V&V Best Practices

CASSS, CMC Strategy Forum
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Suttons Creek, Inc.

Solving the problem of **Complexity.**
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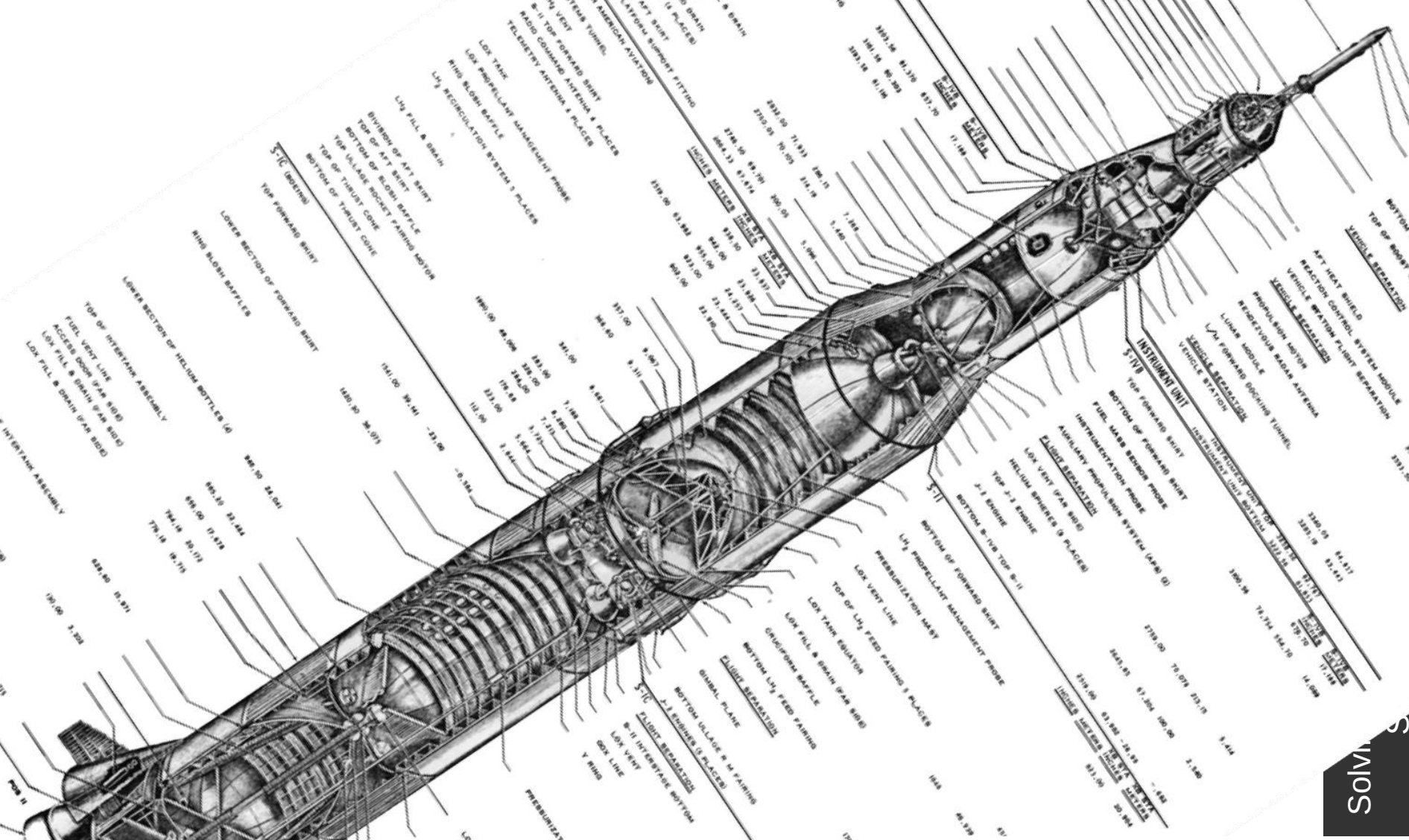


SHEET 1 OF 2 SATURN APOLLO 500 SERIES

THE BOEING COMPANY
SPACE DIVISION, LAUNCH SYSTEMS BRANCH
HUNTSVILLE, ALA 35807

SATURN V APOLLO FLIGHT CONFIGURATION

DRAWING ORIGINATED BY:	DATE: 1 JANUARY 1968
HUNTSVILLE ENGINEERING	DRAWN BY: DON SPRAGUE

21CFR820.30 & FDA Guidance

CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 820 -- QUALITY SYSTEM REGULATION

Subpart C--Design Controls

Sec. 820.30 Design controls.

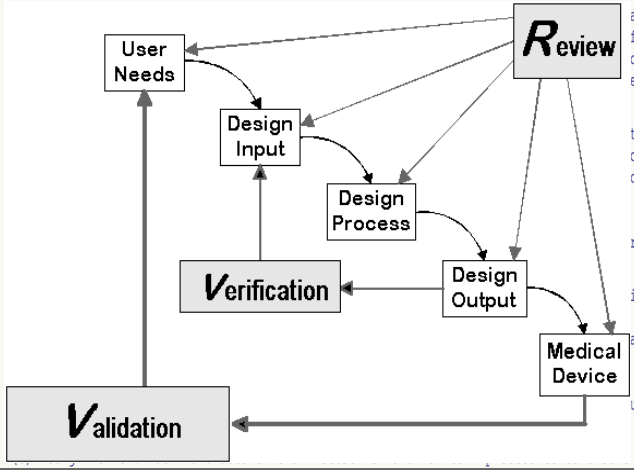
(a) *General.* (1) Each manufacturer of any class III or class II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.

(2) The following class I devices are subject to design controls:

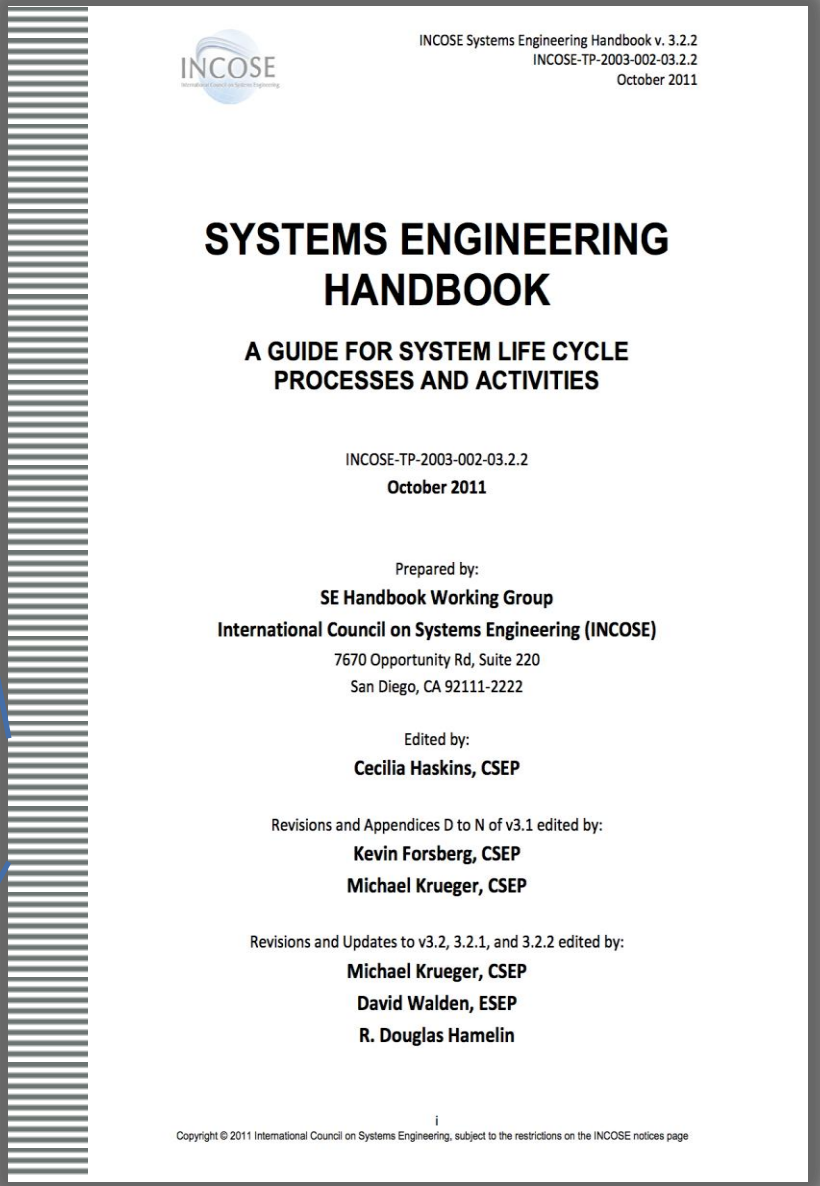
(i) Devices automated with computer software; and

(ii) The devices listed in the following chart.

Section	Device
868.6810	Catheter, Tracheobronchial Suction.
878.4460	Glove, Surgeon's.
880.6760	Restraint, Protective.
892.5650	System, Applicator, Radionuclide, Manual.
892.5740	Source, Radionuclide Teletherapy.



INCOSE System Engineering Handbook



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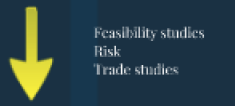
Combination Product System

Outcomes (User Needs) Level



System Level

Sub-System Level

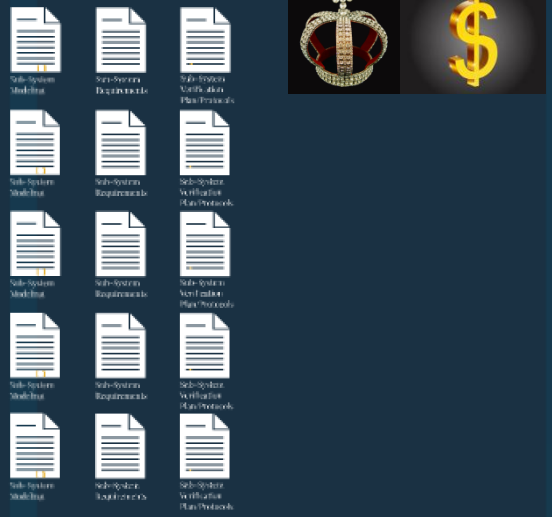
Drug

Device

Packaging

Labeling

Container

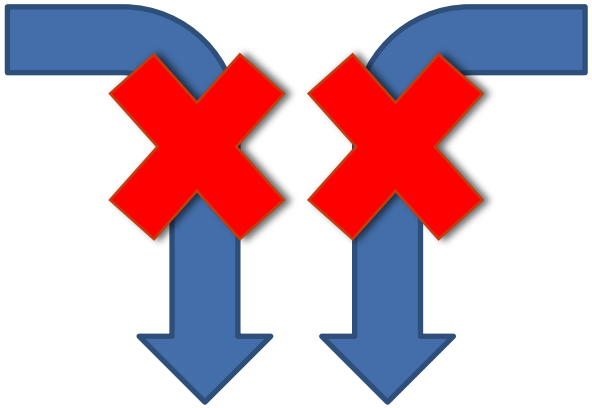


“Good” Engineering and Regulatory go hand-in-hand

- Setup your document tree during the planning design phase
- Review deliverables with regulatory before proceeding
- The process that produces a document is what matters, but without the document, what really happened?
- Assurance cases (i.e. for infusion pumps) are an example of how engineering failed to deliver sufficient artifacts and follow good engineering practice.

Many V&V Issues start with Requirements Issues

Vendor Specifications



Requirements

Unstructured Brainstorming

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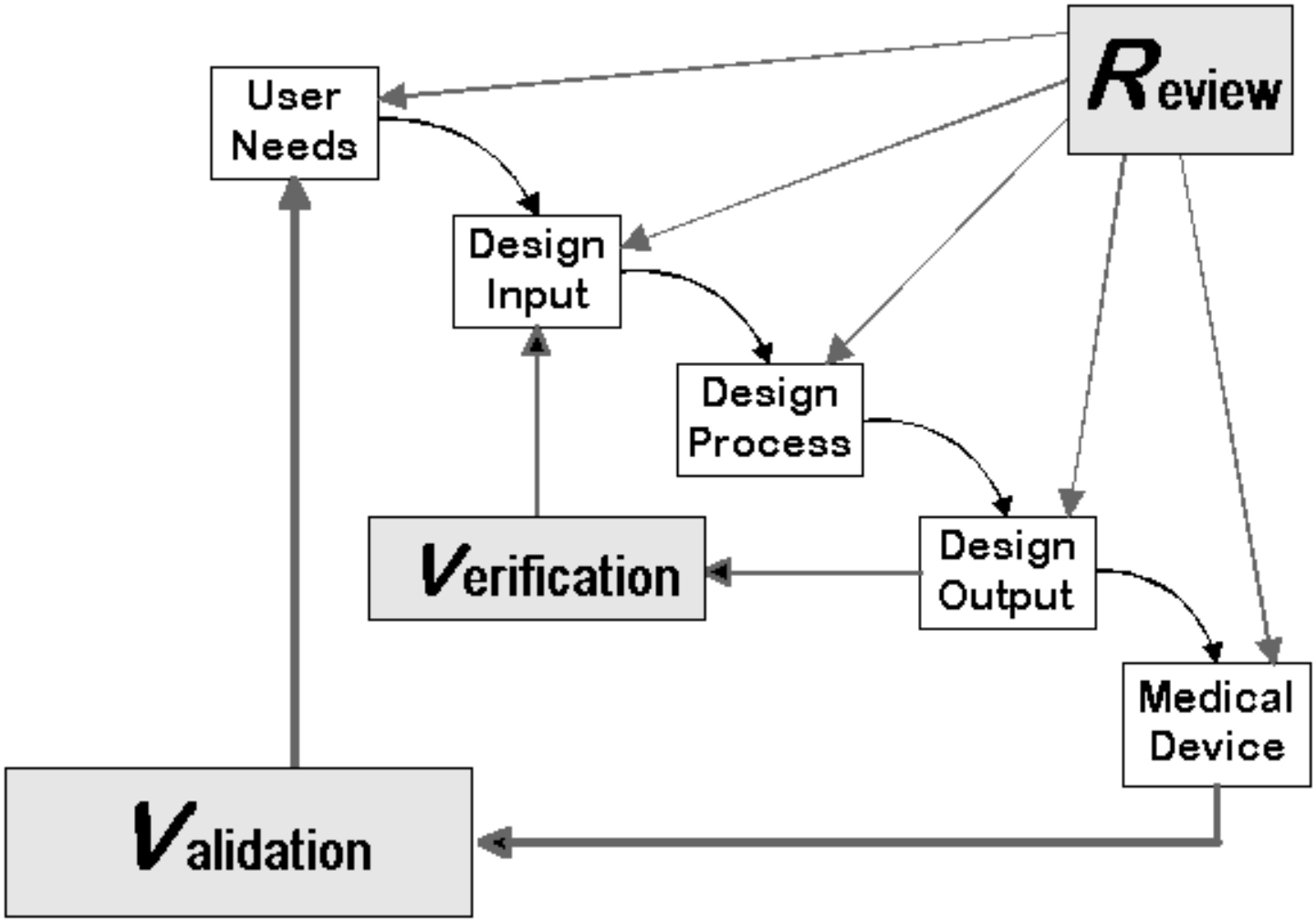
Verification vs Validation

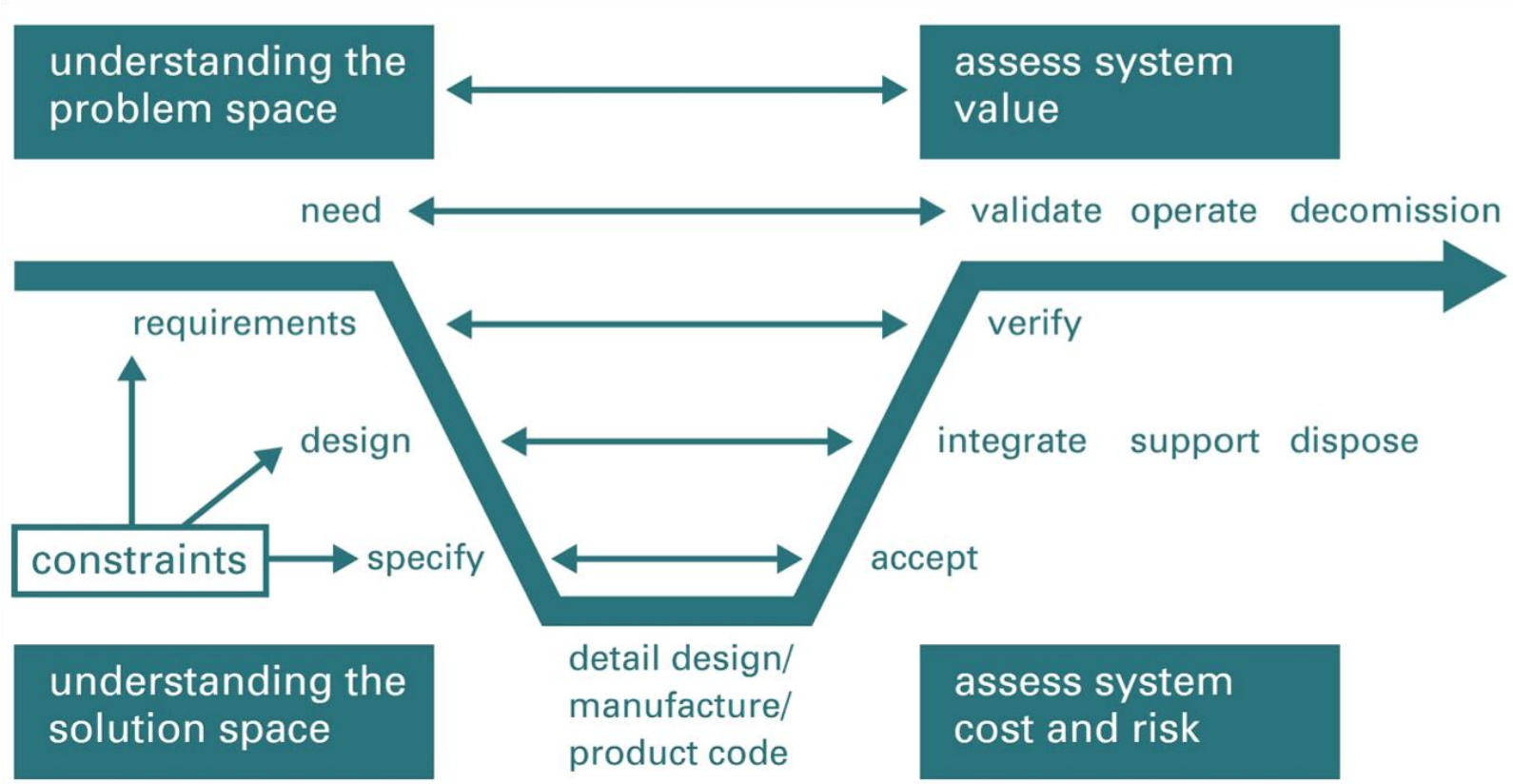
- 820.3(z) Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.
  - (1) Process Validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.
  - (2) Design Validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).
- 820.3(aa) Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

- Source: Design Control Guidance for Medical Device Manufacturers - FDA 21 CFR 820.30 and Sub-clause 4.4 of ISO 9001

Verification vs Validation



V-model in Lifecycle Context



R. Beasly, Rolls-Royce Aero

820.30(f) – Design Verification

- Each manufacturer shall establish and maintain procedures for verifying the device design.
- Design verification shall confirm that the design output meets the design input requirements.
- The result of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

System Level

System Modeling

System Requirements

System Verification Plan/Protocols

Verification

- Typical document tree:
  - Plan
  - Protocols
  - Reports
  - Summary
- Suitable methods:
  - Inspection
  - Demonstration
  - Test
  - Analysis
- Keep up with trace matrices in real-time with the project phase

Verification Protocols

- Content
  - Acceptance criteria
  - Sample Size
  - Materials Traceability
  - Pre and post-conditions
  - Procedure
  - Requirement tags (GENSYS-0034)
  - Standards references (ISO11608-1 5.4g)
- Best Practices and Challenges:
  - Reliability
  - Create methods and templates – Stop repeating work
  - Integration testing
  - Placebo versus Drug Product
    - Testing with vendors and materials limitations

Verification Reports

- Data analysis plans
- Content
  - Requirement tags (GENSYS-0034)
  - Standards references (ISO11608-1 5.4g)
  - Pass/Fail
  - Deviations and Discrepancies
  - Do not disposition
- Create templates
- RA ←→ Engineering - Avoid re-writing for filing

Common Verification Evidence

- Injection Time
- Dosage Accuracy
- Injection Depth
- Atmospheric pressures
- Temperature Testing
- Drop testing
- Transportation testing – including atmospheric conditions
- Accelerated Aging
- Real-time Aging
- Standards-based testing

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Driving Standards Through the Combo Product Process

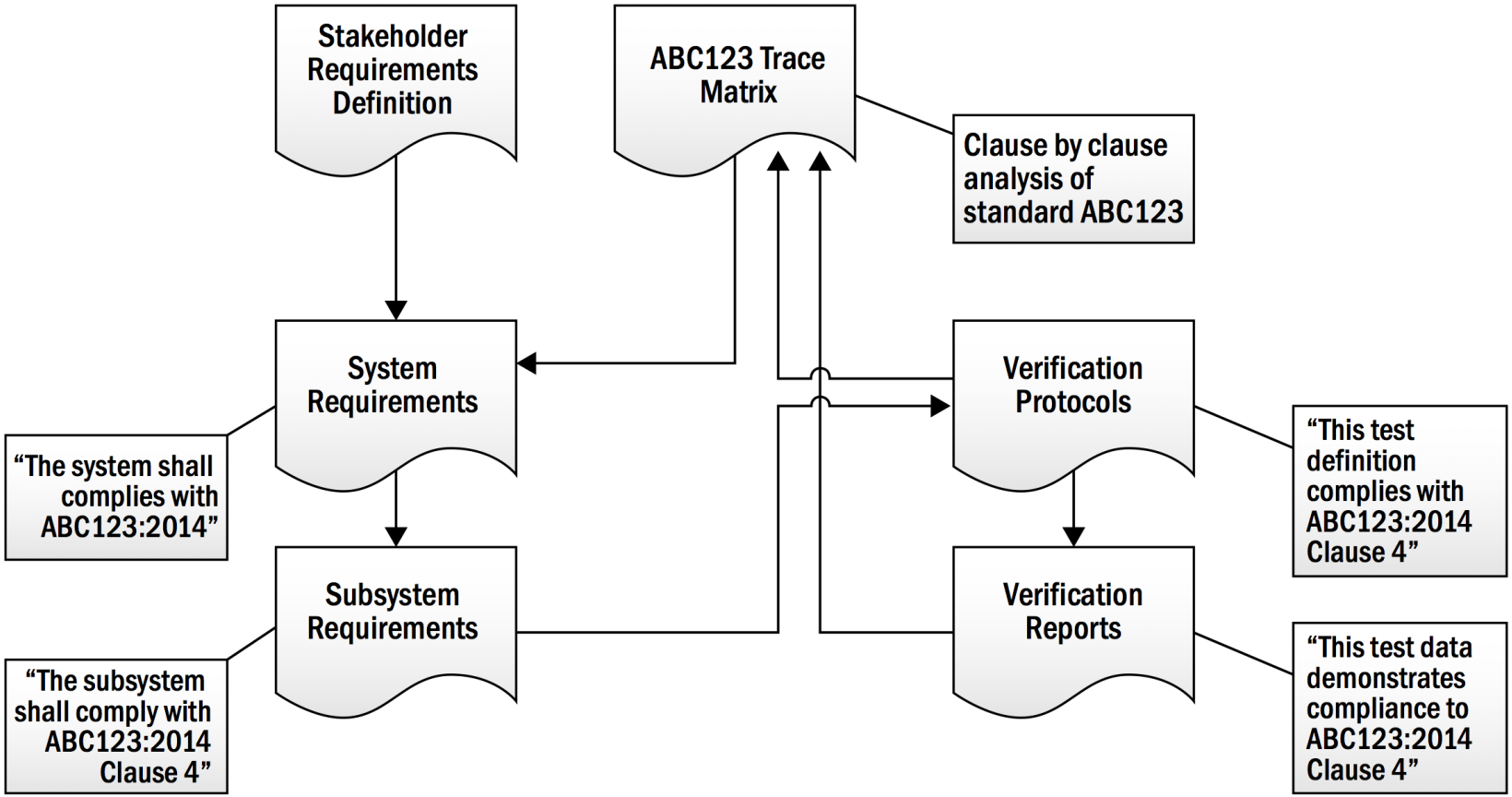


Figure 1. Model of standards throughout medical device program documentation

Badelt, Atherton, 2014

Standards Driven Verification

- ISO11608
  - Sets requirements
  - Sets test methods
  - Define test limits – k values

Autoinjector Combination Product ISO 11608-1 Applicable Requirements			
ISO 11608-1 Section/ Clause ID	**11608-1 Title**	**Applies**	**Evidence/Trace (To be filled in during V&V Phase)**
5.5 v)	Biocompatibility	A	
5.5 w)	Test method without acceptance criteria	A	
6	Reagent and apparatus	N/A	Header
6.1	Gauge R&R	A	
6.2	Use drug product or equivalent for testing	A	
6.3	Balance has 1% resolution	A	
6.4	Test surface for free-fall testing	A	
7	Determination of dose accuracy	N/A	Header
7.1	Dose accuracy matrix	A	
7.2	Dosing regions	N/A	Autoinjector is single dose
7.3	Dose settings	N/A	Header
7.3.1	Multi-dose containers (system designations A and C)	N/A	Autoinjector is single dose

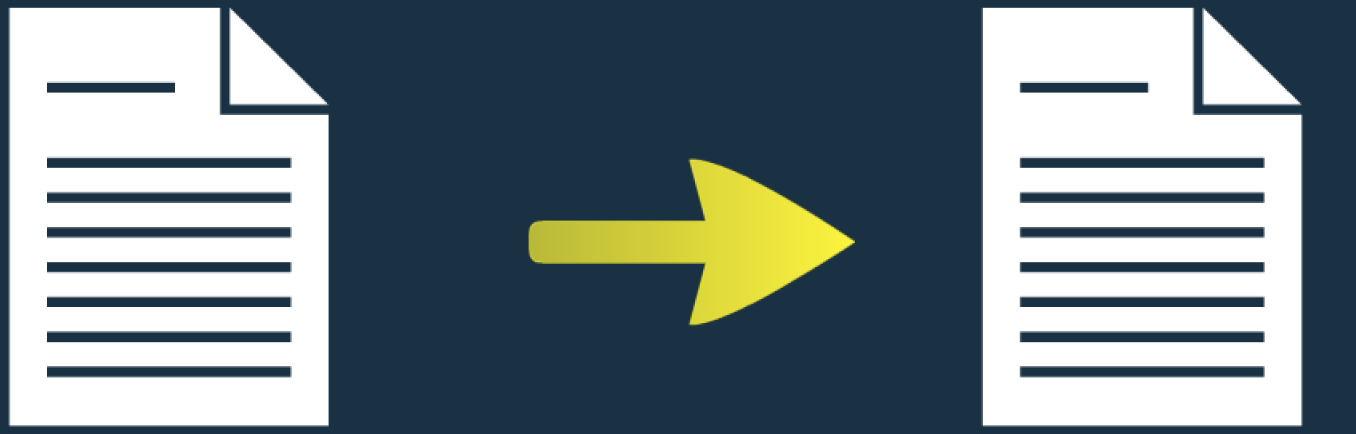
Standards Driven Verification

- Pros and Cons: In-house versus Certified Test Labs
- Within the system requirements - List of what applies:
  - ISO 11608-1
  - ISO 11608-5
  - ISO 23908
  - ASTM D4169
  - ISO 10993-1 - Evaluation and Testing
    - ISO 10993-5 - Cytotoxicity
    - ISO 10993-10 – Sensitivity and Irritation
  - IEC60601-1 – Electromedical devices
- Caveat – Follow standards, but take a risk-driven approach

820.30(g) – Design Validation

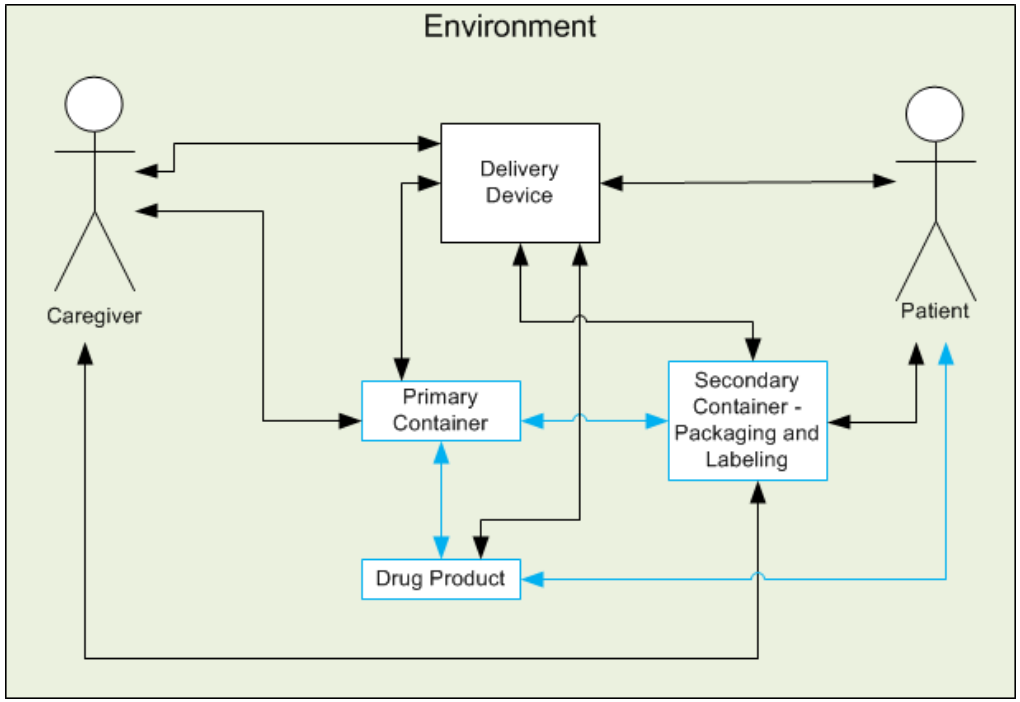
- Each manufacturer shall establish and maintain procedures for validating the device design.
- Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, of their equivalents.
- Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions.
- Design validation shall include software validation and risk analysis, where appropriate.
- The results of the design validation, including identification of the design, method(s), the date, and the individuals9s) performing the validation, shall be documented in the DHF.

User Needs (Outcomes) Level



Sources of Validation Evidence

- Clinical Trials
- Human factors analysis
  - Be careful adding onto your summative



DHF

- Plans
- Requirements
- Risk Management File
- Specifications
- Verification Reports
- Verification Protocols
- Validation Protocols
- Validation Reports
- Usability Engineering Summary File
- Change Control Records

Post-Approval Changes

- Common problems in the verification “story” come from poor requirements.
- Assuming a vendor specification as your requirement can lead to problems
- Appropriate identification of the correct requirement allows for assessment of the design change against that requirement