

Process Validation and ICH Q7

David Amspacher

Chemist, Division of Lifecycle API
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation & Research (CDER)

SBIA API Workshop – March 3-4, 2020



Learning Objectives

- Why does the FDA want us to validate our process?
- How do we validate our process?
 - Process Design
 - Process Qualification
 - Process Verification
- How does the FDA use validation data?

Regulatory Authority



- FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100).

What is Process Validation?

- Process Validation is the documented evidence that a process can produce an intermediate or API meeting its predetermined specifications
- Challenge Question
 - True or False
 - Most drug master files contain a summary of validation data upon initial submission

What is Process Validation?



- Process Validation is the documented evidence that a process can produce an intermediate or API meeting its predetermined specifications
- Challenge Question
 - True or False
 - Most drug master files contain a summary of validation data upon initial submission
 - True
 - Most drug master files that support ANDAs contain validation data

Completeness Assessment



- If the validation has been performed, the DMF holder should provide a validation summary
 - For sterilized API the full sterilization process validation and method validation of sterility tests should be provided
- Before any batch from the process is commercially distributed a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process
- This assurance should be obtained from data from pilot and/or commercial scale studies



Challenge Question

- ICH M4Q section 3.2.S.2.5 states that “Process validation and/or evaluation studies for aseptic processing and sterilization should be included.”
- True or False
- My process is not aseptic and does not involve sterilization, this means that I do not need to provide a validation



Challenge Question

- ICH M4Q section 3.2.S.2.5 states that “Process validation and/or evaluation studies for aseptic processing and sterilization should be included.”
- True or False
- My process is not aseptic and does not involve sterilization, this means that I do not need to provide a validation
- False
- This states that studies for aseptic processing and sterilization should be included, not that validation of a non-sterile process is excluded

Why Do We Validate



- Effective process validation contributes significantly to assuring drug quality
- Quality, safety, and efficacy are designed into the product
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing
- Each step of a manufacturing process is controlled to assure that the finished product meets specifications

How Do We Validate

- Collect and evaluate data
 - From the process design stage through commercial production,
- Establish scientific evidence that a process is capable of consistently delivering quality product
- Prospective validation should normally be performed for all API processes as defined in ICH Q7 12.12
- Should be completed before the commercial distribution of the final drug product manufactured from that API

Stage 1 – Process Design

- The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities
- Identify process parameters that could affect the critical quality attributes of the API
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control

Stage 2 – Process Qualification



- Process design is evaluated to determine if the process is capable of reproducible commercial manufacturing
- Critical process parameters should be controlled and monitored during process validation studies
- Process validation should confirm that the impurity profile for each API is within the limits specified
- A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained

Stage 3 – Continued Process Verification



- After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change

Challenge Question

- True or False
 - We only have to do 3 validation runs

Challenge Question



- False
- Neither the CGMP regulations nor FDA policy specifies a minimum number of batches to validate a manufacturing process
- We strongly recommend objective measures (e.g., statistical metrics) wherever feasible and meaningful to achieve adequate assurance
- The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches
- The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination.

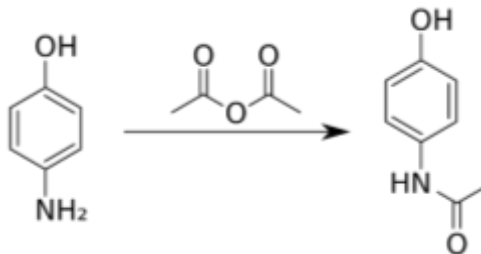
How we use validation data



- The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product
- Aspects of drug substances and manufacturing processes that are critical to product quality should be determined and control strategies justified.
- The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls
- Quality cannot be tested into products, quality should be built in by design

In process limits

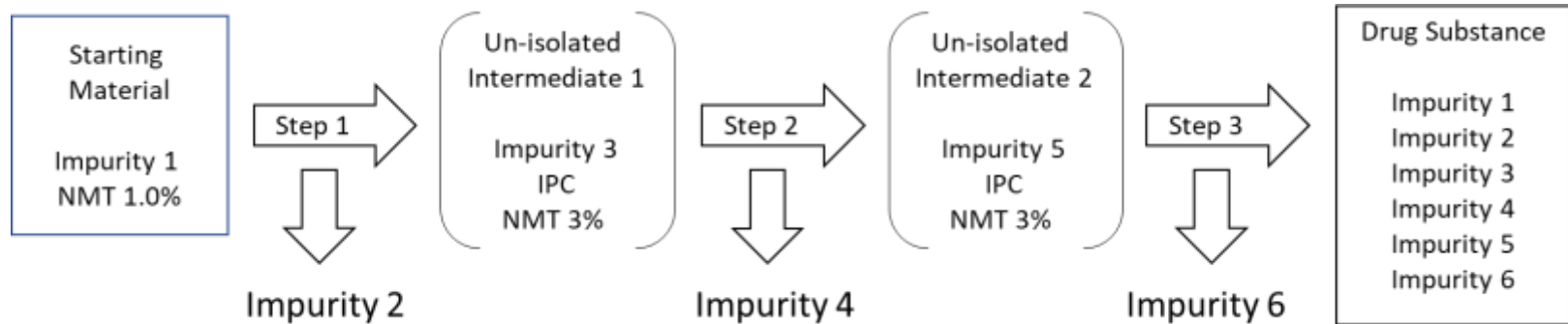
- Starts in 3.2.S.2.2
 - A table of starting material and reagent input weights that also includes molecular weight, moles and molar equivalents, output weight of product, and % yield, for each stage of the process



Reactant/Reagent	Weight	Molecular Weight	Moles	Equivalents	Output	% Yield
4-aminophenol	100kg	109.128	916.35	1	-	-
Acetic anhydride	140.32kg	102.089	1374.53	1.5	-	-
Acetaminophen	-	151.165	687.26	.75	103.89kg	75%
Solvent	1000L	-	-	10 vol	-	-

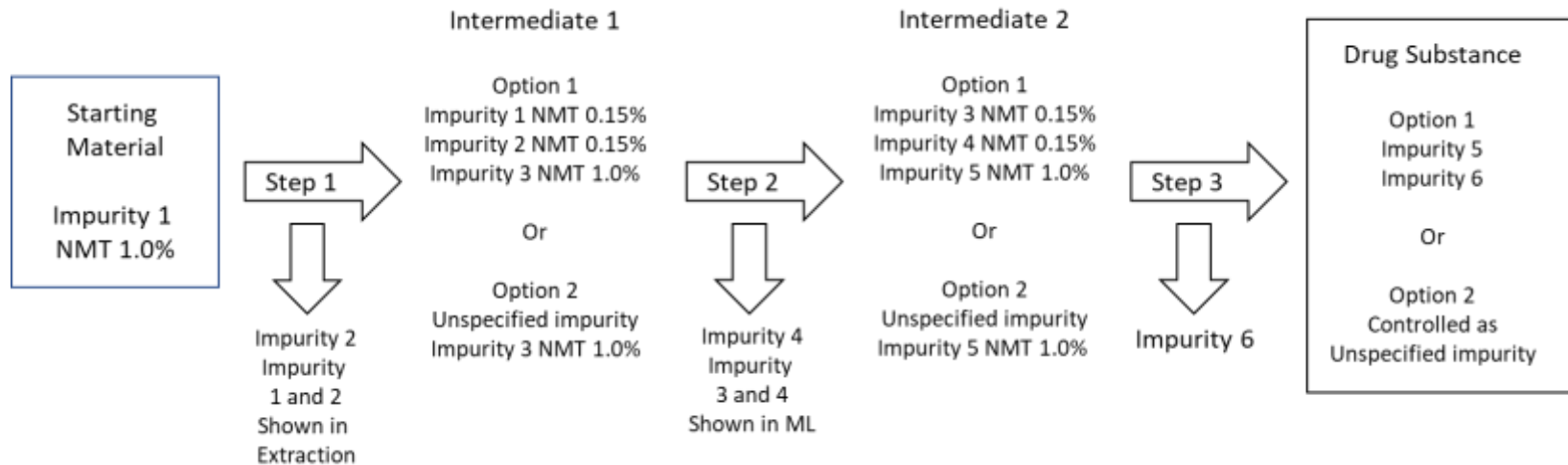
How we use validation data

- Opportunities exist to develop more flexible regulatory approaches. To realize this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters
- No Flexibility



How we use validation data

- Traceability, analytical data of SMs, intermediates, in process tests and final drug substance in tabular format





How we use validation data

- Gives us the ability to follow the fate and purge of impurities
- We want to know what impurities are possible and how they are purged and how you know that they are purged

In process limits

- In addition to sampling requirements, the CGMP regulations also provide norms for establishing in-process specifications as an aspect of process validation
- In-process material should be controlled to assure that the final drug product will meet its quality requirements
- In-process specifications shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate

How we use validation data

- The limits for the tests in the intermediate specifications need to be appropriate for the levels of the observed data
- Intermediate 3

Test	Limit	Batch 2020-001	Batch 2020-002	Batch 2020-003
Related Substances by HPLC				
Impurity 1	NMT 10.0%	0.31%	0.25%	0.20%
Impurity 2	NMT 1.0%	0.98%	0.95%	0.92%
Impurity 3	NMT 2.0%	1.25%	0.75%	1.00%
Impurity 4	NMT 5.0%	ND	ND	ND
Impurity 5	NMT 0.10%	ND	ND	ND
Impurity 6	NMT 10.0%	0.10%	0.15%	9.50%

Reporting impurity content of batches



- Analytical results should be provided in the application for all batches of the drug substance
- Any impurity at a level above the identification threshold in any batch manufactured by the proposed commercial process should be identified
- Any degradation product observed in stability studies at recommended storage conditions at a level above the identification threshold should be identified

Listing of impurities in specifications



- Specification for a drug substance should include a list of impurities
- Impurities should be based on the impurities found in batches manufactured by the proposed commercial process
- Individual impurities with specific acceptance criteria included in the specification for the new drug substance are referred to as "specified impurities"
- A rationale for the inclusion or exclusion of impurities in the specification should be presented and include a discussion of the impurity profiles observed in batches manufactured by the proposed commercial process

Listing of impurities in specifications



- Organic Impurities
 - Summarize the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance
 - Based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials
 - limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved

Summary



- Process Validation is the documented evidence that a process can produce an intermediate or API meeting its predetermined specifications
- Effective process validation contributes significantly to assuring drug quality
- Opportunities exist to develop more flexible regulatory approaches. To realize this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters

Thank You!



- For questions regarding the content of this presentation, please type them into the “Q&A Box” so that they can be addressed during the panel Q&A after this session.
- Send questions regarding this presentation to: DMFWorkshop2021@fda.hhs.gov by 3/19/2021 for inclusion in the follow-on webinar April 9, 2021.
- Please refer to the following presentations on March 3rd and 4th for additional information:
 - *Common CMC Issues in Type II DMFs and How to Avoid Them*
 - *ICH M7(R1) – Chemistry and manufacturing control (CMC) Perspective on Hazard Assessment*