Questions Prepared for and Derived from the FDA Additive Manufacturing Workshop

The following questions pertain to all stages of medical device development using additive manufacturing (AM). Collectively, they helped to inform the content of the workshop, were derived from the workshop, or are common questions asked of the industry. During the workshop many participants were able to address these questions through presentations and group discussion. This list is a way to ensure every stakeholder has the opportunity to comment on aspects of AM that are important to medical device quality, safety, and effectiveness. We recognize that some of these concerns have established answers for traditional manufacturing techniques however those answers may not always apply to AM processes for medical devices. The FDA is focused on the AM-specific aspects of each question and/or how they may differ from traditional manufacturing processes.

Please use these questions as a guide when sending comments to the docket.
http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-0432-0001

Materials
- Printability:
  - What properties make a material printable?
  - What are the different challenges based on the material type (polymer, metal, ceramic)?
  - Is there a material type or specific material that leads to more consistent build success?
  - For material additives, is their role in the printing process understood? Do they present a leachability risk?
  - For processes where the final material is created in the printer, how well do we understand the *in situ* changes that occur? How does material stability change?
    - How do you account for material changes from the printing process? (e.g. aluminum volatization in E-beam process, polymer thermal history in SLS)
    - How many times can you reuse material in a vat/powder bed and achieve a viable part. How and how often do you monitor viability?
    - What new biocompatibility concerns arise as a result of the material being 3D-printed?

- Processes and monitoring:
  - How do die swell, viscoelasticity, and other material parameters affecting printing of polymers?
  - What are best practices to maintain quality control for raw materials (e.g. lot history, spec sheets, validation)?
  - Does 3D printing create post-processing material challenges? E.g. effect of anisotropy on polishing/deburring, post-printing cure, heat treatments, post-printing machining (tapping, drilling)
  - How do the final manufacturing steps (e.g. polishing, machining) affect the final properties?
  - Given the many possible modes of failure of a device, what do we know about material choice and its relation to specific failure modes?

- Physical
- Safety/effectiveness
- Biocompatibility

- New Materials: What challenges are there for developing new materials?
    - How do you identify potential new Additive Manufacturing Materials? Specifically for medical devices?
    - What special considerations exist for printing soft materials?
    - What is the current best practice to print hydrogels and other soft materials?
    - What additional performance, safety or effectiveness concerns arise when a drug or biologic is incorporated into a material?
    - How do composite reinforcement or material heterogeneity alter the printability of the base material?
    - When in the development process do you consider the printability or biocompatibility of additives (crosslinkers, initiators, UV absorbent dyes) when designing a new polymer system?
    - How do you determine shelf life of raw and final 3D printed materials? How do you determine storage conditions?

Printing Characteristics and Parameters

Parameters:
- What are the critical parameters in the AM space for a successful printing process? What needs to be considered?
    - type of printer; does it depend on the final part? (e.g. implant vs. loadbearing implant vs. non-implanted)
    - type of material
    - components of the printer; including energy sources;
    - material composition details; (e.g. does homogeneity of mixtures need to be maintained?)
    - logistics of different phases of the printing process;
    - any parallel or series production processes
    - finishing protocols
    - any accessory devices used at any point in the process;
    - environmental parameters (humidity, ambient lab conditions)
    - support materials/layers and the software setting that controls them
- What ranges of settings are critical for each printer? How narrow of a range is needed/acceptable?
- What parameters can you track to ensure a successful build process?
    - How closely should you monitor and document the parameters?
    - Are there stages where close monitoring is critical and other stages less important?
    - How can closed loop monitoring and control help ensure print quality?

Characteristics:
- What do you consider to be a successful build?
    - How strict can the criteria be for a successful build?

- o What are the specific considerations for rejecting a part or whole run?
- o How much printing variability is acceptable for quality assurance? How is it mitigated by post-processing?
- o If there is a printing deviation mid print, does the job automatically fail or can the build be restarted?
- What are the most important parameters for successful 3D printing of permanent implants, resorbable implants, and load bearing implants?
  - o Material
  - o Design
  - o Specification range
- How standardized are print finishing steps? What concerns arise from different finishing methods?
- What is the relationship between raw material characteristics and 3D printing parameter to a final quality measure?
  - o What knowledge base is needed to produce a high quality final device from raw material (e.g. institutional experience, from the OEM, in the literature)
- What is the limiting factor determining feature resolution? What metrics assess the actual resolution of a print?
- Can printers of the same make, model,and series be used interchangeably? Can printers of the same company or technology be used interchangeably? If not, what information/specific parameter ranges need to be identified and how many trial runs need to be done to show you have met your specifications?
- How are material contaminations or other deviations measured during printing?
- Do the internal surface structures and properties matter if the material is not degradable?

Design, Printing, and Post Printing Validation

- Design:
  - o How does the clinician interact with the software or engineers to make the design patient-specific?
    - ▪ feature selection
    - ▪ version control
    - ▪ software locked design limits
  - o How do you determine the worst case design scenario with a continuum of designs rather than a finite set of designs.
    - ▪ Do you test each parameter to determine worst case?
    - ▪ Does computational modeling play a role?
    - ▪ How do you account for printing anisotropy in computational material models?
  - o How are non-patient design factors – surgeon usability, tool use, etc. incorporated into the process?
  - o How does design validation for general 3D printing/proto-typing need to be adapted, taking into account the nature of medical devices that may be:
    - ▪ implantable or non-implantable,
    - ▪ load bearing or non-load bearing,

- patient matched or prescribed stock sizes?
  - How true to a patient scan does the print have to be?
  - How is traceability measured from patient image/design file to the final device?
  - How is the software used in 3D printing different or the same as the software used in other automated manufacturing processes?
    - What are typical concerns for interoperability/compatibility of software programs and versions using different file types, printers, and other accessories to produce safe and effective medical devices?
  - Does software validation account for all of the physical properties identified by the evolving parameter space for medical devices or combination products?
  - How are fail safe measures approached in the validation process to prevent users from exceeding design specifications and other set parameter ranges?

- Printing
  - How does validation of medical device print differ from other 3D printing applications?
  - What steps are essential for validating the printing of medical devices and/or combination products?
  - How are the parameters in process validation evaluated to be predictive of devices that conform to established specifications?
  - How do you address differences in printers in the validation process, considering both different printers of the same model and dissimilar models?
    - Must they be verified by testing samples from each printed batch?
    - How different is each printing technology in terms of *a priori* validations?
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- Post
  - What non-destructive testing methods are available for device validation or verification (e.g. volumetric subsurface imaging like micro-CT, optical coherence tomography)? What quantitative validation metrics can imaging provide?
  - What characteristics are most indicative of quality?
  - Are there examples from other industries where validation detected an issue that might have otherwise caused a failure? Can these be success stories for the medical device industry?
  - Are dimensional limits based on the as printed part or the post machined part?
  - Are there best practices, tests, and controls to assess quality of a build? How many of these quality measures must be device specific? (Printer or vendor specific?)

- Repeatability:
  - How do you approach reproducibility (1) across printers (2) at different locations of the printer bed within the same run?
  - How does reliable and reproducible (e.g. # of parts out of spec) compare to other methods of manufacture?
  - How do you define your acceptance criteria for a final device? (run, lot, day, etc.)

Safety and Functional Assessment of 3D printed devices: Mechanical and Physical Considerations
- How do you determine, through testing, that what you have printed is what you intended to print?
  - What are the material and interfacial (i.e., between printed voxel) properties that ultimately determine the mechanical properties of the printed product?
  - How do you confirm that the surface and internal properties of the printed part are acceptable?
- Will the broad specification of design space, rather than discrete, toleranced sizes, mask property variations within a specific print and result in changes in performance, biocompatibility, overall safety or effectiveness?
- How do you measure porosity and density of the final part? How dense is dense enough?
- How do you determine worst case build(s) for a patient matched device?
  - Orientation and print characteristics
  - How does post-processing alter the mechanics?
  - Is there a consistency concern in the final mechanical properties (1) metals or (2) polymers?
- Are there additional concerns for resorbable polymers that are not covered by existing testing (e.g., performance related to osteo-conduction, osteo-inductions, osteo-integration, osteo-genic potential, etc.)
- What new standards must be developed to adequately allow for testing of designs that do not fit traditional specifications?

Safety and Functional Assessment of 3D printed devices: (Micro)Biological Considerations (Including Sterility and Biocompatibility)
- Biocompatibility
  - How is the surface-to-volume ratio assessed?
  - How does surface-volume ratio affect
    - pre-clinical biocompatibility testing?
    - leachable testing?
    - degradation, both desired and undesired?
  - How well are standard biocompatibility testing protocols adapted to assess the bioactivity of AM materials (polymers, metals, and calcium-based raw materials)?

- Final Cleaning
  - What are the best ways to clean excess materials from a printed complex part?
  - How do you verify sufficient excess material is removed from complex structures, including any post-process contamination (e.g. residual oil and bioburden)?
  - For powder-based systems: How can we minimize non-fused particles inside of a completed device? What is an acceptable number/size of remaining particles?

- Sterilization
  - What characteristics of the device are most critical to consider when defining the appropriate sterilization modality?

- How do classic sterilization methods need to be adapted for 3D-printed products? (e.g. terminal sterilization and in-process sterilization)
  - Is degassing different for 3D printed components?
  - How should the metrics of the residue be expressed?
  - Should metrics include level of residue per device? As the level of residue relative to the surface area?
  - How would the surface area of a scaffolded device be measured?
- What post-sterilization testing should be considered to ensure the device remains safe and effective?
- What sterility assurance products are available to help ensure that the processed devices are sterile? Where is the worst case location to test for sterility?
- How does sterilization affect device material characteristics and performance?
- How are endotoxin limits evaluated?