

# Introduction of Assurance Case Method and its Application in Regulatory Science

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# Introduction of GessNet™

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We provide cutting-edge software tools and expert consulting for medical product risk management.

We help medical device and drug manufacturers to gain and sustain a competitive advantage in product quality, safety, cybersecurity, innovation, time to market, productivity, and regulatory compliance.

# Problem for Regulatory Science to Solve

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Reduce regulatory burden and time-to-market for products requiring FDA oversight while ensuring the safety and efficacy of the products.

# Common Challenge in Regulatory Science

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## **Practice:**

- Industry provides the data (e.g. clinical data, specs and reports), and regulators review and analyze the data, and draw a regulatory conclusion.
- The data is provided in certain formats that don't directly point to why the desired conclusion should be drawn, or how the data collectively supports the desired conclusion.

## **Challenge:**

- Data set is large and becoming increasingly complex as medical products advance (e.g. Drug with AI driven delivery system).
- The time and effort needed for the regulators to review, connect the dots, and draw the conclusions is challenging, especially with user fee goals and innovation initiatives.

# Assurance Case – An Excellent Tool for Overcoming the Challenge

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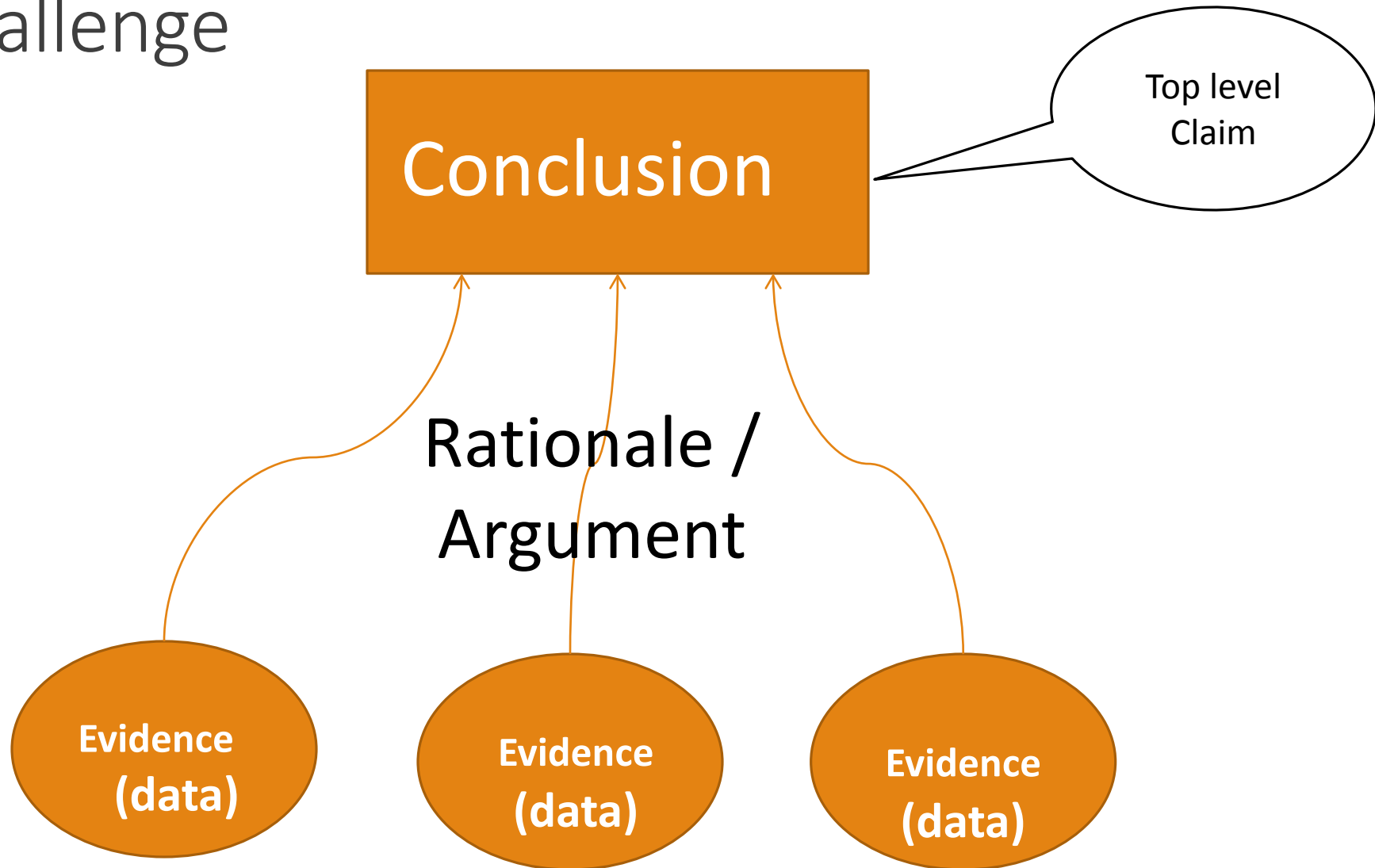
## Assurance Case

*A documented body of **evidence** that provides a convincing and valid **argument** that a specified set of critical **claims** (assertions) regarding a product/system's properties are adequately justified for a given application in a given environment.*

## Safety/Efficacy Assurance Case (Safety/Efficacy Case)

*A structured argument, supported by a body of evidence, that provides a compelling, comprehensible and valid case that a product is safe/effective for a given application in a given environment.*

# Assurance Case – An Excellent Tool for Overcoming the Challenge



# Assurance Case is The argument

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The argument (rationale) is the entire set of claims and all the associated elements that exist between the evidence and the conclusion. This creates a sequence of claims the truth of each following from the previous claim.

The argument provides structure and organizes the data so that the data provides support for the theory that leads to the conclusion.

# Assurance Case Terms

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**Conclusion** – top level statement we want the reviewer to accept

**Claim** – an assertion about the product/system

**Context** – information about the product/system including use and environmental conditions

**Assumptions** – items commonly agreed on, uncontested claims

**Argument** – a reason put forward in support of a point of view

**Evidence** – Data



# Example of Claims and Sub-Claims

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## Top Claim:

Combination product (e.g. iDose- a generic drug administered by a “patch” pump) is adequately safe for its intended use

## Sub-claims:

1. The generic drug (abc) provides the same clinical benefit as the RLD
2. The risks associated to the combination products are reduced to an acceptable level
3. ....

# Types of Reasoning - Approach

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**Deterministic (deductive)** – the validity of the claim can be established from logical assertions using axioms and proofs

**Probabilistic (inductive)** – the validity of the claim can be justified from the probabilities given by the supporting evidence

**Qualitative (abductive or defeasible)** – the validity of the claim is the best explanation for the evidence and so it is presumed true until there is cause to not believe it

# Confidence Argument

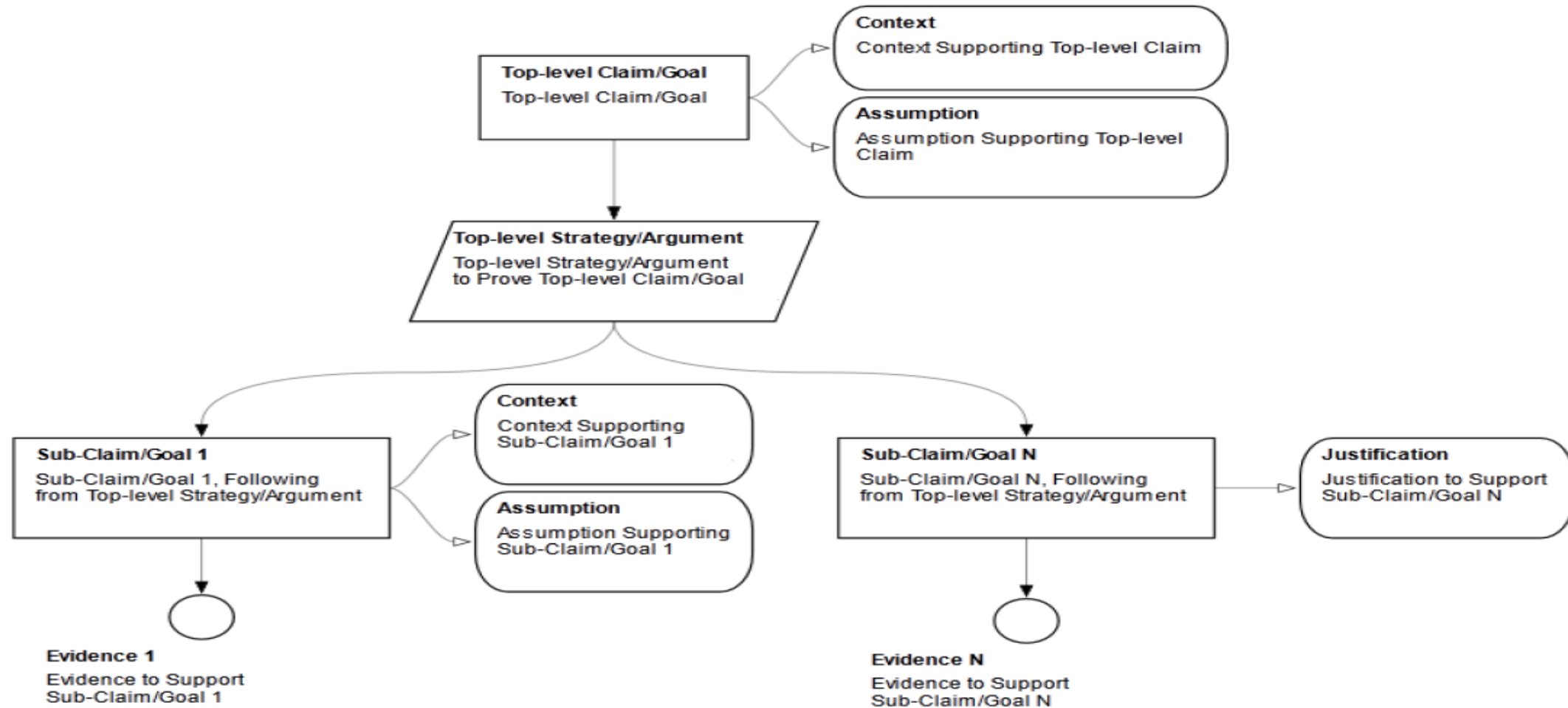
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## Justification on the Reasoning

**Example for Confidence in Evidence:** An expression of the process related to generating the evidence, including but not limited to:

- For testing/analysis results: test/analysis method validation, sample size justification etc.
- For tool-derived evidence: tool qualification, validation, and assurance
- Experience and competence of the personnel

# Assurance Case General Form



# Example: Safety Assurance Case for Drug Delivery Infusion Pump Pre-Market Submission (FDA TPLC Infusion Pump Guidance and AAMI TIR38)

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## Claim

The device design is adequately safe for its intended use, use conditions and use environments

## Context

- What device? - as defined/specified by intended use, device specs etc.
- What is different/changed (e.g. new user interface)?

## Argument

- A. Device design is adequately verified and validated
- B. Risks are identified and mitigated
- C. Device is adequately reliable to ensure safety over its operational time

# Example: Infusion Pump Safety Assurance Case Argument Structure – Graphical Format

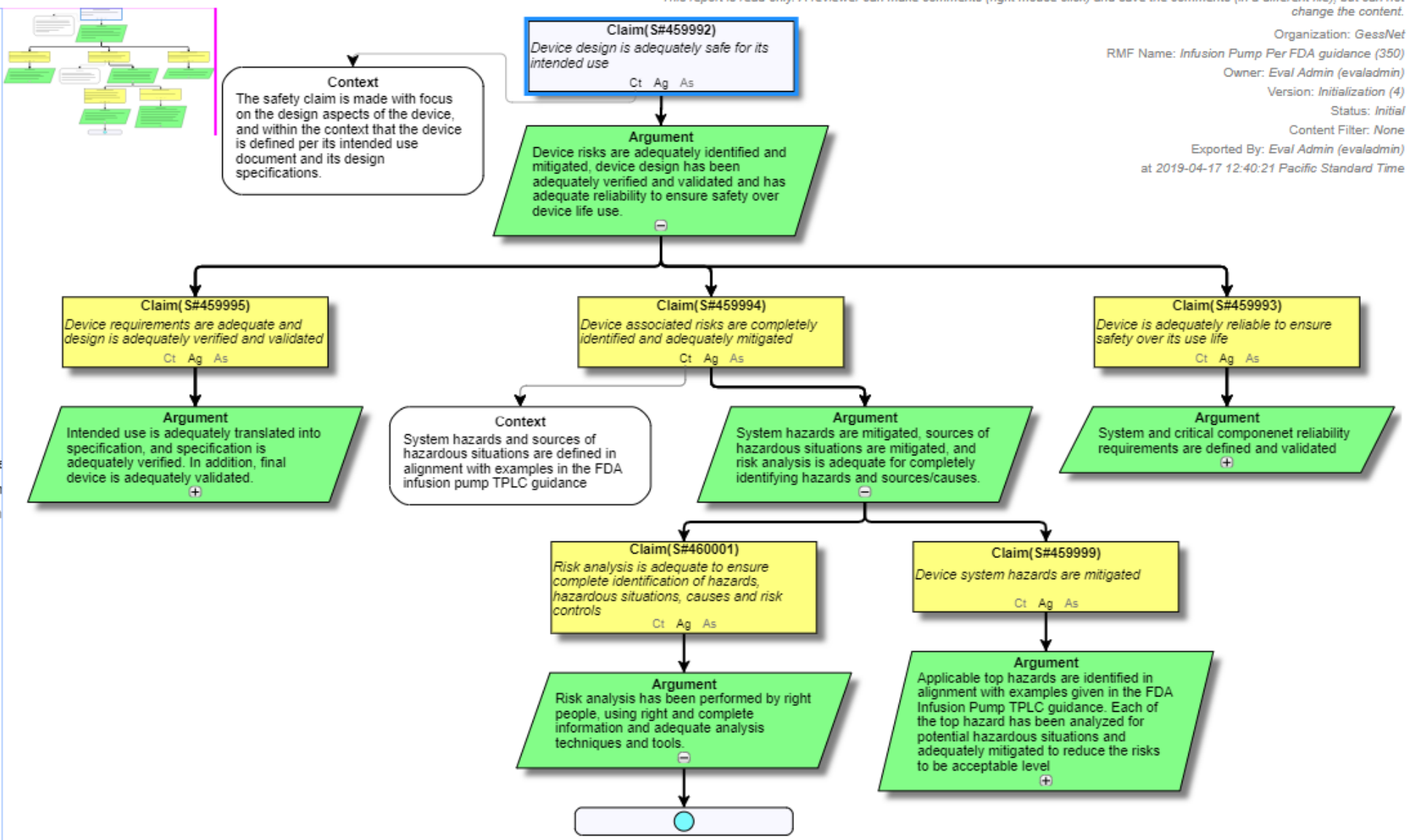
Key word or ID Search Clear Show Comments Save with Comments

Assurance Case Report generated by TurboAC™ Software. © GessNet™

Heat Map















Ph \ Seve	TBD	Not Appli	Negligibl	Marginal	Significa	Catastro
TBD	3	0	0	0	7	0
Not Appli	0	0	0	0	0	0
1: 1-1	0	0	0	0	0	0
2: 2-2	0	0	0	0	0	0
3: 3-3	0	0	0	0	0	0
4: 4-4	0	0	0	0	1	0
5: 5-5	0	0	0	0	0	0
6: 6-6	0	0	0	0	0	0

- + Safety Harms
- Device design is adequately safe for its intended use
    - + Device requirements are adequate and design is adequately verified
    - Device associated risks are completely identified and adequately mitigated
      - Risk analysis is adequate to ensure complete identification of hazards
      - Device system hazards are mitigated
        - + (S#459991)Infusion (Delivery) Error
        - + (S#459987)Biological/Chemical Hazards
        - + (S#459988)Incorrect Therapy
        - + (S#459989)Traumatic Injury
    - + Device is adequately reliable to ensure safety over its use life



Organization: GessNet  
 RMF Name: Infusion Pump Per FDA guidance (350)  
 Owner: Eval Admin (evaladmin)  
 Version: Initialization (4)  
 Status: Initial  
 Content Filter: None  
 Exported By: Eval Admin (evaladmin)  
 at 2019-04-17 12:40:21 Pacific Standard Time

# Example: Infusion Pump Safety Assurance Case Argument Structure in Tabular Format

Assurance Case Claim: [Device design is adequately safe for its intended use]	ID	Context(Ct) & Assumption(As)	Argument	Evidence & Reference
  <i>Device design is adequately safe for its intended use</i>	S#459992	Ct: The safety claim is made with focus on the design aspects of the device, and within the context that the device is defined per its intended use document and its design specifications. As:	Device risks are adequately identified and mitigated, device design has been adequately verified and validated and has adequate reliability to ensure safety over device life use.	  (S#546688) Intended Use Doc #0125 
  <i>Device requirements are adequate and design is adequately verified and validated</i>	S#459995	Ct: As:	Intended use is adequately translated into specification, and specification is adequately verified. In addition, final device is adequately validated.	
  <i>Device associated risks are completely identified and adequately mitigated</i>	S#459994	Ct: System hazards and sources of hazardous situations are defined in alignment with examples in the FDA infusion pump TPLC guidance As:	System hazards are mitigated, sources of hazardous situations are mitigated, and risk analysis is adequate for completely identifying hazards and sources/causes.	
  <i>Device is adequately reliable to ensure safety over its use life</i>	S#459993	Ct: As:	System and critical component reliability requirements are defined and validated	

# Lessons Learned from Medical Device Safety Assurance Cases

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- *“Even the worst Assurance Cases provide much better and easier to review information than those submissions without assurance cases”*
- Have a common structure of the top level claim and sub claims established in the first place would have made the adoption process much easier. Surprisingly we might not even have a clear answer for what “the product is safe means” at high level.
- Safety Argument is incomplete without a clearly defined context of what is the product, and whether the final product is what document says (V&V).
- Assurance cases are much easier than many thought. Establishment of common argument structure and advancement of the tools for developing assurance cases has significantly reduced the man power needed.
- Use of the word of “claim” doesn’t get manufacturers into legal troubles. No manufacturers ever got into legal issues because of their use of the word claim in assurance cases.
- When being developed in parallel with the product development, the safety assurance case becomes an effective tool to assure safety. Development of Safety Assurance Cases Exercises “Whys”, and Drives Improvement in Risk Management and V&V.
- Assurance case practices have the potential to reduce regulatory burden. Assurance cases are top down and goal driven approach, which will help both the manufacturers and regulators to take a true risk based approach, rather than get buried in compliance driven paperwork.



# Hypothesis for Generic Drug Assurance Case – Argument Structure

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**Top Claim:** The generic drug (abc) is effectively substituted and provide the same clinical benefit as the RLD (Xyz)

**Sub Claims:**

1. The generic drug is pharmaceutically equivalent to the RLD.
2. The manufacturer is capable of manufacturing the drug product consistently and the process is validated.
3. The API is the same as that of the RLD.
4. The generic drug is bioequivalent to the RLD.
5. The excipients, used in the generic drug are safe.
6. The drug is stable within the expiration date, when stored under labeled conditions.
7. The container/closure system and/or delivery system in which the drug product is safe and delivery the drug when administered per instruction for use.
8. The prescribing information is the same as the RLD's.

# Final Thoughts

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- 1. Uses of Assurance Cases in Premarket can reduce time-to-market.** Assurance case is an effective communication method that can improve the effectiveness and productivity of regulatory submissions and review processes.
- 2. Practices Assurance cases during Total Product Life Cycle can reduce regulatory burden.** Assurance case is a goal driven top-down approach. Constructing assurance cases involves critical thinking. When being proactively developed, the assurance case becomes an excellent tool to focus on what is truly important for the goal and assure the safety of the product.
- 3. CDER and Drug Industry should consider an assurance case pilot study, particularly on products with approval backlog, products with complexity (e.g. combination products with device constituent parts), or products that involve large amount of supporting data.**

# Other Resources/References of Assurance Case Applications

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1. Drug Delivery Combination Products
2. **Use Assurance Case method to design and predict Clinical Study thru leveraging real world evidence and/or simulation data** (researching project)
3. Cybersecurity
4. AI and Machine Learning driven Products
5. US NASA and FAA Project Safety Cases
6. Some European Countries (e.g. UK) Mission Critical Defense or Governmental Projects
7. UK National Health Service for HIT
8. Canadian eSafety Guidelines
9. Australian E-Safety Standard

**Other potential Uses** : quality control, drug pharmacology, data integrity

# Questions?

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