HPLC (Nitrogen used to clear probe surface)	Non-Critical	1	2	Y	N	N		

^ If the answer is "yes" to any of the questions (page 4) **BOLD** the number(s) that correspond to the question.

