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Roche

System Theoretic Process Analysis of a Pharmacovigilance Signal Management Process

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advancing safety **together**

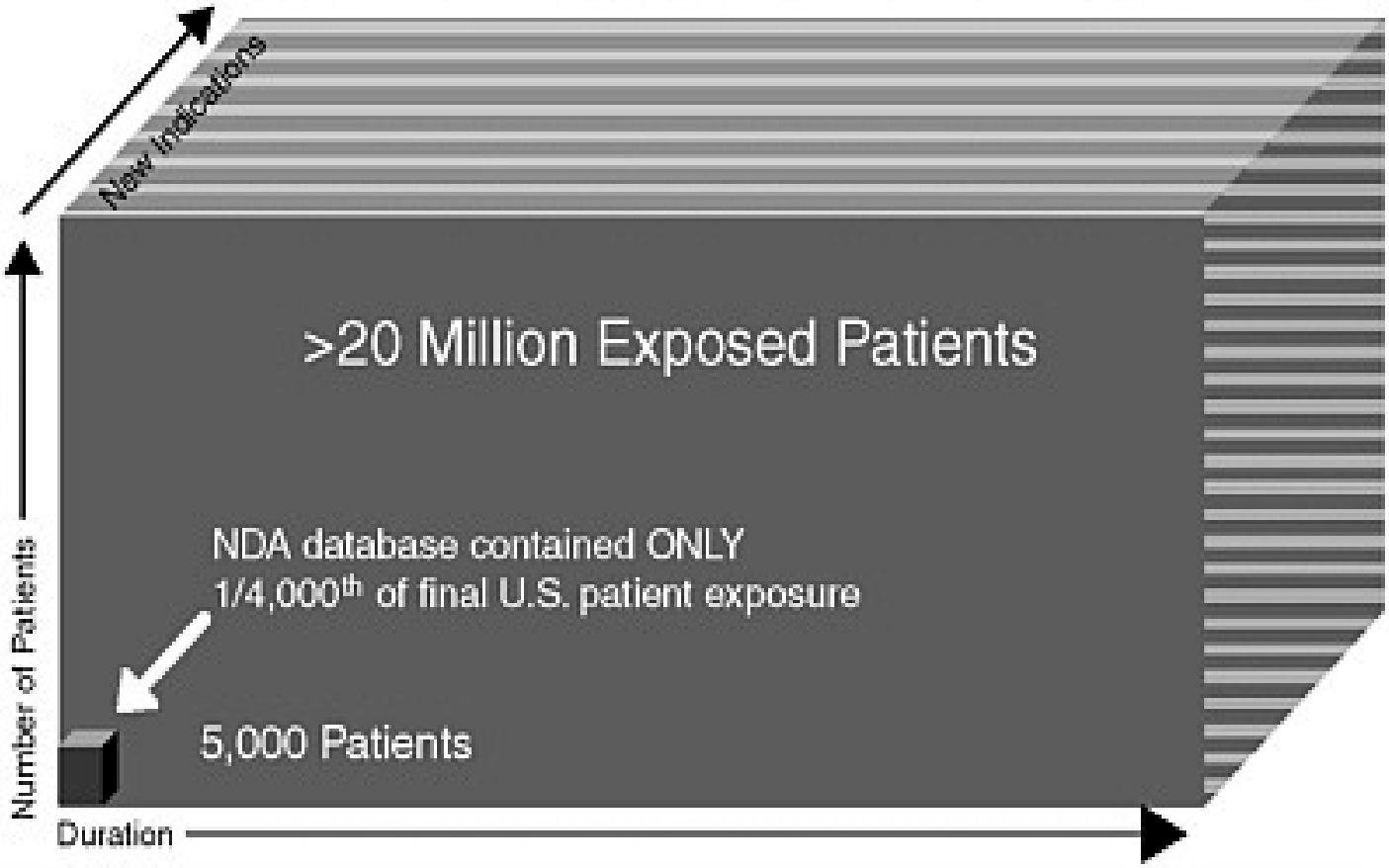
Background and disclaimer

- This presentation represents the results of an STPA analysis conducted for purposes of quality management of the Roche safety signal management process.
- Martin Rejzek and Christian Hilbes of the Zürcher Hochschule für Angewandte Wissenschaften (ZHAW) were engaged by this project as experts on STAMP and STPA.
- The analysis was conducted as a Master's Degree project for Ajibade Adesina at the University of Hertfordshire under supervision of Dr. John Talbot.
- This presentation represents the opinions of the authors and not official positions of Roche or ZHAW.

Agenda

- What is a signal management process?
- How can STPA be applied to it?
- What were the results?
- What can we conclude about STPA in drug safety?

Why we need pharmacovigilance after drug approval



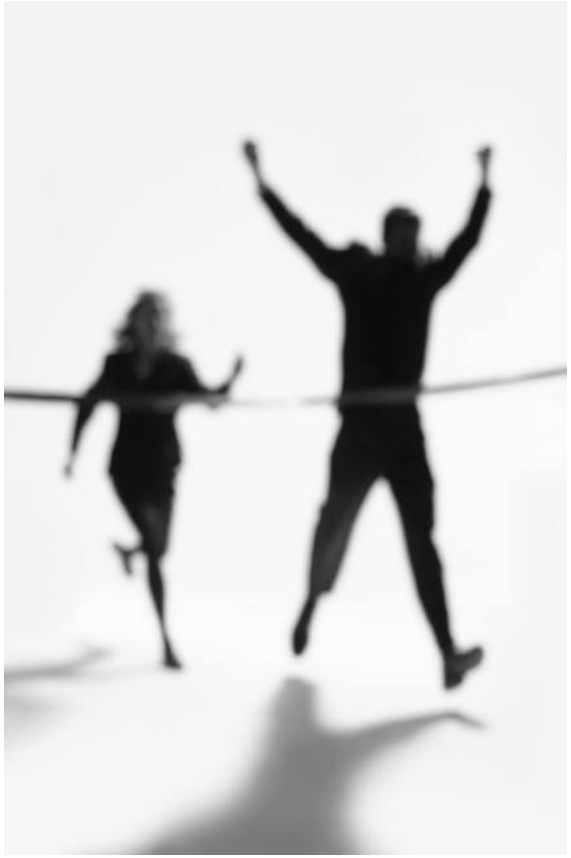
Pharmacovigilance:

What are we being especially vigilant for?

- Rare events
- Events in populations excluded from trials
- Events not easily attributable to the drug, e.g. events which are also related to the underlying disease such as heart attacks for a diabetes drug.
- Examples of drug withdrawals:
  - Thalidomide (birth defects)
  - Rofecoxib (cardiovascular events)
  - Rimonabant (suicide risk)
- Withdrawals are the tip of the iceberg:
  - Mainstay is labeling
  - Also risk-management measures: contraindicate in high-risk patients

Risk management objective

1. All predictable safety risks are identified, understood, communicated & managed proactively
2. Unpredictable safety risks are promptly identified, communicated & managed
3. For each product in development or marketed medicine, the benefits and risks are accurately reflected in up-to-date **reference safety information** ("label"), based on all data available from all sources.



Why not add all adverse events which occur to the label, "just to be on the safe side"?

- **Label fatigue:**
  - Healthcare providers and patients stop paying attention.
- **Listed adverse drug reactions are diagnostic alternatives:**
  - If a drug is mistakenly believed to cause an adverse event, diagnosis of the true cause could be delayed or prevented.
- **Over-labeling may inhibit patients from using potentially life-saving medication.**

- **Labels should include only bona fide adverse drug reactions supported by scientific and medical evidence**

What is *signal management* in the context of pharmacovigilance

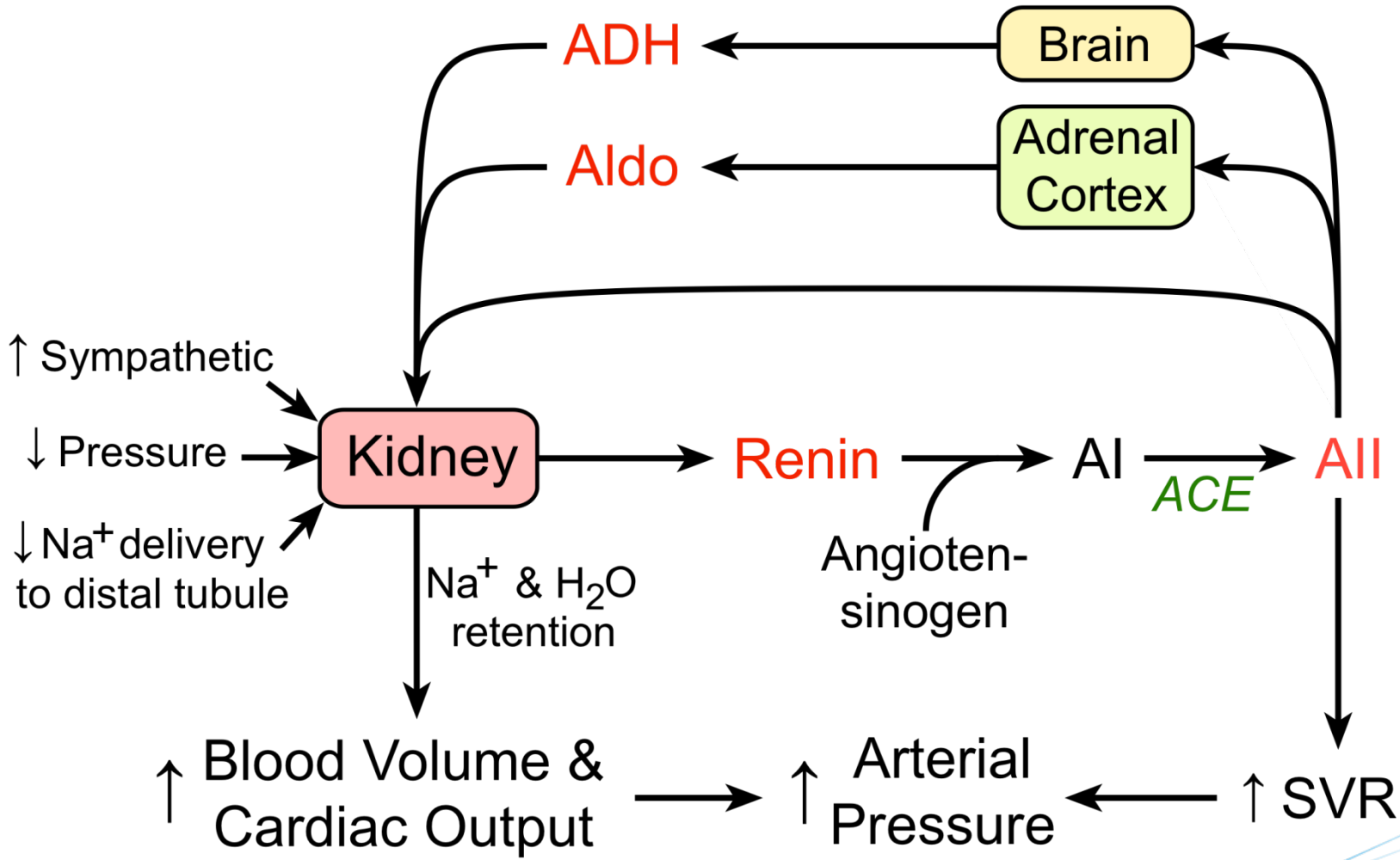
- Definition of a *signal*
  - "**Information that arises** from one or multiple sources (including observations and experiments), which **suggests a new potentially causal association**, or a new aspect of a known association, **between an intervention and an event** or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is **judged** to be of sufficient likelihood to **justify verificatory and, when necessary, remedial actions**." (CIOMS, following Hauben et al.)
- Signal detection: Identify new signals
- Signal Management: Figure out if the drug causes the event
- "Judgment"!...Does STPA apply??

Why STPA?

- EU Good Pharmacovigilance Practices Module I mandates that we monitor the performance and effectiveness of the pharmacovigilance system and its quality system.
- As part of this, we decided to perform a formal risk analysis to:
  - Identify key process risks
  - Support development of metrics and key performance indicators
- Brian Edwards (NDA Inc., ACRES, ex-MHRA)
  - Indicated that STPA held promise for drug safety
  - Introduced Roche to STPA experts at ZHAW
- Articles by Dokas and by Leveson on metrics ("early warning signs" / "leading indicators")

Biological Feedback Control System

"Homeostasis"

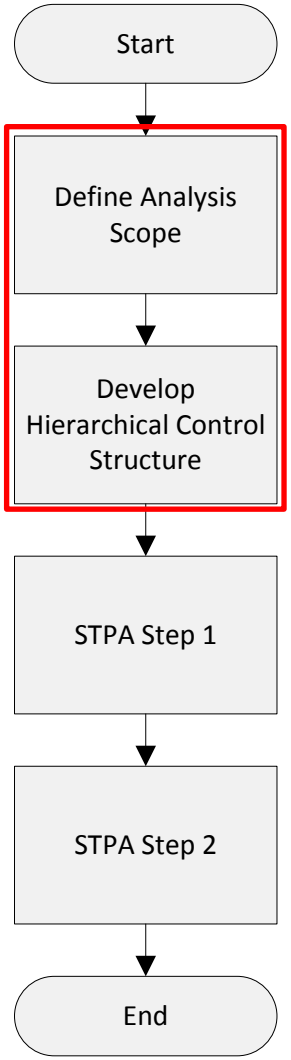


Source: http://www.cvphysiology.com/

STPA at Zurich University of Applied Sciences (ZHAW)

- Proton Therapy Safety Assessment, PSI (2011)
  - PhD of Blandine Antoine at MIT (Prof. Leveson)
- Steam Generator Feedwater Control, swissnuclear
  - Safety Assessment of new Control System Design
  - Methodology for systematic Hierarchical Control Structure generation and STPA Analysis of embedded systems
- Safety Driven Design Machinery Sector, Curtiss Wright
  - Application of STPA in regulatory context (EU Machinery Directive, ISO 12100)
  - STPA Extension for UML Case Tool
  - Integration of STPA in Product Lifecycle, especially design process

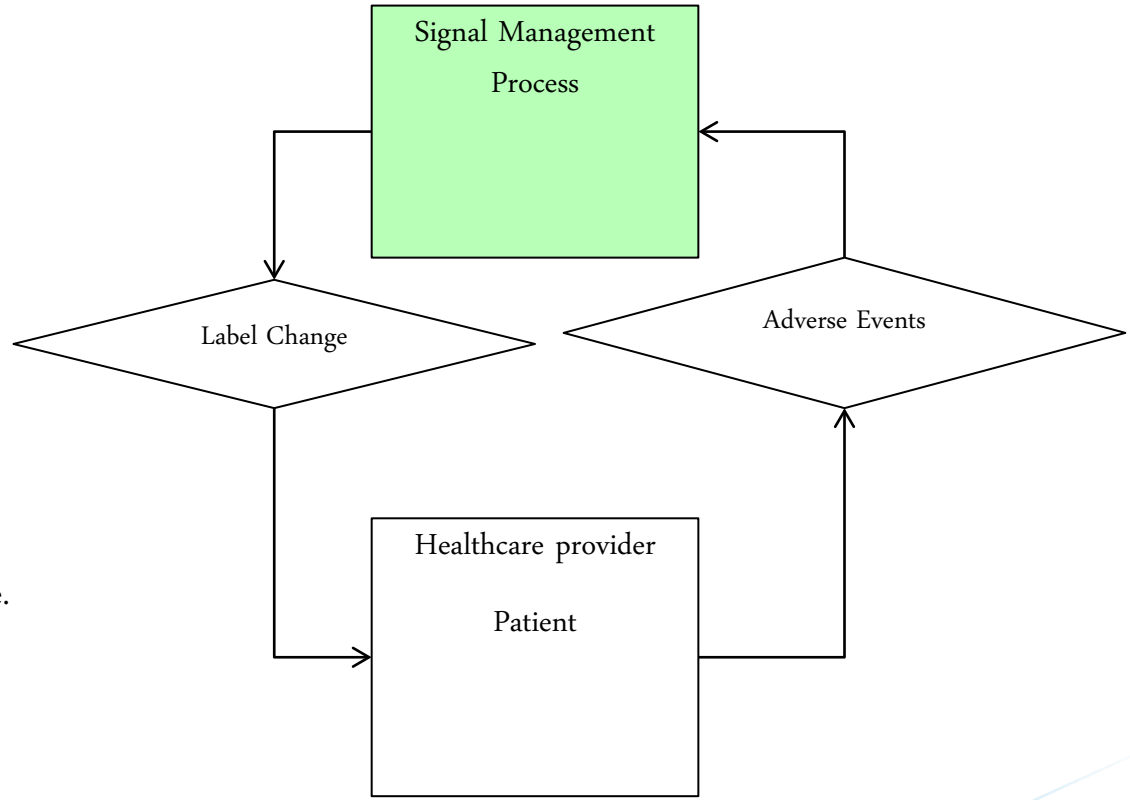
Preliminary steps



Can signal detection be modeled as a feedback control system?

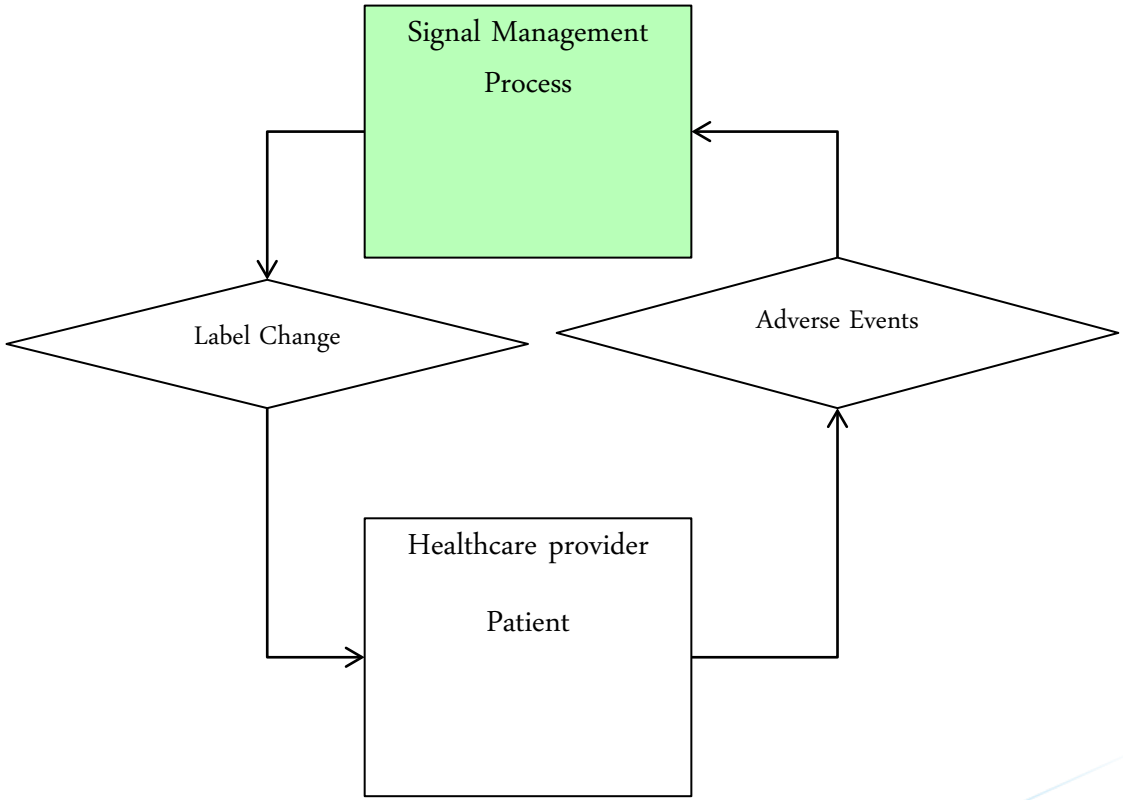
A: Yes

- Unexpected drug-related adverse events occur:
  - Signal management process senses adverse events not on label
  - After ascertaining causality, a label change is initiated
  - Label information to healthcare provider now accurately reflects adverse drug reactions
- Process aims to ensure that Reference Safety Information accurately reflects patient experience.



System enforcing safety constraint

- "Safe state" for the process: Label is accurate.
  - HCPs and patients are informed
  - Company is in compliance
  - Benefit-risk balance can be accurately assessed
- Does *not* mean that patients stop experiencing ADRs

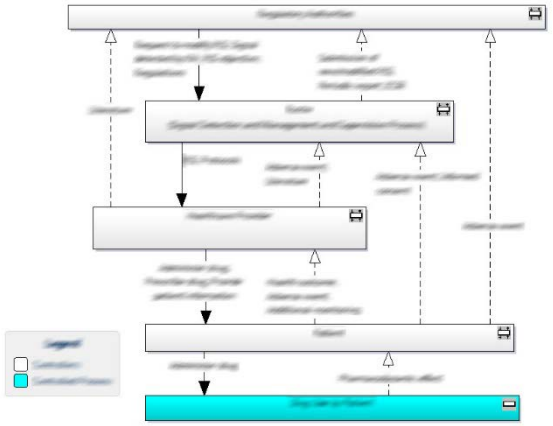


Assumptions of the STPA

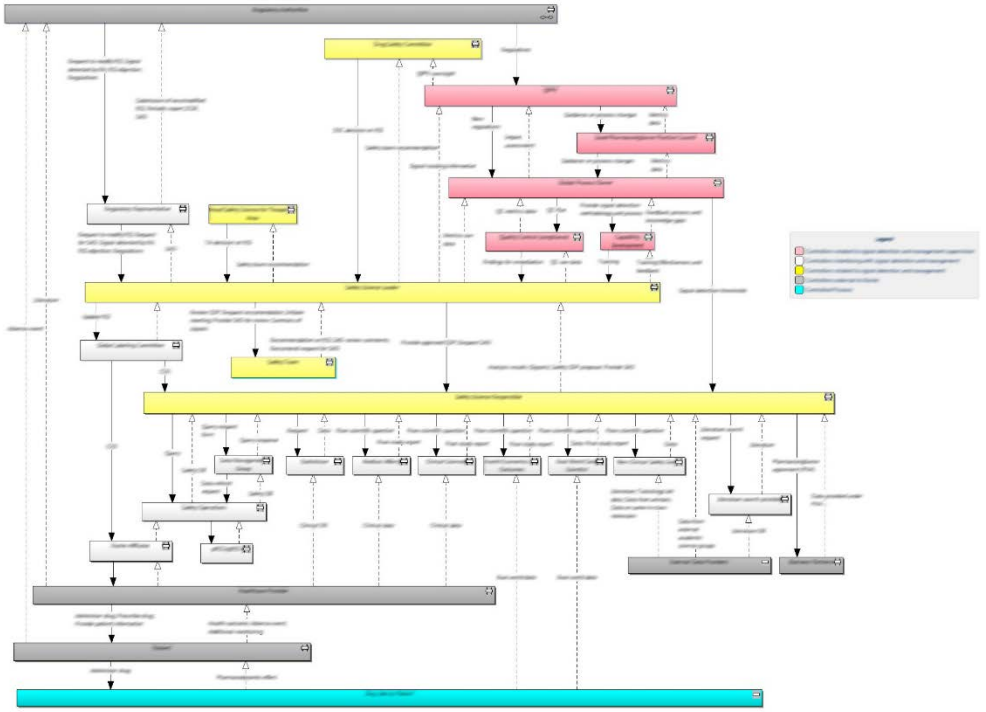
- Process is dependent on medical judgment, which we can't directly assess or control
- Assume that review of decisions by a second qualified individual or governance body reduces the risk of an error in judgment.
  - Focus on unsafe control actions that result in review being bypassed or rendered ineffective
- Focus on eliminating single points of failure
- Conflict-of-interest is within scope of this analysis
- Intentional harm to the company or patients (like GermanWings accident scenario) is out of scope of this analysis.

Roche Signal Management HCS

Overview Representation



Refinement



2 HCS Diagram representations

28 Controllers

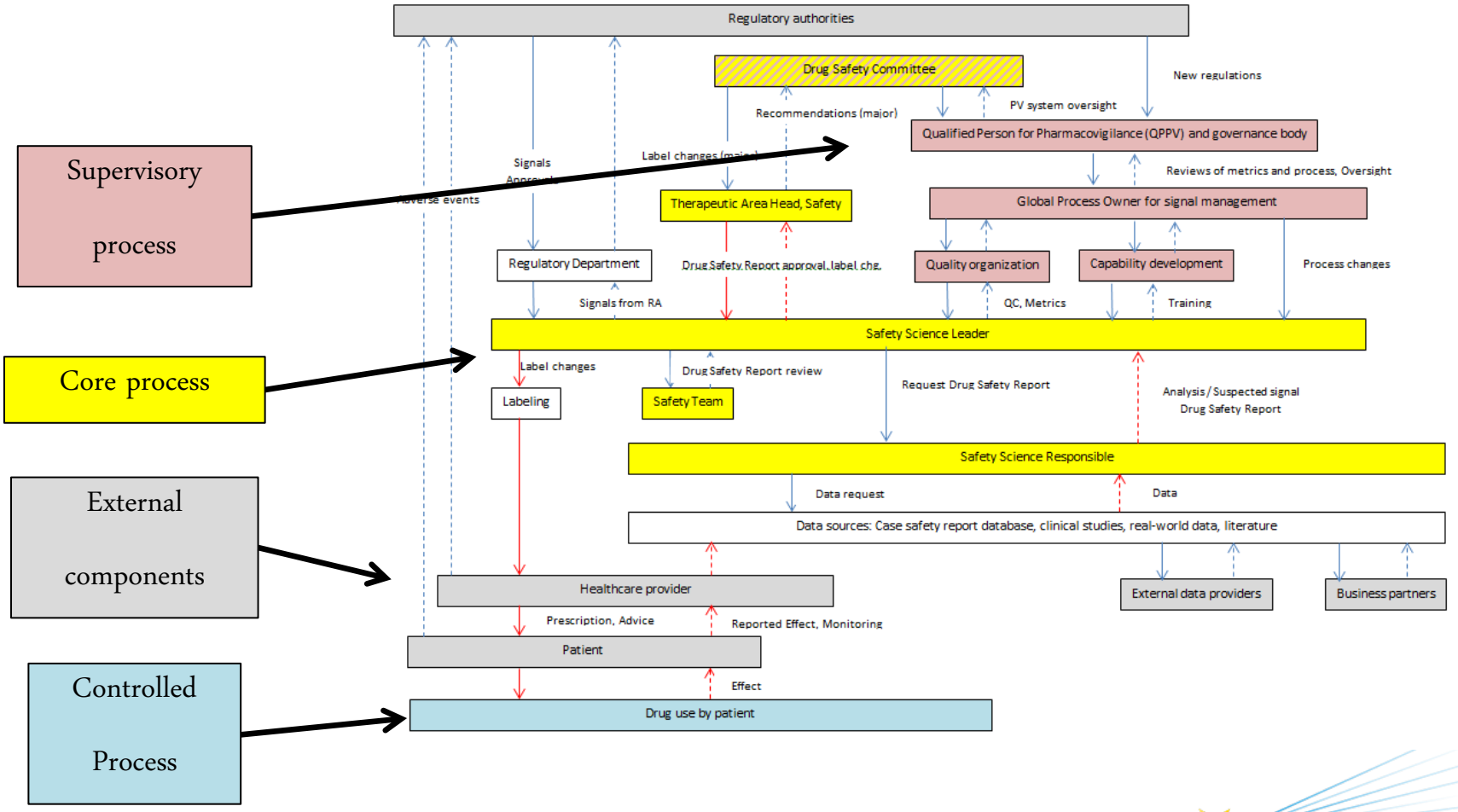
45 Control Actions

(linked to 32 control action connectors)

56 Feedbacks

(linked to 41 feedback connectors)

Roche Signal Management HCS (simplified)



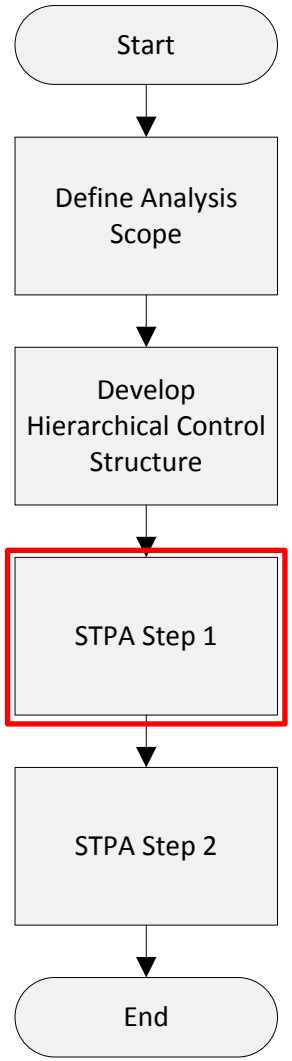
System losses

- SL1: Avoidable product-related harm to patient
- SL2: Regulatory non-compliance resulting in damage to reputation and financial implications
- SL3: Loss in patient benefit due to skewed benefit-risk assessment and inappropriate labelling

System hazards

- SH1: Adverse drug reaction missing from the label
- SH2: Frequency, severity, duration of ADR incorrectly labeled
- SH3: Important risk factor or interaction not described
- SH4: Failure to track signal information
- SH5: Failure to consider all available data for signal management purposes
- SH6: Failure to follow EU GVP Module I Quality Systems
- SH7: Failure to follow EU GVP Module IX Signal Management
- SH8: Incorrect labelling leads to failure to obtain product approval
- SH9: Adverse event is inappropriately added to the label

STPA Step 1



Keywords used:

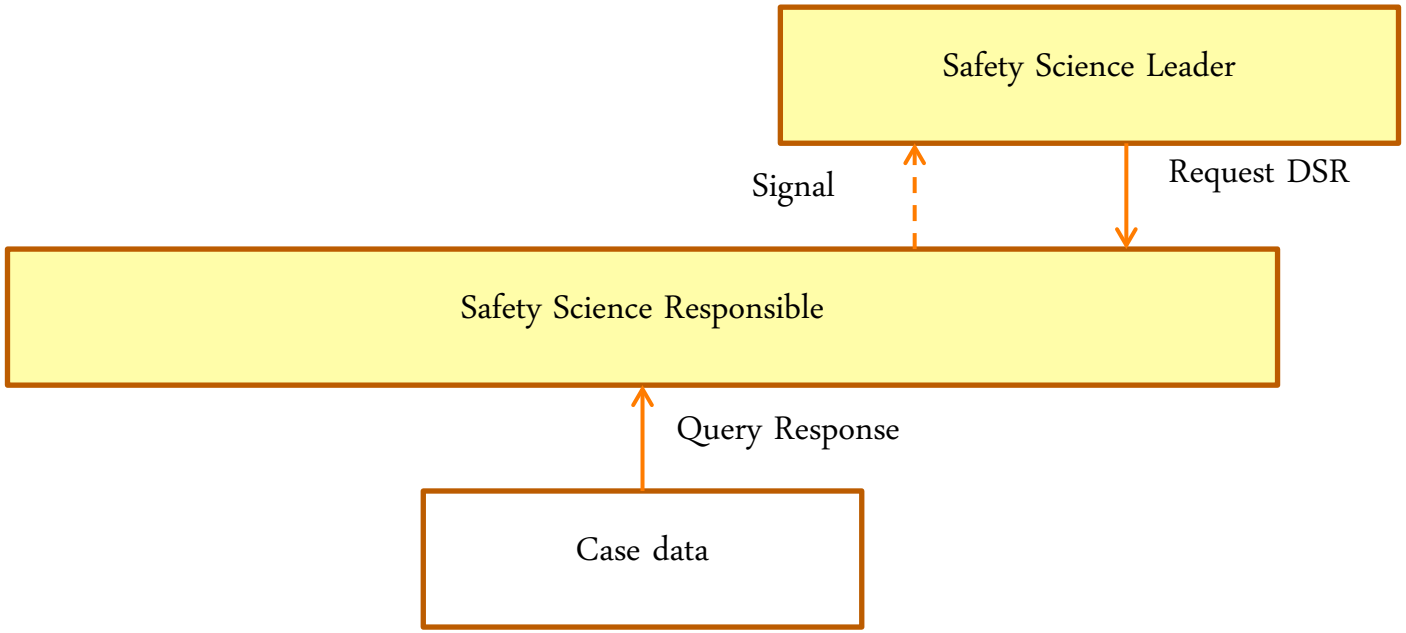
1. Control actions required for safety are not issued
2. Control action issued when not expected
3. Incorrect control actions are issued
4. Control actions are issued too early or too late or out of sequence
5. Safe control actions are stopped too soon or applied too long

STPA Step 1: Identifying unsafe control actions

STPA Step 1: Example

Control Action: *Request Drug Safety Report (DSR)*

- Is it potentially hazardous when …
  - *Request Drug Safety Report* is not provided when expected?
- Yes: Signal is not evaluated

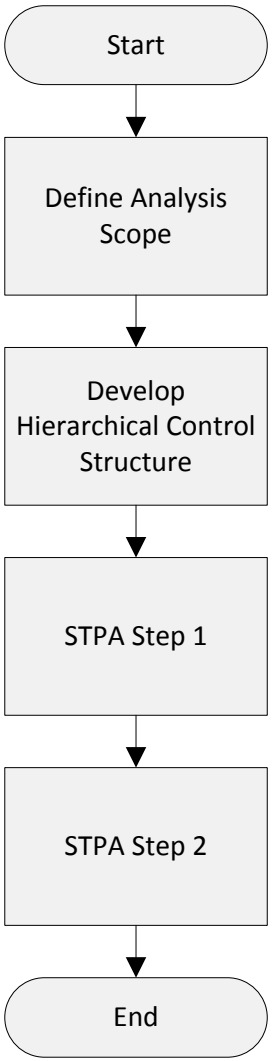


Illustrative Example

Unsafe control action examples

- Specification for writing Drug Safety Report is incorrect
- Author of Drug Safety Report is not correctly trained
- Safety Team reviews the incorrect version of a Drug Safety Report
- Creation of Drug Safety Report is not tracked in Signal Tracking System (as required by regulations)
- Decision to change label provided late

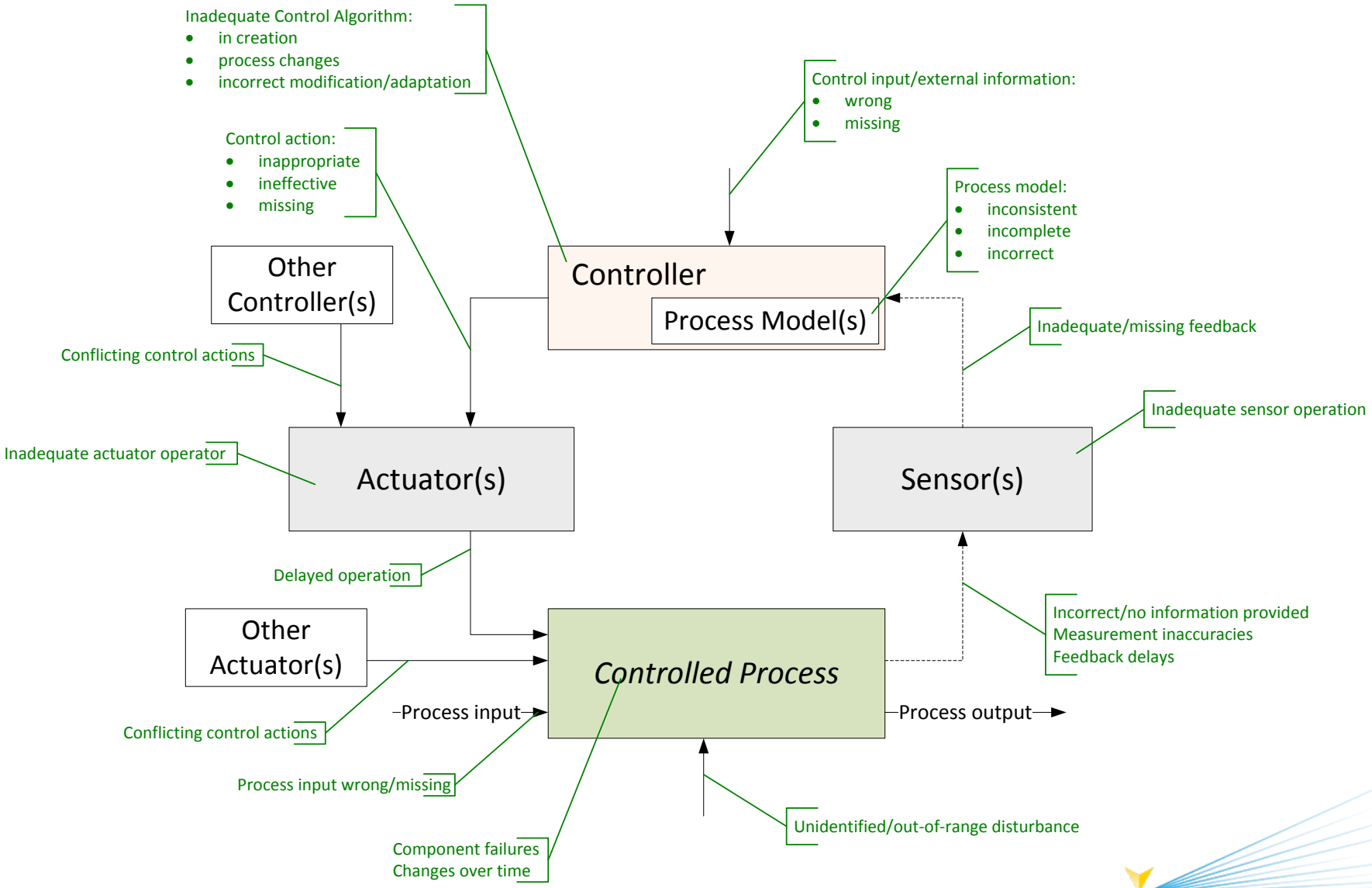
STPA Step 2



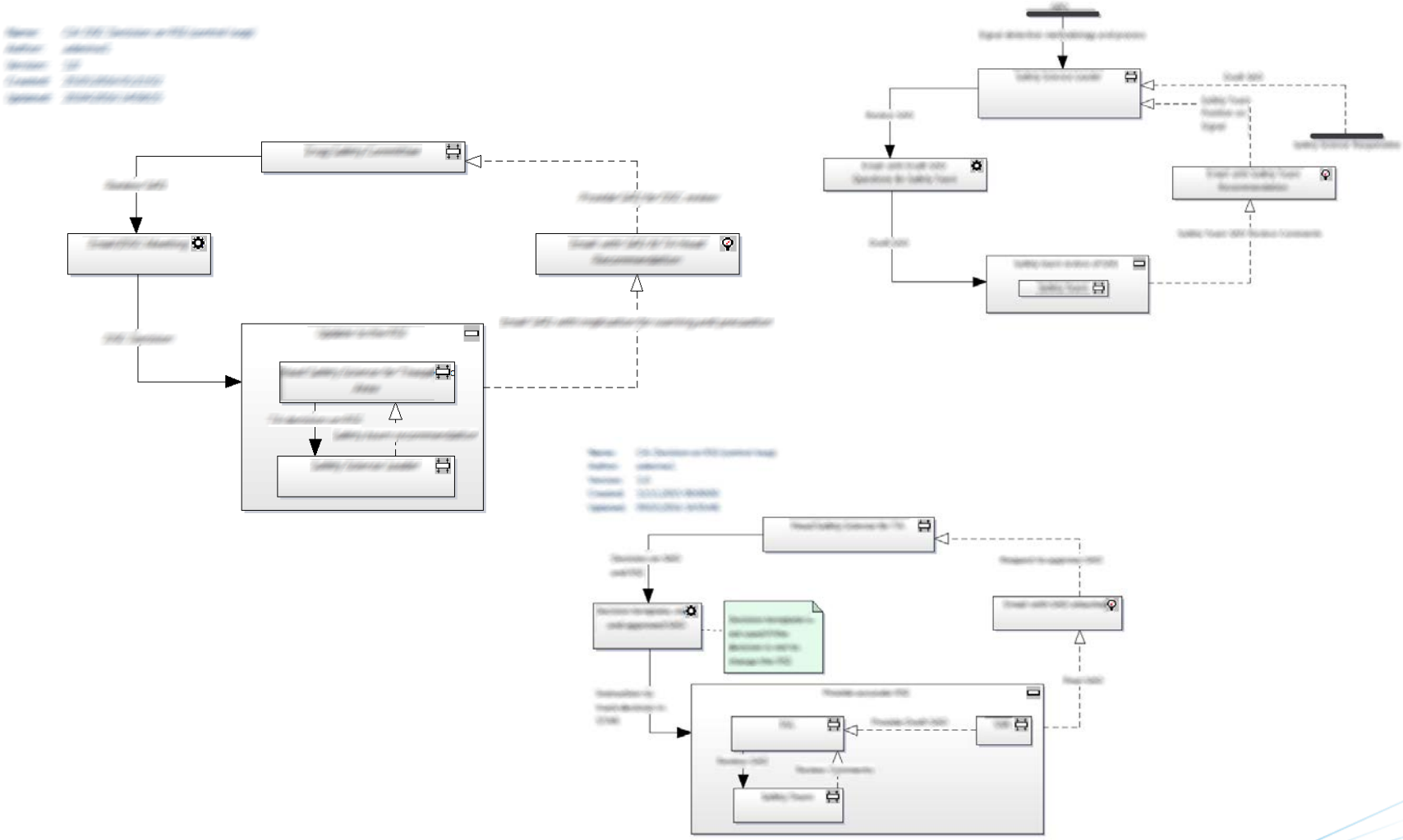
STPA Step 1: Identifying unsafe control actions

STPA Step 2: Determining how unsafe control actions could occur

STPA Step 2


Inadequate Control Algorithm:
in creation
process changes
incorrect modification/adaptation
Control input/external information:
wrong
missing
Control action:
inappropriate
ineffective
missing
Process model:
inconsistent
incomplete
incorrect
Other Controller(s)
Controller
Process Model(s)
Conflicting control actions
Inadequate/missing feedback
Inadequate sensor operation
Inadequate actuator operator
Actuator(s)
Sensor(s)
Delayed operation
Other Actuator(s)
Controlled Process
Incorrect/no information provided
Measurement inaccuracies
Feedback delays
Process input
Process output
Conflicting control actions
Process input wrong/missing
Unidentified/out-of-range disturbance
Component failures
Changes over time

STPA Step 2 Hierarchical control loop examples



STPA Step 2 Example

- Unsafe control action:
  - Safety Science Leader does not provide the control action "Request Drug Safety Report" to Safety Science Responsible
- This can be caused by …
  - Safety Science Responsible fails to provide *Signal* to Safety Science Leader

Illustrative Example

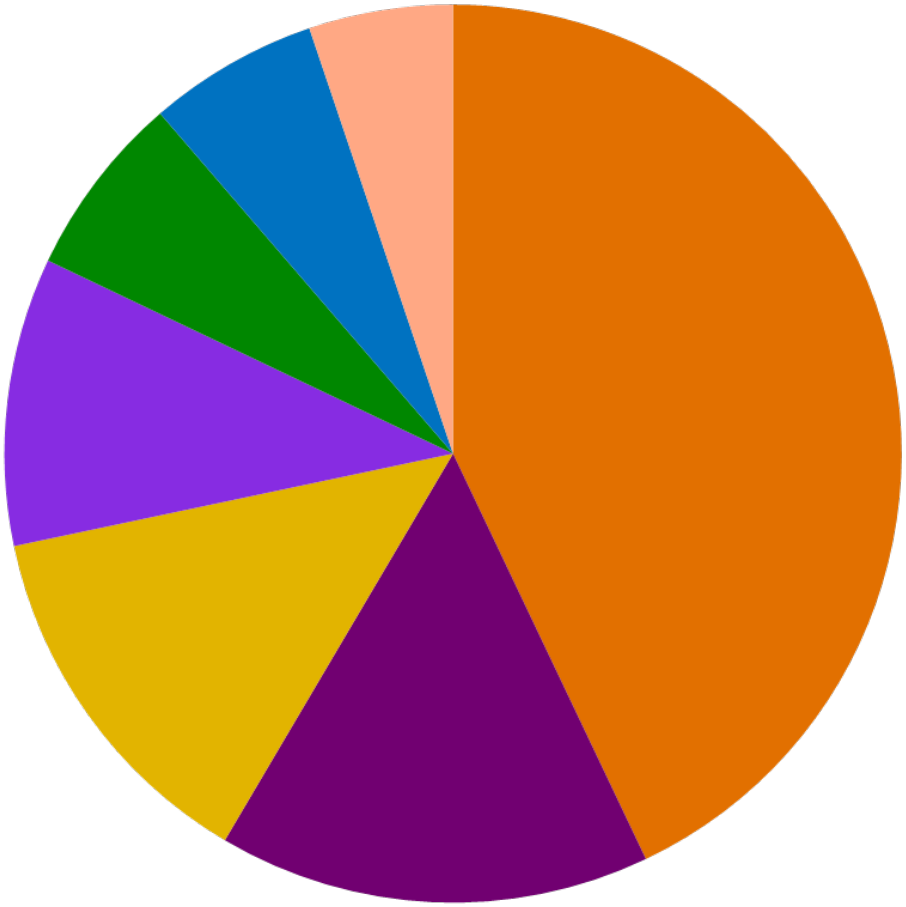
STPA Step 2 Example

- Unsafe control action:
  - Safety Science Leader does not provide the control action “Request Drug Safety Report” to Safety Science Responsible
- This can be caused by …
  - Safety Science Responsible fails to provide *Signal* to Safety Science Leader
- Examples of corresponding scenarios:
  - Safety Science Responsible misreads the Signal Detection Plan, which describes routine signal detection activities that he/she is supposed to carry out.
  - There is conflicting data on causality from various sources, and Safety Science Responsible fails to give greatest weight to the evidence with the highest quality (in accordance with training).

Coverage report

- Over 200 scenarios in Step 2
- Eliminated about 10% based on low rating for:
  - Severity: not consequential
  - Occurrence: very low likelihood
  - Detectability: impossible to identify when scenario occurs
  - (also eliminated duplicates)
- Which are already covered by existing control mechanisms?
- What process changes can be recommended to cover?
- What metrics can be recommended for early warning?
- What changes are recommended to infrastructure / other processes?

Analysis outcome by scenario



- Already adequately covered
- Duplicates or near-duplicates
- Validated existing or planned metrics
- Not evaluated due to low likelihood, low risk, or inability to detect
- Resulted in a recommendation for signal mgt. metrics
- Resulted in a recommendation for signal mgt. process
- Resulted in a recommendation for infrastructure or another process

Results Obtained

- Validation of existing or planned metrics
- Recommended new or changed signal mgt. metrics
- Recommended changes in signal management process
- Recommended changes in infrastructure or other processes

- Over 20 recommendations in total

Examples of Metrics

- **Number and status of proposed and ongoing process improvements.** Covers supervisory process. Evaluates capacity to continuously improve the process.
- **Planning documents requiring revision in order to obtain approval.** Early warning of need to improve guidance to teams on signal detection planning.
- **Errors detected in reports by regulatory authorities who receive them.** Errors to be graded for severity. Systematic way to identify any deficiencies in the report creation, review, and approval process.

Examples of process improvements

- **Systematically review signals detected externally and communicated to us**, to assess whether our current detection thresholds in our statistical signal-detection software are too high.
- Ensure that versioning in **our document management system prevents reports from being modified** after review and before approval sign-off.
- **Provide "quality culture / speak-up" training** to eliminate reluctance of Safety Scientists to question their managers on scientific and medical judgment matters. (Analogy to problems in aviation industry in Korea.)

Examples: Suggestions for other processes

- "Process for process changes" calls for an impact assessment in one step, followed by an implementation plan in the next step. STPA recommended a formal step to **ensure that each point in the impact assessment was addressed** in the implementation plan, or, alternatively, a post-implementation check that all of the items in the impact assessment have been fully addressed.
- The STPA recommended that we maintain **metrics on corrections to quality dashboard information**. This recommendation covers scenarios in which incorrect dashboard information leads to inappropriate reactions.

Conclusions

- STPA of the signal management process produced 26 recommendations, many related to metrics and early indicators, some of which were unlikely to have resulted from other methodologies.
- STPA can be successfully run for a pharmaceutical-development business process.
- STPA considers interfaces, infrastructure, and human factors.
- STPA is well-suited for the generation and validation of process metrics.
- STPA can be adjusted for wide or narrow scope, due to its hierarchical approach.
- STPA is thorough, systematic, and resource-intensive (several person-months for this complex process). Thus it is best suited to high-risk areas, and areas where other methodologies have failed to effectively identify process risks and root causes.

Questions?

Doing now what patients need next