Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

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

This document 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 document, 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.

Commissioning:
A planned, documented and managed approach to the start-up and delivery of systems (e.g. facilities, equipment, and software) to the end-user that results in a safe and functional environment that meets established design and user requirements.

impact PAT systems may then have their laboratory instrument system further categorized per document 032 which addresses qualification of laboratory equipment.

In addition to validation of the PAT system, the validation of the PAT-associated analytical test method may also be required depending on the impact assessment. Note that a PAT application that is determined to have no impact or indirect impact does not require analytical method validation, however method validation may be needed to assure reliability of the data. If a PAT system is direct impact, and the answer to questions 4 and/or 5 is "yes", then the analytical test method should also be validated. When one direct impact PAT system is used to support multiple analytical test methods (e.g. an HPLC PAT system used to monitor reaction endpoints for multiple API processes), the PAT system should be qualified separately from the validation of the analytical test method.
Validation of analytical test methods for PAT applications is outside the scope of this document.

Component Level Impact Assessment
Primary considerations when determining if a system component is critical or not are listed in are listed in the following questions.

1- Does the system component control or perform a direct impact function, or provide verification that a direct impact function has acceptable performance? And

2- Does the system component produce, monitor, evaluate, store or report direct impact data?

Impact / Risk Assessment Examples
Three examples of Impact Assessments have been prepared using the same PAT system to show how then extent of validation will vary based on intended use of the data. The concept of increasing levels of Commissioning and Qualification requirements as they relate to these three examples is shown at a high level in the chart in Appendix 6. These examples provide a representation of impact assessment results, and are attached in Appendices 1, 2, and 3 and are briefly described in the table below.

Application description	System boundary	Intended Use	Regulatory Registered Test?	Other Quality Tests as Back-up?	Direct/Indirect/ No Impact	Validation Elements typically required (see PQS V7101)
Example 1: HPLC and data collection system interfacing to a reactor.	PAT system. Boundary does NOT include direct product contact surfaces (i.e. sample loop).	To determine reaction completion: for quality	No	Yes	Indirect	None, Commissioning only
Example 2: Same as above	PAT system, including direct product contact surfaces	Reaction completion: for quality	Yes	No	Direct	Commissioning, Component Level Impact Assessment, User Requirements, Specifications, Validation Plan, Protocols, Validation Report, Approved SOPs, Change Control
Example 3: Same as above	PAT system. Boundary does not include direct product contact surfaces (i.e. sample loop).	Reaction completion: for yield	No	No	No Impact	None, Commissioning only

Example 1 (Appendix 1): Indirect Impact: A non-regulatory test conducted using PAT that is independently verified by other established quality tests. For example, an on-line PAT application

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

System No.	System Name/ Description	System Impact Assessment	Basis used for Impact Assessment [A]					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.

[A] 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 [A]		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		

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

