Safety Assurance Cases
for
Infusion Pumps:
Lessons Learned

Richard Chapman
FDA
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The Problem

• In 2005-2006, FDA formed a working group to develop recommendations to reduce the number and severity of infusion pump recalls. The efforts of this group culminated with the Infusion Pump Improvement Initiative of April 2010.
• The improvement initiative included a guidance document, which increases the premarket review requirements for pumps as a means to improve safety of these devices.

• www.fda.gov/infusionpumps
External Infusion Pump Guidance

- The new infusion pump guidance steers manufacturers to the top level safety claims based on a comprehensive analysis of the hazards associated with the use of infusion pumps.

- The guidance does this by recommending the use of ASSURANCE CASES to organize the content of 510(k) premarket submissions.

External Infusion Pump Guidance

- New draft Special Controls Guidance in ...?...Soon
  - Incorporates lessons learned and industry comments
  - Industry will have another opportunity for comment

What has changed?

- Reorganized – the bulk of the guidance is now under the Assurance Case
- Use Errors/Human Factors within assurance case framework
- Risk Management Report eliminated
- The need for a Clinical Evaluation (or not) is an output of your safety case analysis
The Confidence Argument

• A New Approach to creating Clear Safety Arguments
  Richard Hawkins, Tim Kelly, John Knight and Patrick Graydon

The Confidence Argument

• FDA assumes you have a Quality System in place and that you are following the Quality System Regulation and practice Design Controls

The Confidence Argument

• "We also asked that you include a confidence argument in order to assure that the list of hazardous situations for your device is complete. Your response letter simply states that you are confident that the hazards analysis is complete. The purpose of the confidence argument is to demonstrate that sufficient analysis has been conducted on similar systems to assure that known hazards have been identified. Please update your confidence argument to describe the inputs into your hazards analysis."
510(K) AND SCIENCE REPORT
RECOMMENDATIONS:
• Original: CDRH should adopt an assurance case framework for 510(k) submissions.
• Modified: We plan to implement an assurance case pilot program for infusion pumps, conduct an assessment of the pilot, and then seek public input before determining next steps to assure that we proceed in a way that addresses the concerns raised in public comments.

On-going Efforts within FDA
• OSEL/DESE – Generic Infusion Pump
  – PCA Pump
  – Insulin Infusion Pump
  – Collaboration with Academics
• GHDB – “Accelerating clearance of 510(k) MCM devices through the use of safety assurance case templates” – Syringes, needles, catheters.
• GHDB/DESE – Software deficiencies in safety case terminology

On-going Efforts within FDA
Discussion with other groups within FDA.
Staff College Training opportunities.
Collaborate with AAMI and ADVAMED
Safe and Effective

Reasoning

- Legal system
  - Risk based / Logical
    - Reasonable suspicion – temporary loss of liberty
    - Probable cause – arrest
    - Beyond a reasonable doubt – Loss of life or liberty
    - Civil court – preponderance of evidence – loss of money
- Scientific Method
  - Hypothesis
  - Experiments, methods, to test the hypothesis
  - Statistical measures of the reliability of data
  - Discussion and conclusions

Safety Assurance Framework

- A process for distilling the REASONS for product integrity from the totality of activities and resources employed to realize it.
- … and for making an argument as to why the evidence, your test data and analyses, supports the claims
What is a Safety Case?
A structured argument, supported by a body of evidence, that provides a compelling, comprehensible and valid case that a system is safe for a given application in a given environment.

- This type of assurance case contains a structured argument (rationale) demonstrating that the evidence it contains is sufficient to show that the system is safe.
- The argument is commensurate with the potential risk and the system’s complexity.

Safety Engineering
- The safety assurance case is a method for reasoning about systems appropriate for scientists and engineers.
- A safety case is the best way to both document and review a submittal based on a risk management approach because the argument shows the proportionality of the mitigation.

Safety Engineering
- Safety Case
  - Claims
    - Top Level Claim – Infusion pump is reasonably safe and effective for its intended use.
    - Users
    - Environment
  - Evidence
  - Arguments
How does this relate to FDA premarket processes

- A 510(k) is mostly a checklist
- FDA asserts that we know what we want
- Sponsor just follows the checklist
- Once upon a time a checklist was a way to assure coverage and completion and equitable application
- As systems become more complex this becomes less true

So what do premarket technical regulators really look for?

What the design trade-offs actually were:

- Are they safe?
- Who made them and stands by them?
- Why they were made this way?
- How they were verified as the right ones?
- Can they be reeled back if something goes wrong later?
- Are they at or near the currently accepted state of the art?
- Can manufacturing realize the product once approved with the same trade-offs?
- Will they persist in continued use?

Hazard Analysis

- Start with the hazards and hazardous situations
- The claim is that you have mitigated the hazard or the hazardous situation.
- Determine the properties of the system that will make it safe.
- Generate safety requirements
Hazard Analysis

- Hazard Analysis
  - ISO 14971 – Application of Risk Management to Medical Devices

Evidence

- Lack of clear definition of evidence and how to evaluate it:
  - Guidance Documents, Standards
  - Checklist
    - Presence versus quality
  - Domain Experts
- Evidence is:
  - Test data
  - Results from experiments
  - Historical performance
  - Compliance with standards
  - Analysis
  - Scientific and engineering information from the literature

What is a Safety Argument

- This infusion pump is safe because
  - The safety requirements are defined in my
    - Safety requirements analysis, derived requirements ...
    - Legislation, policy ...
- The safety requirements are met through our
  - Safety analysis of design, use ...
  - Hazard management through problem reporting
  - Observing failures are at a 'safe' level
  - Appropriate quantity, quality and rigor of evidence
- Safety management continues to be adequate because we have
  - SMS
  - staff competence
  - ongoing independent scrutiny ...
Format

- Narrative
- Tabular
- Graphical

- All are acceptable formats
- Tools – any are acceptable

Graphical representation

Safety Case Reports

- The Safety Case
  - A complex body of interdependent and evolving documentation
  - Created and managed by the manufacturer
  - Not easily auditable or reviewable

- Safety Case Reports
  - A ‘snapshot’ of the rationale and content of a safety case at an appropriate milestone
  - Shows that any arbitrary set of requirements has been met
Safety Case Reports
- Reviewable against the project expectation at the milestone
- May need several report types for various stakeholders
- May need several updates over time

Implications for manufacturers
- The Safety Case will evolve over the life of the system
- While the structure of the Safety Case will broadly remain constant,
  - the status of the evidence will change, e.g., planned test coverage will be replaced by evidence of test results
  - the relative weight of the arguments may change, e.g., compliance with a process standard might be replaced by proven in use
- Therefore plan for multiple reports
  - Obtain agreement on the argument structure first
  - Use identification of evidence as management tool

Problems
- Unjustified Arbitrary specifications
- Claims with no evidence
- Biocompatibility and Sterilization
- Software Anomalies
- Labeling
- Validation Testing
- Failure to comply with Standards
- Failure to address issues associated with MDRs and Recalls
Problems

• Human Factors
Deficiencies

• “There is no context provided for the top level claim to define the indications for use, which include drug type, route of administration, user population, use environments for which safety is being assured.”

Deficiencies

• “The safety case does not identify safety related requirements implemented to control hazards (e.g., dose accuracy, dose continuity, air-in-line, occlusion, etc.) and does not argue why these safety requirements are reasonably acceptable within the context of the indications for use, operating environments and users.”

Deficiencies

• “The evidence supporting the safety claims have not been provided within your 510(k). Please provide the evidence identified within your safety assurance case.”
Deficiencies

- “Mitigations are identified. However, no argument as to why the mitigation is comprehensive and appropriate is included.”

What can FDA do to help

- Redacted deficiencies?

Examples

  - Infusion pump specific
    - [http://www.sei.cmu.edu/reports/09tn018.pdf](http://www.sei.cmu.edu/reports/09tn018.pdf)
Suitability of Evidence

Assurance (of a Requirement for Evidence) The degree of confidence that the set of safety evidence satisfies the requirement for evidence.

- Relevance - The extent to which an item of evidence entails the requirement for evidence
- Trustworthiness - The perceived ability to rely on the character, ability, strength or truth of the evidence
- Independence - The extent to which complementary items of evidence follow diverse approaches in fulfilling the requirement for evidence
Suitability of Evidence

**Relevance** - The extent to which an item of evidence entails the requirement for evidence

- **Directness** - The extent to which an item of evidence directly fulfills the requirement for evidence
  - Direct – e.g., timing data
  - Indirect – e.g., competence of personnel
- **Coverage** - The proportion of the requirement for evidence which the evidence addresses
  - Thorough – e.g., a technique which provides evidence of the handling of all runtime exceptions
  - Less thorough – e.g., a technique which provides evidence of the handling of divide by zero

**Trustworthiness** - The perceived ability to rely on the character, ability, strength or truth of the evidence

- The trustworthiness of evidence is an expression of the process evidence related to generating the evidence. These factors include, but are not limited to:
  - “Buggy-ness” – how many “faults” there are in the evidence presented;
  - Level of review;
  - For tool-derived evidence: Tool Qualification and Assurance;
  - Experience and Competence of the personnel.

**Independence** - The extent to which complementary items of evidence follow diverse approaches in fulfilling the requirement for evidence

- Independent - Manual code inspection and static analysis are independent methods to eliminate software defects
- Not Independent - Human factors testing by software developers is the fox watching the henhouse
Argumentation

The action or operation of inferring a conclusion from propositions premised.

- **Premise** - A previous statement or proposition from which another is inferred or follows as a conclusion

- **Conclusion** - A judgment or statement arrived at by any reasoning process
  - Deductive - If premises are true, then the conclusion must also be true
  - Inductive - The conclusion follows from the premises not with necessity but only with probability
  - Abductive - Inference to the best explanation
  - Argument by Analogy

- Beware of logical fallacies
  - Argument by analogy
  - Drawing the wrong conclusion
  - Omission of key data
  - Etc.

- The strongest arguments are both valid and sound
  - **Valid** - If premises are true, conclusion is true
  - **Sound** - Argument which is valid and has true premises

- Weaker Argument
  - **Consistent** - If premises are true, conclusion may be true. True with some probability.