REVIEW

Process Verification & Validation for Medical Devices Using Additive Manufacturing

The American Society of Mechanical Engineers®
ASME®

ASME
SETTING THE STANDARD

This paper is intended for educational purposes only and does not replace independent professional judgment. Statements of fact and opinions expressed are those of the author individually and, unless expressly stated to the contrary, are not the opinion or position of Johnson & Johnson or its affiliates or any of the organizations represented by the ASME Medical AM/3DP Advisors.

Introduction

Process verification and process validation are two important—and commonly misunderstood—activities in the development of medical devices. This document explains the differences between these two activities and how they apply to additive manufacturing (AM) for medical devices. A list of other helpful documents and resources is included at the end of this document.

One point of clarification: process verification and process validation are required activities for medical device manufacturers who are required to obtain regulatory clearance to sell their device. Currently, process verification and process validation are not required for medical devices where regulatory clearance is not required, such as point-of-care printing at a hospital.

Standards

In the United States, Title 21 of the Code of Federal Regulations (CFR) contains a section for the design, manufacture and distribution of medical devices (Title 21, Part 820). Within part 820 is subpart 75 (21CFR820.75), which specifically addresses process validation requirements. For medical device manufacturers who follow to the requirements of the International Standards Organization (ISO), the corresponding requirements for process validation are found in ISO 13485, Section 7.5.6.

Both 21CFR820 and ISO13485 contain requirements for design verification and design validation, as well as for process verification and process validation. Design verification and design validation are separate activities from process verification and process validation. This document focuses specifically on process verification and process validation (see Figure 1). A good source of information regarding design verification and design validation is the FDA guidance document, "Design Control Guidance for Medical Device Manufacturers."

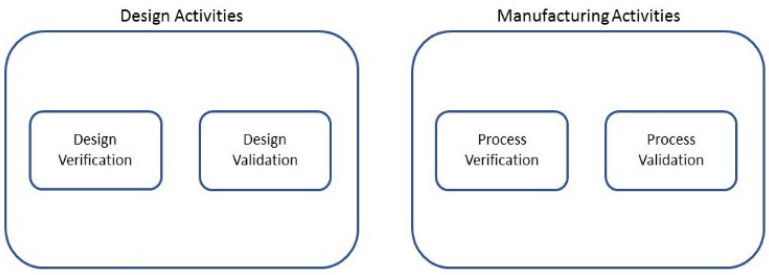

Figure 1- Design Verification and Validation / Process Verification and Validation

Subtractive Manufacturing vs. Additive Manufacturing

The differences between process verification and process validation will be more easily understood after a discussion about the differences between subtractive manufacturing and additive manufacturing.

In subtractive manufacturing, raw material is typically supplied in some form of bar stock. The bar stock is loaded into a machine such as a milling machine, lathe, screw machine, EDM, etc. Material is then removed ("cutting chips") to create the finished part. The important point is that the form of the raw material is not altered; material is simply removed from the starting raw material to make the finished part.

In additive manufacturing, raw material is supplied in various forms such as powder, liquid, filament, etc. In the course of making the finished device, the raw material is converted from its original form into a finished form. The conversion of the raw material from one form to distinguishes Additive Manufacturing from Subtractive Manufacturing. See Figure 2.

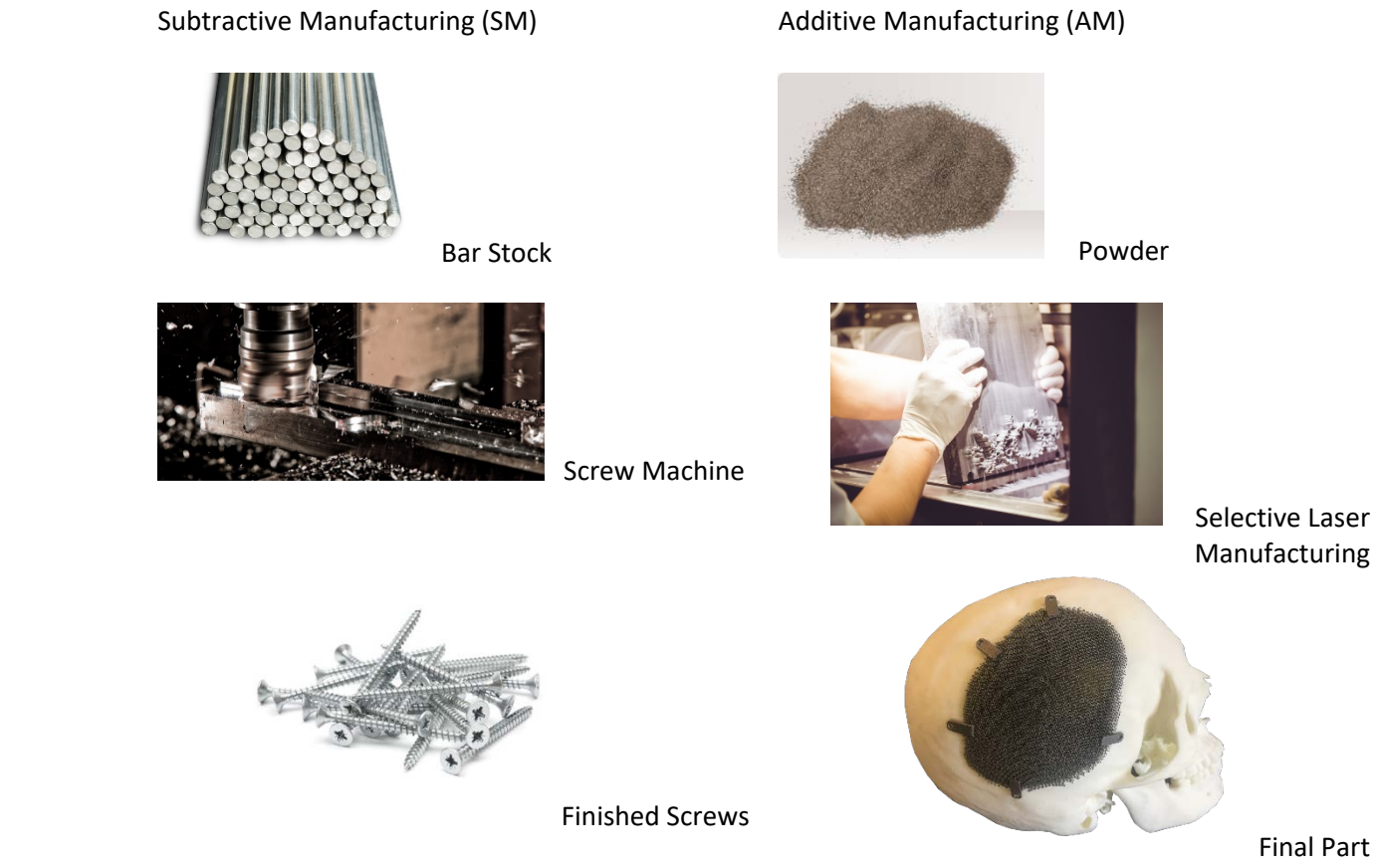

Figure 2- Comparison of Subtractive Manufacturing and Additive Manufacturing (courtesy Karen Gasko, DePuy-Synthes) (Powder image source: Flickr/Jayesh Group)

Process Verification vs. Process Validation: What's the Difference?

It's not uncommon to encounter situations in the medical device industry where the terms "process verification" and "process validation" are used interchangeably. This is a common mistake; it's important to spend some time to describe both terms and to clarify the differences.

Before discussing the differences between process verification and process validation, it is necessary to understand the link between design verification/validation and process verification/validation activities. In virtually all medical devices, there are certain features or characteristics of the device that are important for the device to function properly; these features are often used to create the product specifications. In the Six Sigma process excellence world, these features or characteristics are commonly referred to as "CTQs" (critical-to-quality). Some common examples of CTQs are:

- Dimensions and tolerances
- Clearance or interference fit between mating parts
- Raw material mechanical properties such as tensile strength, hardness, density
- Raw material chemical composition
- Part weight
- Strength of a packaging seal

To demonstrate that the manufactured medical device meets the design specifications, there must be documented proof that the CTQs have been met. Typically, there are two ways to do this: process verification or process validation.

Process Verification- If a CTQ can be measured, it is said that the CTQ can be verified. For example, the length of a bone screw can be verified by measuring it with calipers; the weight of an instrument can be verified by weighing it on a scale.

Process Validation- The first sentence of 21CFR820.75 states:

"Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures."

So, what does that mean? Validation comes into play when the test method used to check the CTQ would alter or destroy the device. Validation also is needed if the verification method to ensure a CTQ has been met is either inadequate of cost-prohibitive. For example, the peel strength of the heat-sealed lid is often a CTQ for a sterile package. The peel strength CTQ could be tested by measuring the amount of force required to peel the lid off, but it's somewhat pointless to do this on a production basis, because the package would be destroyed in the course of proving that the CTQ was met. In a situation like this, process validation on the heat sealing process would be performed.

Manufacturing processes that require process validation are commonly referred to as "special processes." Examples of special processes are injection molding, extrusion, package sealing, and additive manufacturing. At a high level, process validation is nothing more than a series of activities executed before commencing production to show that the output from a special process will consistently meet the device CTQs.

Figure 3 shows a decision tree that can be used to determine when process validation is needed.

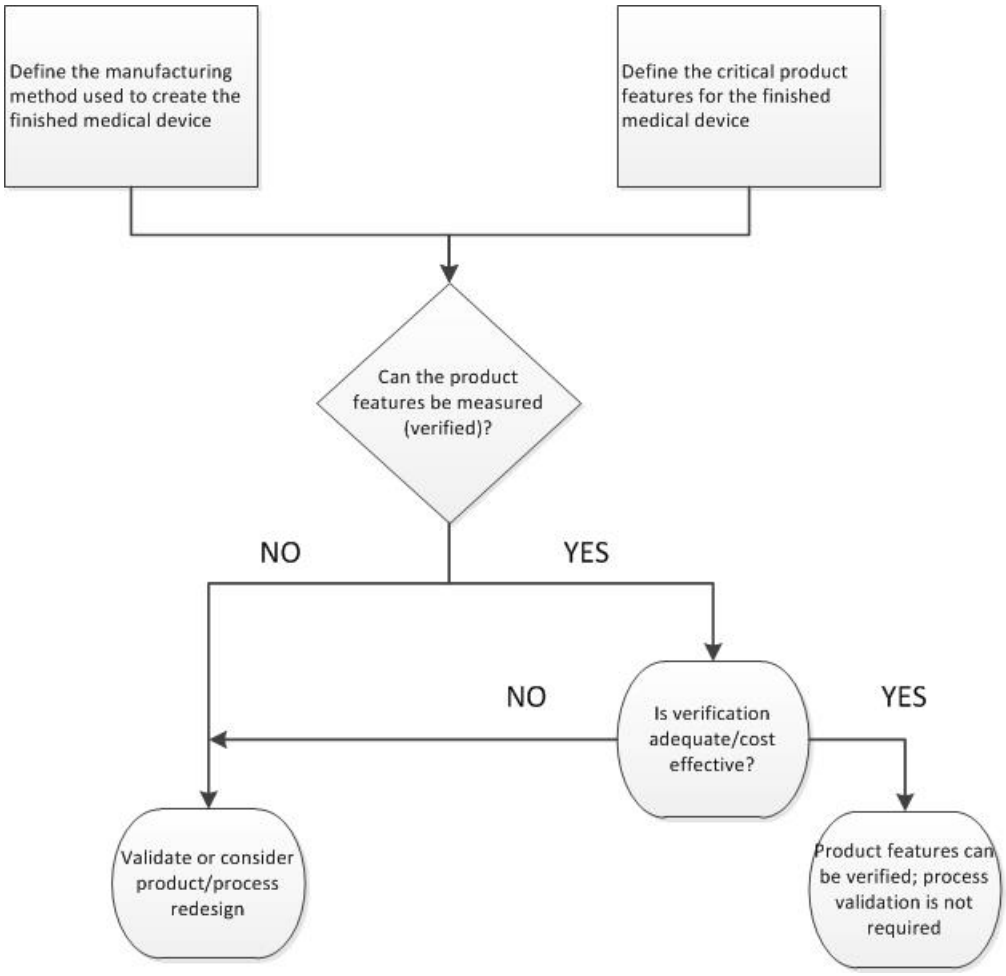

Figure 3- Process Validation Decision Tree

Process Flow

Prior to commencing process validation activities, it is highly recommended to create a detailed flowchart that describes the entire manufacturing process. When thinking about validation for AM, it's easy to become focused on the printing step. However, there are usually several activities that happen upstream to the printing process, and several activities that happen downstream from the printing process. All of these steps should be defined to fully understand the entire manufacturing process. Additionally, at each step in the manufacturing process, the inputs to and the outputs from the step should be identified. Inputs are sometimes referred to as "X's"; outputs are referred to as "Y's". The Figure 4 shows an example of a flowchart for a 3D printing process.

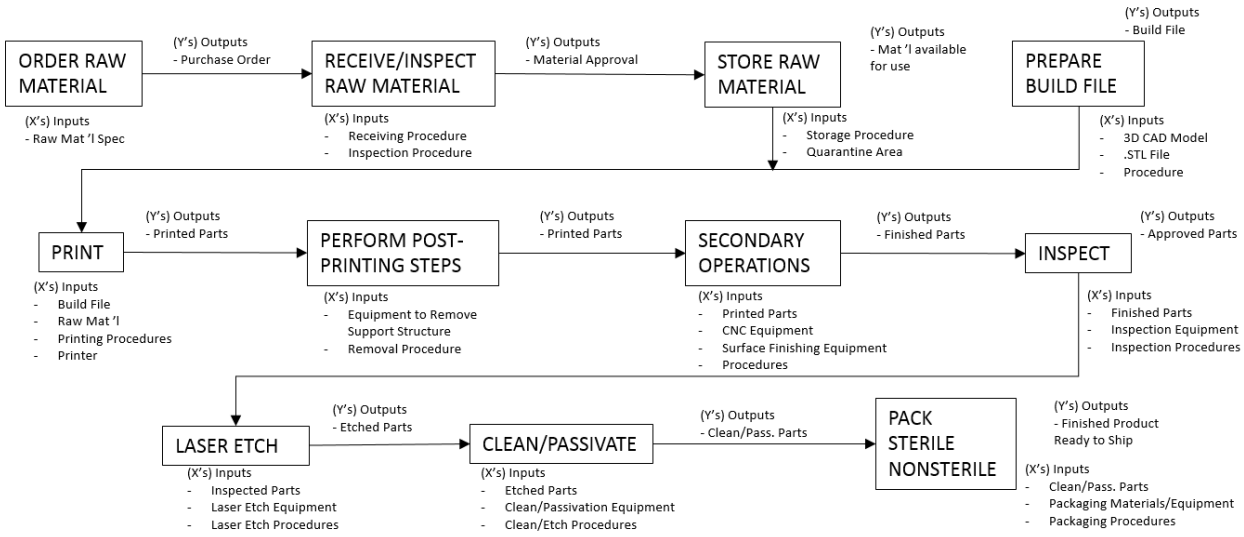

Figure 4- Manufacturing Process Flowchart

Elements of Process Validation

A typical process validation comprises four main elements: Installation Qualification (IQ), Process Characterization, Operation Qualification (OQ), and Performance Qualification (PQ). Figure 5 below shows the phases of the process validation.

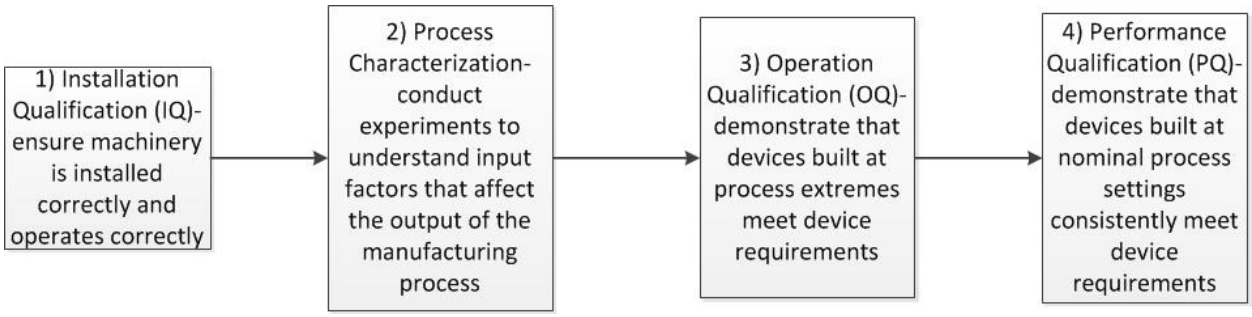

Figure 5- Phases of Process Validation

1. Installation Qualification (IQ)- Simply stated, the IQ is a formal activity to demonstrate that all manufacturing equipment used to produce the medical device has been installed correctly and operates per the manufacturer's specifications. Prior to installing the equipment, an IQ protocol is written to describe the equipment to be installed, the method of installation, and acceptance criteria used to demonstrate that the installation was successful. The equipment is then installed, and the protocol is executed. Finally, an IQ report is generated to document successful installation and operation of the equipment.

2. Process Characterization- Once IQ is complete, the next step is to conduct Process Characterization. The purpose of Process Characterization is to understand how the process inputs (X's) affect the process outputs (Y's). Using the process inputs (X's) in the flowchart described in the previous section, a series of experiments is conducted to determine which process inputs affect the process output (Y's), and the allowable limits that produce an acceptable output. The results of these experiments will be used to establish a processing window for the Operation Qualification (OQ).

3. Operation Qualification (OQ)- The purpose of OQ is to prove that parts made to the limits of the processing window will meet the design requirements. The first step is to develop the production processing window based on results from the Process Characterization step. The next step is to write an OQ protocol that describes the parts to be tested, the processing window extremes to be challenged, the number of parts to be produced at each processing window extreme, the test method used to evaluate the parts, and the acceptance criteria. The protocol is then executed, and the results are documented in an OQ report.

4. Performance Qualification (PQ)- The PQ demonstrates that the manufacturing process can produce a consistent result using the nominal process setting every time the process is run. The idea is to demonstrate that the process can produce the same result consistently when considering the various sources of common-cause variation, such as manufacturing shut-downs for maintenance, change-overs from one job to the next, raw material lot changes, etc. The first step is to establish the nominal processing settings. Typically, these settings are midway between the extremes established in OQ. The next step is to write a protocol that describes the parts to be tested, the nominal processing window, the number of simulated production runs, the number of parts to be produced per run, the test method used to evaluate the parts, and the pass/fail criteria. The protocol is then executed, and the results are documented in a PQ report.

Validation: Focus on Additive Manufacturing

The previous section describes the general concept for process validation. This methodology has been used for years in the medical device industry for special processes such as injection molding, extrusion, package sealing, etc. Process validation for AM follows this same general methodology, with the following exception.

One distinction of AM compared to other special processes is the flexibility offered by AM. In most special processes, tooling is required in conjunction with the processing machine to produce a device; injection molding requires a mold, extrusion requires a die, and heat sealed packaging requires a nest and heated platen. If a molding machine were run by itself without a mold, or if an extruder were run by itself without a die, the result would simply be a pile of extruded, melted plastic on the manufacturing floor. In AM, because the build is created virtually without the need for tooling, many of the constraints imposed by the need for tooling (molds, dies, nests, etc.) are removed. Some of the more common process inputs that are fixed with traditional special processes, yet are variable with AM, are listed in the table below.

Table 1- Comparison of Constraints Between Special Processes and AM

Process Variable	Additive Manufacturing	Traditional Special Processes
	Fixed or Variable?	Fixed or Variable?
Type of Part	Variable	Fixed
Part Orientation in Space (i, j, k)	Variable	Fixed
Part Location in Space (x, y, z)	Variable	Fixed
Variety of Parts / Range of Sizes	Variable	Fixed
Number of Parts per Build	Variable	Fixed

During process characterization, the variables listed in the table above should be tested with test coupons to determine a "worst case" build file to be used in OQ and PQ. For example, it may be found during process characterization that smaller coupons are weaker than larger coupons, or that coupons printed in a horizontal orientation are weaker than coupons printed in a vertical orientation. In this case, the build file used for OQ and PQ would include small coupons printed in a horizontal orientation.

Additionally, some other variables that could be considered during process characterization are:

- Power of the energy delivery system (temperature, laser power, etc.)
- Layer thickness, filament diameter, etc.
- Raw material reuse
- Raw material shelf life
- Post-print curing, rinsing, heat treating, hot isostatic pressing (HIP), etc.
- Raw material variation
    - Particle size and distribution for powders
    - Diameter for filaments
    - Viscosity and pot life for fluids
- Printing chamber temperature, humidity, inert gas flow rate
- Printer speed, path, etc.

Once Process Characterization has been completed, the process window has been defined, and the worst case build file has been established, the OQ and PQ can be executed. The OQ high and OQ low builds would confirm the operating window extremes, and then a series of PQ builds at nominal process settings would confirm that the process can produce the same result over time. Once the validation is successfully completed and the device is cleared for sale, the process should be monitored and controlled during ongoing production (see Figure 6).

Note that validation is not a "one-and-done" activity. Some events that could trigger the need for revalidation are:

- Design change that creates a new worst-case condition
- Addition of a new part size in a part family where the new part size represents a new worst case
- Relocation of the validated manufacturing equipment (moving the printer to a different room, etc.)
- Addition of new manufacturing equipment (adding a second printer to increase manufacturing capacity, etc.)

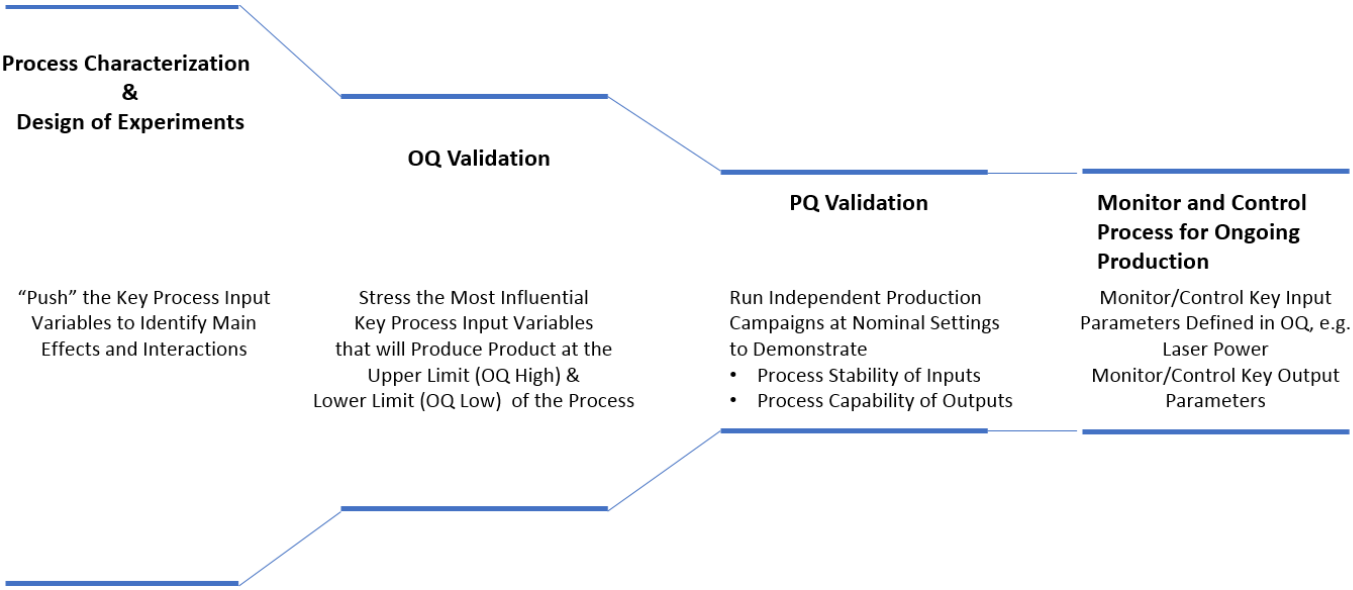

Figure 6- The Various Steps in Process Validation (courtesy of Karen Gasko, DePuy-Synthes)

Helpful Documents and Resources

Below is a list of documents and websites that are useful to understand process validation more fully.

Documents

- Title 21, section 820.75 of the Code of Federal Regulations (CFR)-
- ISO 13485 section 7.5.6- www.iso.org
- FDA Guidance Document, "Technical Considerations for Additive Manufactured Devices"
- FDA Guidance Document, "Design Control Guidance for Medical Device Manufacturers"
- Global Harmonization Task Force \, "Quality Management Systems- Process Validation Guidance"

Websites

- US Food and Drug Administration
    - Search FDA database of recognized consensus standards
- V&V 40 Verification and Validation in Computational Modeling of Medical Devices
- V&V 50 Verification and Validation of Computational Modeling for Advanced Manufacturing
- Medical Additive Manufacturing/3D Printing Resources

Acknowledgements

This document was developed by the ASME Medical Additive Manufacturing/3D Printing advisors as an informational document. Dan Fritzinger, DePuy Synthes led the effort and drafted the document. April Krivoniak, UPMC and Sean McEligot, provided important perspectives from the point-of-care manufacturing. The document was reviewed by the advisors:

- Amy Alexander, MS, Senior Biomedical Engineer, Mayo Clinic
- Anthony Atala, MD, Director, Wake Forest Institute for Regenerative Medicine
- Roland Chen, Assistant Professor, Washington State University
- Andy Christensen, President, Somaden
- Rex Christensen, Associate Professor, Weber State University
- Mary Christie, Senior Manager for Content, Healthcare Solutions, Stratasys
- Meghan McCarthy, Project Lead, NIH 3D Printing & Biovisualization, Exchange
- James Coburn, Senior Advisor for Emerging Technologies, FDA
- Michael Coleman, Development Engineer, HCL
- Caralynn Collens, CEO, Dimension Inx
- Daniel Crawford, CEO, Axial3D
- David Dean, PhD, Associate Professor, The Ohio State University
- Carl Dekker, President, Met-L-Flo
- Hunter Dickens, Biomedical Engineer, Mayo Clinic
- Matthew DiPrima, Materials Scientist, FDA
- Lee Dockstader, Director of Vertical Market Development, HP
- Dima Elissa, CEO, Founder, VisMed3D
- Dave Emmett, Technical Sales Leader, GE Additive
- Alejandro Espinoza, PhD, Assistant Professor, Rush University Medical Center
- Sarah Flora, Director, 3DP Lab, Geisinger Health
- Dan Fritzinger, Global Manager- Instrument and Innovation, DePuy-Synthess
- Lexi Garcia, Outreach Coordinator, ARMI|BioFabUSA
- Giles Gaskell, Marketing Manager, Wenzel America
- Laura Gilmour, Medical Account Manager & Business Development, EOS of North America
- Virginia Goble, Vice President, Marketing & Strategy, Materialise
- Irene Healey, Founder, Principal, New Attitude Prosthetics Designs
- Evan Hochstein, Additive Manufacturing Healthcare Solutions Engineer, Stratasys
- Yu-hui Huang, Resident, University of Minnesota Medical Center
- Rachel Hunt, 3D Printing Marketing Manager, Protolabs
- Adam Jakus, Co-founder & Chief Technology Officer, Dimension Inx
- Joseph Johnnie, Senior Engineer, Center of Device Innovation, Johnson & Johnson
- Benjamin Johnson, Director, Product Development, 3DSystems
- Craig Johnson, Principal Solutions Specialist, Formlabs
- April Krivoniak, Biomedical Engineer, UPMC
- Gene Kulesha, Senior Director, Advanced Engineering, Onkos Surgical
- Shuai Leng, PhD, Associate Professor of Medical Physics, Mayo Clinic
- Peter Liacouras, PhD, Director of Services, 3D Medical Applications Center, Walter Reed National Military Medical Center
- Orlando Lopez, Director, Dental Materials and Biomaterials, Dental Materials & Biomaterials Program, NIH NIDCR
- Gaurav Manchanda, Strategy + Partnerships Lead, Healthcare, Formlabs
- Jane Matsumoto, MD, Radiologist, Mayo Clinic
- Lauralyn McDaniel, Industry Manager, ASME
- Sean McEligot, MHA, Director, Additive Manufacturing Facility, Mayo Clinic
- Katie McKinley, Head of New Business, Axial3D
- Eyal Miller, VP, Head of Healthcare SBU, Stratasys
- Jonathan Morris, MD, Neuroradiologist, Director, 3D Printing Anatomic Modeling, Mayo Clinic
- Robert Morrison, MD, Clinical Instructor and Fellow in Laryngology, University of Michigan
- Reese Myers, Vice President of Product Development, WishBone Medical

- Renee Nester, Associate Manager, Quality Engineering, Johnson & Johnson
- Philip Oris, Director of Business Development Medical & Dental, SLM Solutions
- Ibrahim Ozbolat, PhD, Associate Professor, Penn State University
- Todd Pietila, Global Business Development - Hospital 3D Printing, Materialise
- Michael Pisani, Director of Outreach and Member Services, ARMI
- Michael Raphael, CEO, Direct Dimensions
- Ryan Ratkowski, Product Development Engineer, Avalign Technologies
- Beth Ripley, MD, Director of VHA 3D Printing Network, VA Healthcare Systems
- Becky Robinson-Ziegler, Deputy Chief Regulatory Officer, ARMI|BioFabUSA
- Justin Ryan, PhD, Research Scientist, Rady Children's Hospital
- Ben Salatin, Innovation Specialist, US Department of Veterans Affairs / Albuquerque Veterans Hospital
- Janelle Schrot, Biomedical Engineering Business Development Manager, Materialise USA
- Ramille Shah, PhD, Co-founder and Chief Scientific Officer, Dimension Inx
- Rami Shorti, PhD, Biomechanical Scientist, Intermountain Healthcare
- Brian Strezelecki, Research Engineer, VA Puget Sound Health Care System
- Jude Sudhakar, Prosthodontist, NMC Healthcare
- Dale Swarts, Chief Engineer, Stryker
- Kim Torluemke, VP Quality & Regulatory, Healthcare, 3D Systems
- Mihaela Vlasea, Assistant Professor, University of Waterloo
- Nicole Wake, PhD, Director, 3D Imaging Lab, Montefiore Medical Center
- Katie Weimer, Vice President, Medical Device Healthcare, 3D Systems
- Robert Wesley, 3D Printing Engineer, St. Louis Children's Hospital
- Jan Witowski, MD, Department of Radiology, Massachusetts General Hospital
- Atif Yardimci, PhD, Senior Manager, Biomedical Engineering, Exponent
- Ken Yuen, Manager, Additive Manufacturing Operations &Engineering, Acuitive Technologies
- Stephan Zeidler, Senior Global & Key Accounts Director, GE Additive