Introduction of Assurance Case Method and its Application in Regulatory Science

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Introduction of GessNet™

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

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

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

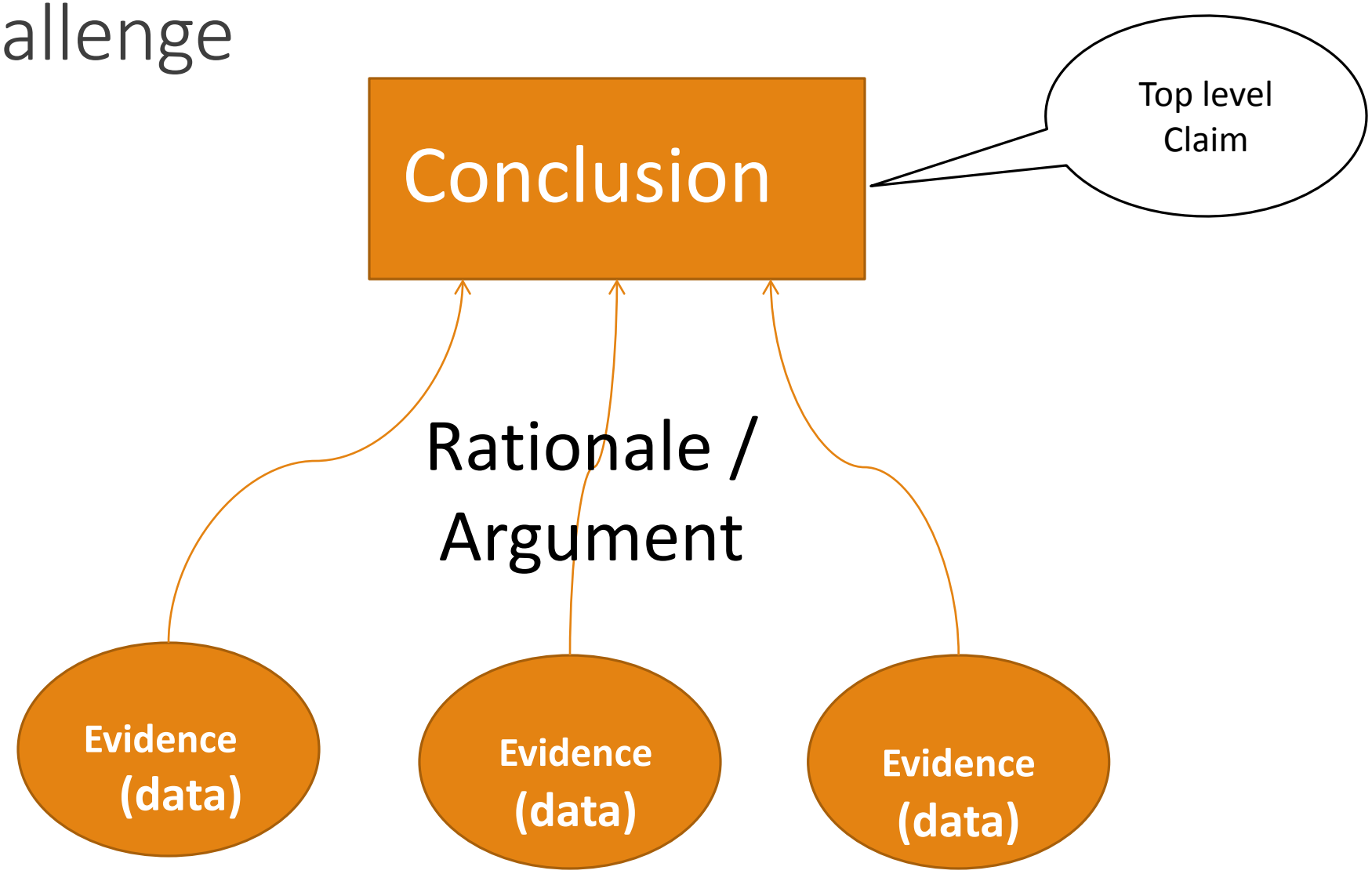
Assurance Case

*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

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

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

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

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

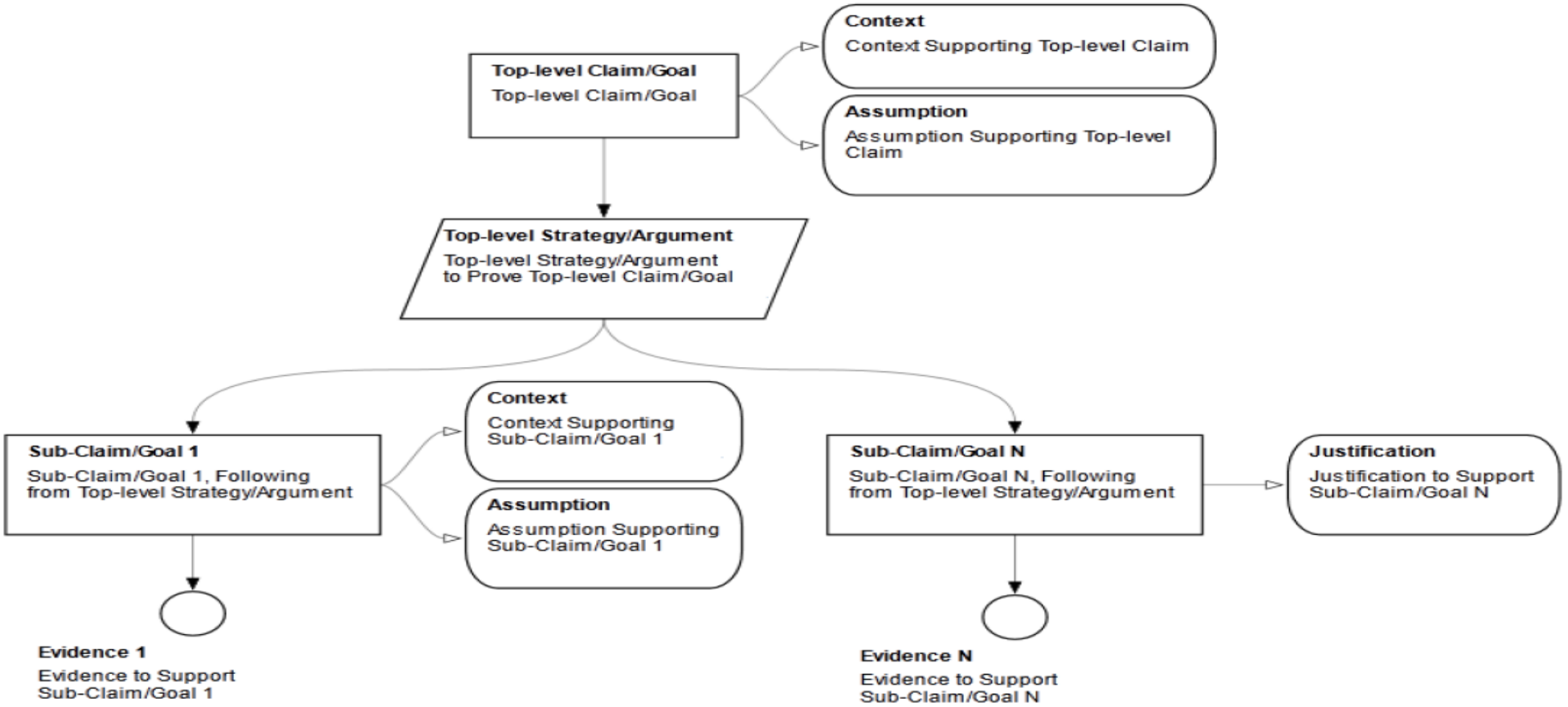
Confidence Argument

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)

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

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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*

☑ 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 verifie
  - − Device associated risks are completely identified and adequately n
    - Risk analysis is adequate to ensure complete identification of h
    - − 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

Claim(S#459992)
Device design is adequately safe for its intended use
Ct Ag As

Context
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.

Argument
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.

Claim(S#459995)
Device requirements are adequate and design is adequately verified and validated
Ct Ag As

Argument
Intended use is adequately translated into specification, and specification is adequately verified. In addition, final device is adequately validated.

Claim(S#459994)
Device associated risks are completely identified and adequately mitigated
Ct Ag As

Context
System hazards and sources of hazardous situations are defined in alignment with examples in the FDA infusion pump TPLC guidance

Argument
System hazards are mitigated, sources of hazardous situations are mitigated, and risk analysis is adequate for completely identifying hazards and sources/causes.

Claim(S#459993)
Device is adequately reliable to ensure safety over its use life
Ct Ag As

Argument
System and critical componenet reliability requirements are defined and validated

Claim(S#460001)
Risk analysis is adequate to ensure complete identification of hazards, hazardous situations, causes and risk controls
Ct Ag As

Argument
Risk analysis has been performed by right people, using right and complete information and adequate analysis techniques and tools.

Claim(S#459999)
Device system hazards are mitigated
Ct Ag As

Argument
Applicable top hazards are identified in alignment with examples given in the FDA Infusion Pump TPLC guidance. Each of the top hazard has been analyzed for potential hazardous situations and adequately mitigated to reduce the risks to be acceptable level

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
Device design is adequately safe for its intended use	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
Device requirements are adequate and design is adequately verified and validated	S#459995	Ct: As:	Intended use is adequately translated into specification, and specification is adequately verified. In addition, final device is adequately validated.	
Device associated risks are completely identified and adequately mitigated	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.	
Device is adequately reliable to ensure safety over its use life	S#459993	Ct: As:	System and critical componenet reliability requirements are defined and validated	

Lessons Learned from Medical Device Safety Assurance Cases

- *"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 clearlly 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

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

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

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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