INTEGRATION OF ISO 11608 INTO A CLINICAL DEVELOPMENT PROGRAM:

Challenges & Pitfalls from the Real World

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Academic & Professional Qualifications:

- B.S. Biomedical Engineering, University of Minnesota
- M.S. Technology Commercialization, University of Texas
- ASQ Six Sigma Green Belt

Carolyn has 10+ years of experience in the Medical Device and Combination Product industries, including 6 years at the FDA leading the Infusion Devices team and a multi-disciplinary background including engineering, software, cybersecurity, human factors, and business. She has participated in over a dozen international standards (infusion devices, needle-based injection systems, on-body delivery systems, and infant incubators) and has been instrumental in working with products without established performance or regulatory standards (pediatric medical devices, novel on body drug delivery systems, and rare disease CPs).

AGENDA

01 **Integration of ISO 11608 – The Role of Regulatory Affairs**

How can RA professionals be an advocate when new standards arise for combination products

02 **Challenges & Pitfalls – Cross-Functional Alignment**

Helping development teams understand how standards are leveraged by regulatory authorities

03 **Challenges & Pitfalls – Importance of Risk Management**

How Risk Management Principles are leveraged in ISO 11608

04 **Challenges & Pitfalls – Timing it Right**

Planning for the time it takes to complete the testing

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INTEGRATION OF ISO 11608 – REGULATORY AFFAIRS

THE ROLE OF REGULATORY AFFAIRS

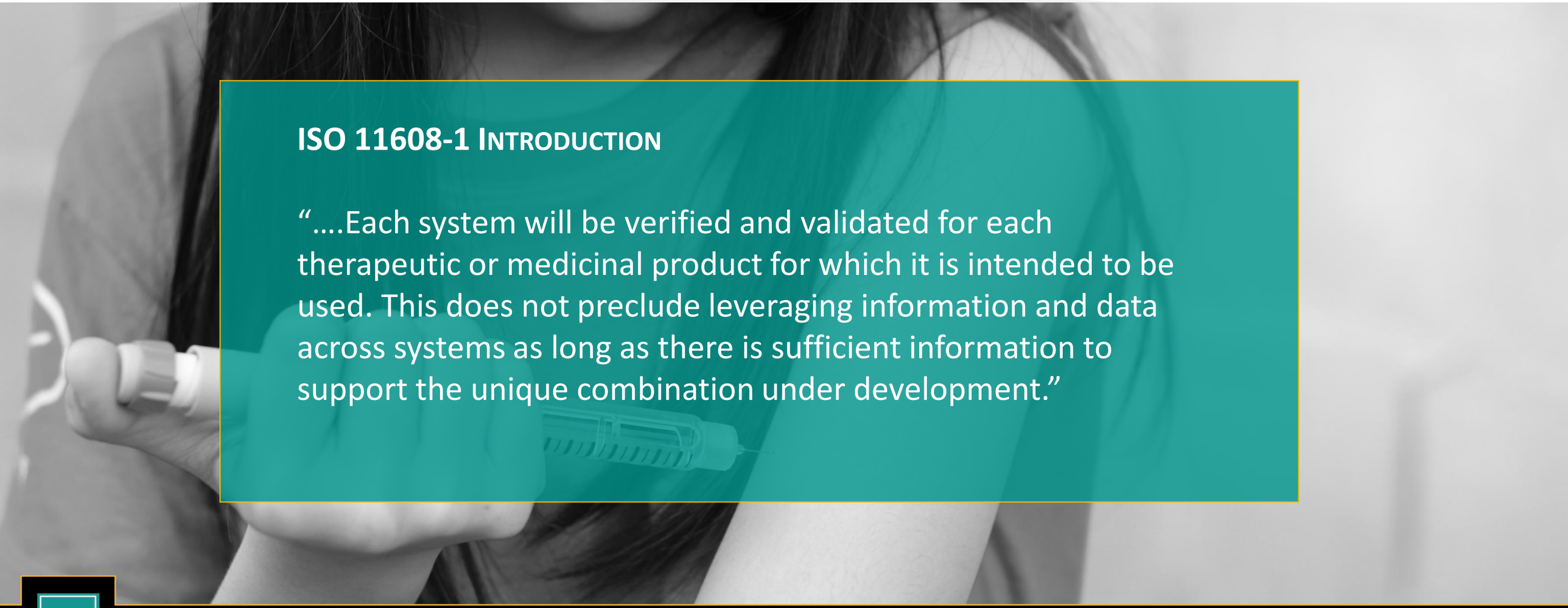
RA Professionals create awareness of new standards and inform testing strategies, in addition to crafting regulatory arguments for compliance with standards usually after the device design is completed. RA facilitates alignment cross functionally.

Perception versus Reality

- RA slows down commercial timelines
- Too much documentation
- Why do I need to justify my design – it works fine
- Following the regulations is too burdensome

- Reduce regulatory risk which can avoid delays in approval
- Can actually minimize documentation if applied appropriately
- An opportunity to make sure the device is still state of the art – continuous product improvement
- Support a culture of quality initiatives within a company

SPECIFIC CHALLENGES WITH INTEGRATION OF ISO 11608



ISO 11608-1 INTRODUCTION

"….Each system will be verified and validated for each therapeutic or medicinal product for which it is intended to be used. This does not preclude leveraging information and data across systems as long as there is sufficient information to support the unique combination under development."

WAYS YOU CAN BE AN ADVOCATE

- Connect integration of new standards to reducing regulatory risk (= $$)
- Stay abreast of changes to standards and push for conformance ahead of regulatory authority recognition
    - Provides a head start in implementing change
    - Anticipate risks in the development timelines
- RA create standard templates for applying standards
- Push for regulatory affairs active participation in design and phase reviews
- Establish and maintain relationships between device supplier & pharma/combination product manufacturer

LET'S TAKE IT TO THE REAL WORLD:
CHALLENGES & PITFALLS

CHALLENGES & PITFALLS FROM THE REAL WORLD

Scenario:

The device is already designed as a platform – I know it won't meet the more rigorous drop test requirement. Regulatory is pushing for a redesign, development teams state the design is fixed, manufacturing has already been validated and we have 2 drugs in the pipeline to use this device in phase 3 clinical studies in the next year.

Cross Functional Alignment

Helping development teams understand how standards are leveraged by regulatory authorities.

Risk Management

How Risk Management Principles are leveraged in ISO 11608.

Timing it Right

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CROSS FUNCTIONAL ALIGNMENT

How can we proactively create alignment?

- Consider standards during design inputs phase
- Use the to be marketed device in Phase 3 clinical studies
- Limit post-clinical design changes
- Take a risk-based approach to arguing requirements
- Determine the primary function at a high level, in coordination with drug stakeholders
- Company-wide education on how standards are actually used by Regulatory Authorities

This is an evolving field and even the most proactive companies can still face challenges

CROSS FUNCTIONAL ALIGNMENT

What if we must be reactive?

- Address these challenges as early as possible and in full communication with partners and cross-functional teams.
- Limit the intended use and do design changes as a lifecycle management activity
- Consider other device options with minimal risk impact of switching
- *LAST RESORT:* Use this to justify deviations, exclusions, substitutions and omissions (obtain concurrence from the appropriate regulatory authority)
    - *"However, it makes it difficult to make a general declaration of conformance to the document. As such, when making any declaration of conformance to this document, specify these deviations, exclusions, substitutions, and omissions supported by adequate justification in the design file."*

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WHAT DOES ISO 11608 SAY ABOUT RISK MANAGEMENT

"Because of the anticipated variation in the designs of NISs, this document tends to specify the results of the design effort instead of the physical and construction requirements used as the basis for NIS design."

"Finally, manufacturers are expected to **follow a risk-based approach** during the design, development, and manufacture of the NIS. … It is expected that a risk management process is applied to justify and document:

- **any exclusions/deviations from requirements, specifications, methods or limits** contained in or referenced in this document when they are not directly applicable and/or appropriate to the system. These new or modified requirements can be more or less restrictive as they are unique to the specific NIS (including the medicinal product); and
- **any substitutions or omissions of requirements, specifications, methods or limits** unique to each specific NIS (including the medicinal product), when those provided in this document are not applicable and/or appropriate to the NIS."

INTEGRATION OF RISK MANAGEMENT IN ISO 11608

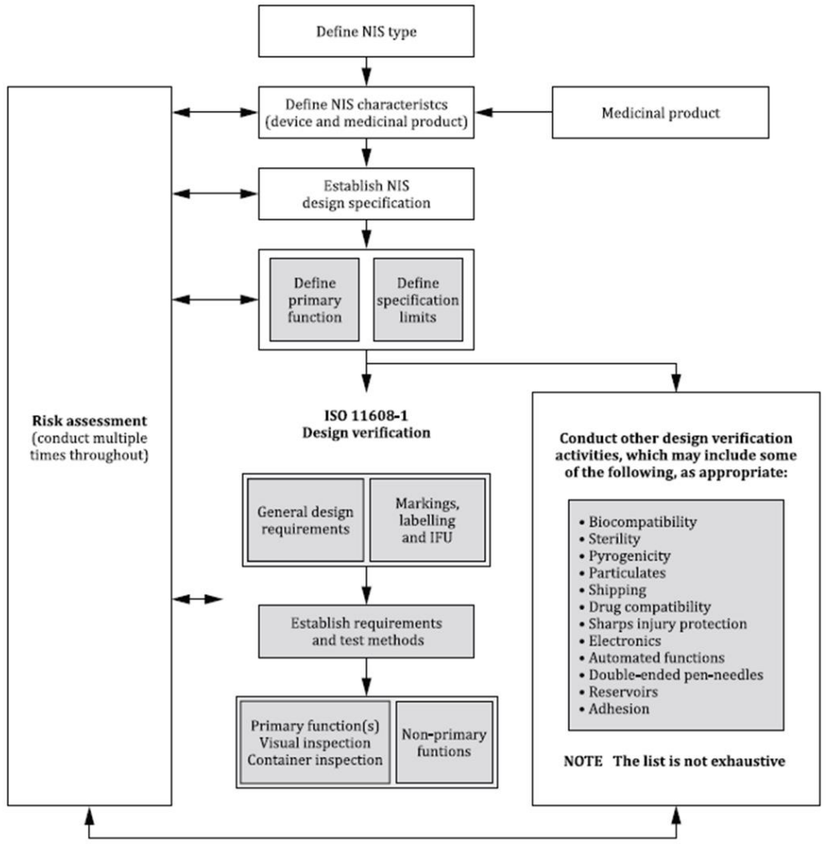

Figure 2 — Design verification flow

- Primary Functions and testing is driven by risk assessments
- Risk evaluation is intended to be an input and output of all major milestones of the ISO 11608 series.
- Inadequate risk assessment at early stages can create significant downstream impact.
- Develop holistic risk management procedures

Key takeaway:

Starting risk management prior to device selection reduces project risk

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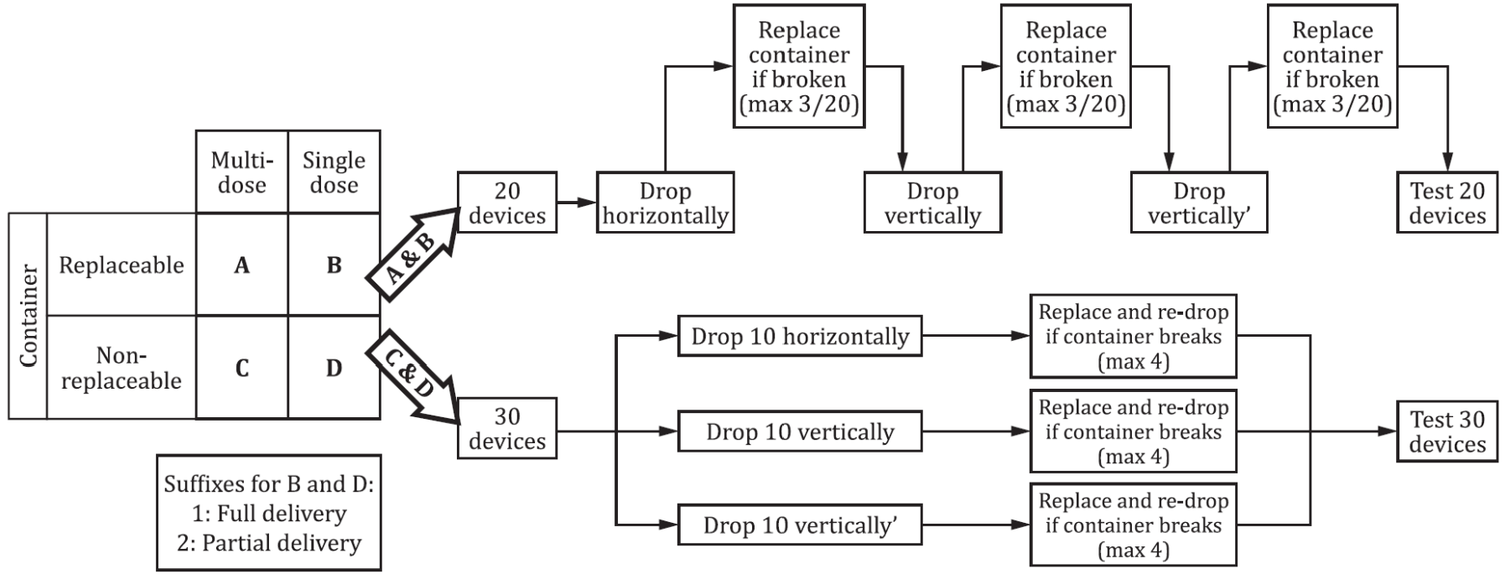
TIMING IT RIGHT

ISO 11608-1 Introduction:

"Because of the anticipated variation in the designs of NISs, this document tends to specify the results of the design effort instead of the physical and construction requirements used as the basis for NIS design."

- Many requirements, such as the drop test and particulates are more rigorous
- Increased number of test conditions (as many as 13 conditions applicable)
- Primary Functions must be tested after pre-conditioning and aging and may include at the maximum, minimum and median values.
- Confidence is at least 95% *unless specified as part of a risk assessment

TIMING IT RIGHT – EXAMPLE DROP TESTING



NOTE "vertically" and "vertically'" (with apostrophe) represent the two vertical orientations described in 10.3.1.

Figure A.1 — Free fall testing for various NIS system designations

TIMING IT RIGHT

ISO 11608-1 Introduction:

"The ISO 11608 series includes requirements for design verification of the NIS's conformance with its design specification. The sampling plans, preconditioning criteria and other aspects of testing specified in these documents are intended to verify the design at a high confidence level. They are not intended to stipulate lot release acceptance criteria (AQL, p-content, probability, etc.) associated with a manufacturing process. …. Finally, it develops the requirement for functional stability and offers additional statistical approaches (e.g. use of variable and attribute data) in satisfying the various NIS design verification requirements."

- Average time to verify compliance with ISO 11608 ranges from 3 to 8+ months based on the complexity of the design (excluding real time aging)
- Aim to get testing done prior to Phase 2, Phase 3 or Bridging Studies to reduce regulatory risk – this is where RA should be involved in clinical timelines

RECAP

Be an advocate
for proactive engagement

Work cross functionally
to educate and plan in a changing regulatory environment

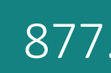
Early + often
is critical for understanding and communicating testing expectations

Involvement in standards committees
reduces program risks

Be smarter about what is justified
risk-based approach ≠ no design changes

With Suttons Creek on your team, quick advice, proven processes and up-to-date knowledge are just a phone call away.

Our team would be happy to be of service.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