
Global Harmonization Task Force Study Group 2

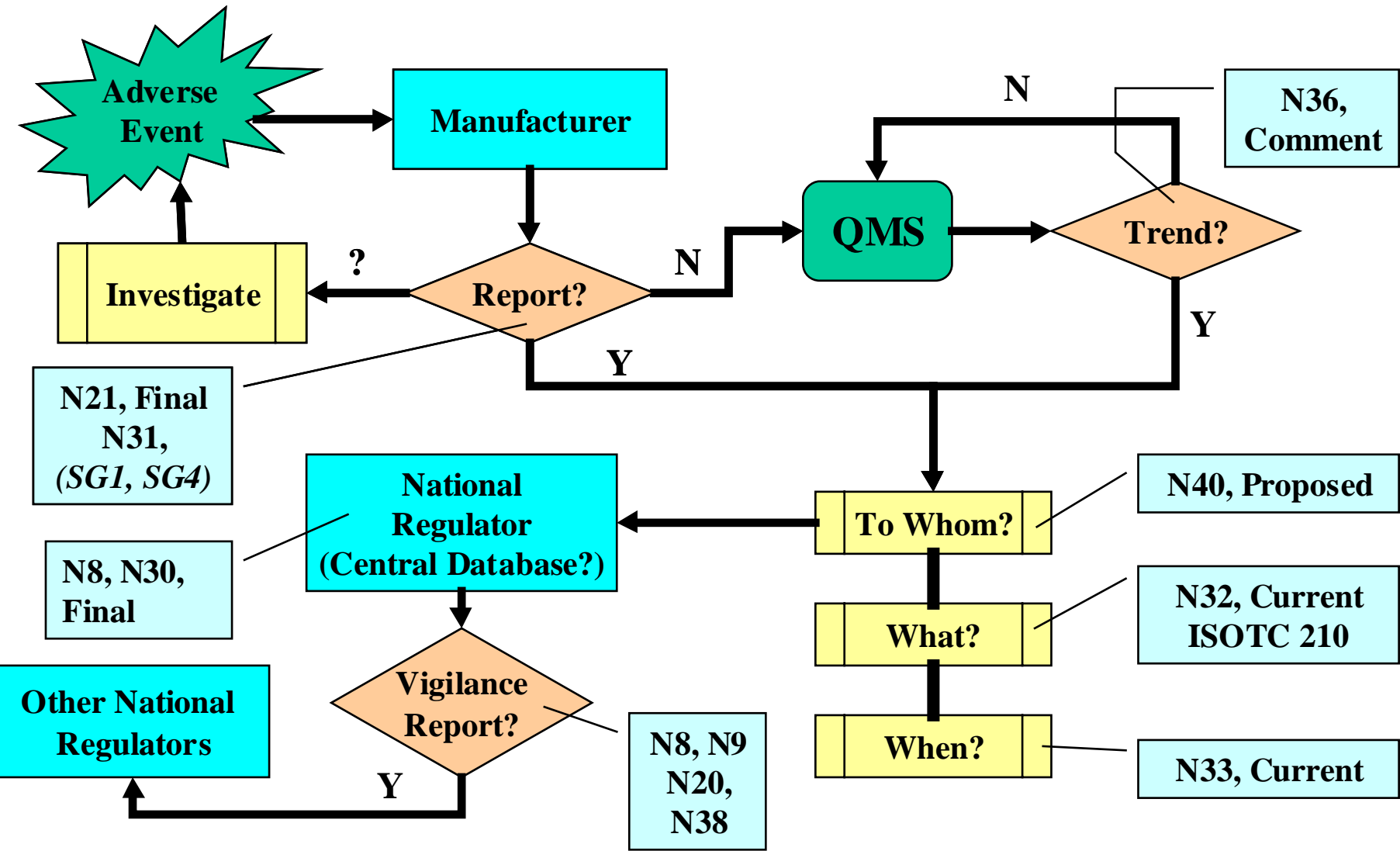
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Presentation Topics

- Adverse Event Reporting Guidance
N21 (Final)
 - Manufacturers Trend Reporting of Adverse Events
N36 (Proposed)
 - Common and Well Characterized Adverse Events
N30 (Information document)
-





AE Reporting Guidance

- The objective of adverse event (AE) reporting and subsequent evaluations is to improve protection of the health and safety of patients, users and others by disseminating information which may
 - reduce the likelihood of adverse events, or
 - prevent repetition of adverse events, or
 - alleviate consequences of such repetition.



AE Reporting Guidance

- For the purpose of the document, the term "manufacturer" means
 - the manufacturer,
 - its authorized representative or
 - any other person who is responsible for placing the device on the market.



AE Reporting Guidance

- The existing regulatory requirements of the participating countries involved in SG2 require medical device manufacturers to notify National Competent Authorities (NCAs) of certain adverse events.



AE Reporting Guidance

- The guidance document represents a global model, which provides guidance on the type of adverse events associated with medical devices that should be reported by manufacturers to a NCA.
- It is based on the regulatory requirements existing in the participating member countries.



AE Reporting Guidance

- The guidance is not identical to current regulatory requirements.
- The document provides a future model towards which existing systems should converge.
- The principles laid down in the document should be considered in the development or amendment of regulatory systems in the participating countries or other countries.



AE Reporting Guidance

- Some NCAs also encourage reporting of adverse events by users.
- The guidance document does not include requirements for user reporting.
- It is recommended that NCAs promptly inform the pertinent manufacturers about reports received directly from users.



AE Reporting Guidance

- The act of reporting to a NCA is not considered an admission of manufacturer, user, or patient liability.
- Submission of a report does not represent a conclusion by the manufacturer that the information is complete or confirmed.
- A report is also not a conclusion that the medical device caused or contributed to the adverse event.
- It is recommended that reports carry a disclaimer.



AE Reporting Guidance

- Any event which meets three basic reporting criteria is considered as an adverse event and should be reported to the relevant NCA.
- Under specified conditions some types of events are exempt from reporting.
- Reporting of adverse events due to use error is not globally harmonized and the reporting requirements are currently being developed.



AE Reporting Guidance

Basic reporting criteria:

1) An event must have occurred.

- Malfunction or deterioration
- Inadequate design or manufacture
- Inaccuracy in labeling
- Significant public health concern
- Other information from testing or literature



AE Reporting Guidance

Basic reporting criteria:

- 2) The manufacturer's device is associated with the event.
- Opinion from healthcare professional
 - Previous similar events
 - Other information available to the manufacturer



AE Reporting Guidance

Basic reporting criteria:

3) The event led to one of the following:

- Death of a patient, user or other person or
- Serious injury of a patient, user or other person
- No death or serious injury, but event might lead to death or serious injury if the event recurs



AE Reporting Guidance

Serious injury is defined as:

- Life threatening illness or injury.
- Permanent impairment of a body function or permanent damage to a body structure.
- A condition requiring medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.



AE Reporting Guidance

- The term “permanent” means irreversible impairment or damage to a body structure or function, excluding minor impairment or damage.
- Medical intervention is not in itself a serious injury. It is the reason that motivated the medical intervention that should be used to assess the reportability of an event.



AE Reporting Guidance

Reporting may be exempted if any one of a set of exemption rules is applicable.

- However if a NCA requires reporting a specific type of event due to a significant public health concern, the exemption is no longer applicable.
- Similarly those adverse events which are subject to an exemption become reportable to the NCA if a change in trend (usually an increase in frequency) or pattern is identified.



AE Reporting Guidance

Exemption rules

Whenever any one of the following exemption rules is met, the adverse event does not need to be reported to a NCA by the manufacturer.



AE Reporting Guidance

Exemption rules

1) Deficiency of a new device found by the user prior to its use.

Regardless of the existence of provisions in the instruction for use provided by the manufacturer, deficiencies of devices that would normally be detected by the user and where no serious injury has occurred, do not need to be reported.



AE Reporting Guidance

Exemption rules

1) *Deficiency of a new device found by the user prior to its use.*

Example-

User performs an inflation test prior to inserting the balloon catheter in the patient as required in the instructions for use accompanying the device. Malfunction on inflation is identified. Another balloon is used. Patient is not injured.



AE Reporting Guidance

Exemption rules

2) Adverse event caused by patient conditions.

When the manufacturer has information that the root cause of the adverse event is due to patient condition, the event does not need to be reported. These conditions could be preexisting or occurring during device use.



AE Reporting Guidance

Exemption rules

2) Adverse event caused by patient conditions.

Example-

Orthopedic surgeon implants a hip joint and warns against sports-related use. Patient chooses to go water skiing and subsequently requires premature revision due to not following directions.



AE Reporting Guidance

Exemption rules

3) Service life of the medical device.

When the only cause for the adverse event was that the device exceeded its service life as specified by the manufacturer and the failure mode is not unusual, the adverse event does not need to be reported.

AE Reporting Guidance

Exemption rules

3) Service life of the medical device.

Example-

Loss of sensing after a pacemaker has reached end of life. Elective replacement indicator has shown up in due time according to device specification. Surgical explantation of pacemaker required.



AE Reporting Guidance

Exemption rules

4) Protection against a fault functioned correctly.

Adverse events which did not lead to serious injury or death, because a design feature protected against a fault becoming a hazard (in accordance with relevant standards or documented design inputs), do not need to be reported.



AE Reporting Guidance

Exemption rules

4) *Protection against a fault functioned correctly.*

Example-

An infusion pump stops, due to a malfunction, but gives an appropriate alarm (e.g. in compliance with relevant standards) and there was no injury to the patient.



AE Reporting Guidance

Exemption rules

5) Remote likelihood of occurrence of death or serious injury.

Adverse events which could lead, but have not yet led, to death or serious injury, but have a remote likelihood of causing death or serious injury, and which have been established and documented as acceptable after risk assessment do not need to be reported.



AE Reporting Guidance

Exemption rules

5) Remote likelihood of occurrence of death or serious injury.

Example-

Manufacturer of pacemaker released on the market identified a software bug and determined that the likelihood of occurrence of a serious injury with a particular setting is remote. No patients experienced adverse health effects.



AE Reporting Guidance

Exemption rules

6) Expected and foreseeable side effects.

Side effects which are clearly identified in the manufacturer's labeling or are clinically well known as being foreseeable and having a certain functional or numerical predictability when the device was used as intended need not be reported.



AE Reporting Guidance

Exemption rules

6) *Expected and foreseeable side effects.*

Example-

Placement of central line catheter results in anxiety reaction and shortness of breath. Both reactions are known and labeled side effects.



AE Reporting Guidance

Exemption rules

7) Adverse events described in an advisory notice.

AE's that occur after a manufacturer has issued an advisory notice need not be reported individually if specified in the notice. Advisory notices include removals from the market, corrective actions, and product recalls. The manufacturer should provide a summary report, the content and frequency of which should be agreed with the relevant NCA.



AE Reporting Guidance

Exemption rules

7) Adverse events described in an advisory notice.

Example-

Manufacturer issued an advisory notice and recall of a coronary stent that migrated due to inadequate inflation of an attached balloon mechanism. Subsequent examples of stent migration were summarized in quarterly recall reports and individual events did not have to be reported.



AE Reporting Guidance

Exemption rules

8) Reporting exemptions granted by NCA.

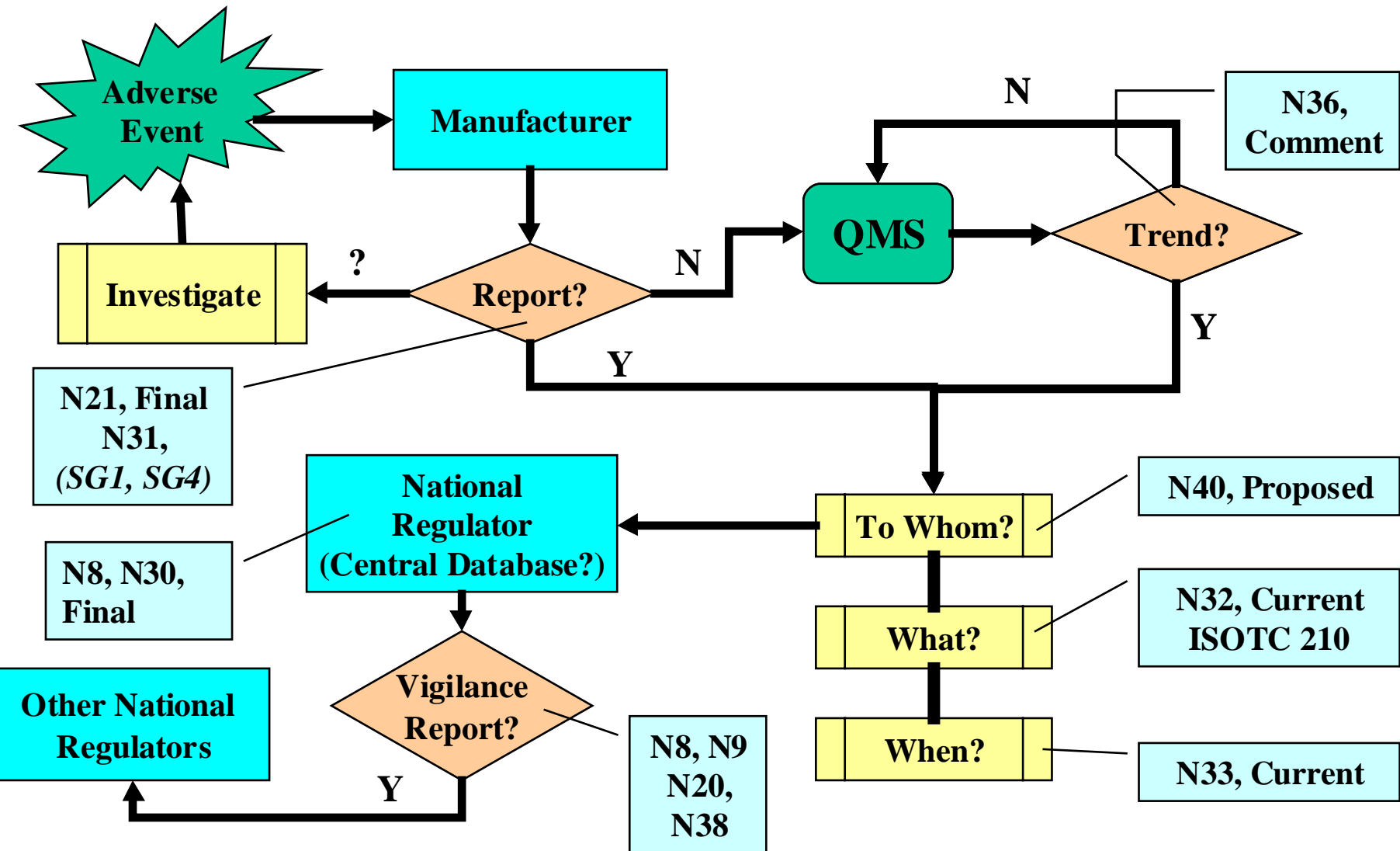
Common and well-documented events may be exempted by a NCA from reporting or changed to periodic reporting upon request by the manufacturer.



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AE Trend Reporting

- Adverse events specifically exempted from reporting become reportable if there is a change in trend (usually an increase in frequency) or pattern is identified.
 - The SG2 document on trend reporting describes the criteria for identifying a significant increase in the rate of adverse events.
 - Not a handbook of statistical techniques
 - Provides guidance to assist manufacturers to perform trending.
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AE Trend Reporting

- Quality management system standards include requirements for trending product complaints including those considered AEs.
- The same methods can be used for trending complaints and trending AEs.
- Trending of complaints may lead to a corrective and preventive action.
- Trending of AEs may lead to a report to a NCA.



AE Trend Reporting

- Basic trending parameters

$$i = n/d \text{ where}$$

i represents a trend data point

n is the number of events in a given time interval

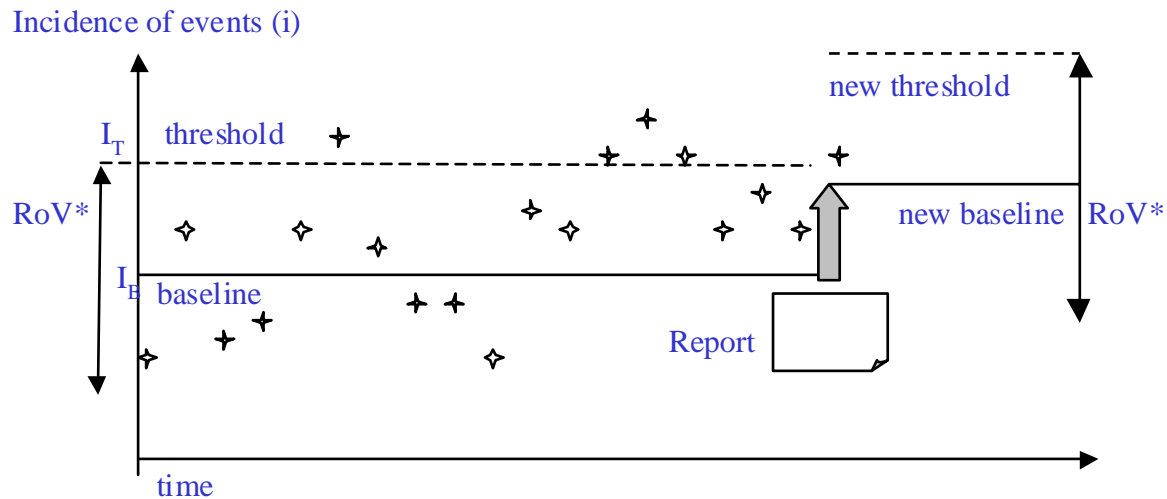
d is the product volume (by clinicians, patients, etc.) in the market during that time interval

i is the observed incidence expressed as a percent.



AE Trend Reporting

- Example of upward shift in trend



* normal Range of Variance

AE Trend Reporting

- Base Line I_B
 - The base line is the expected or normal rate of incidence of an event expressed as a percent of the products in use.
 - Base line values can be established through the use of tools and methods such as risk analysis, reliability models, or historical data.



AE Trend Reporting

- Threshold I_T
 - The threshold, expressed as a percent of products in use, is the incidence rate which is above the expected or normal variation in rate.
 - Threshold values may be established from the expected or measured variation in incidence rate.
 - Threshold values will be different depending on the product category.
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AE Trend Reporting

- Time interval
 - The time interval should be long enough to gather sufficient data for the analysis.
 - The time interval should be short enough to facilitate timely corrective action.
 - For higher volume products a typical time interval may be 1 month.



AE Trend Reporting

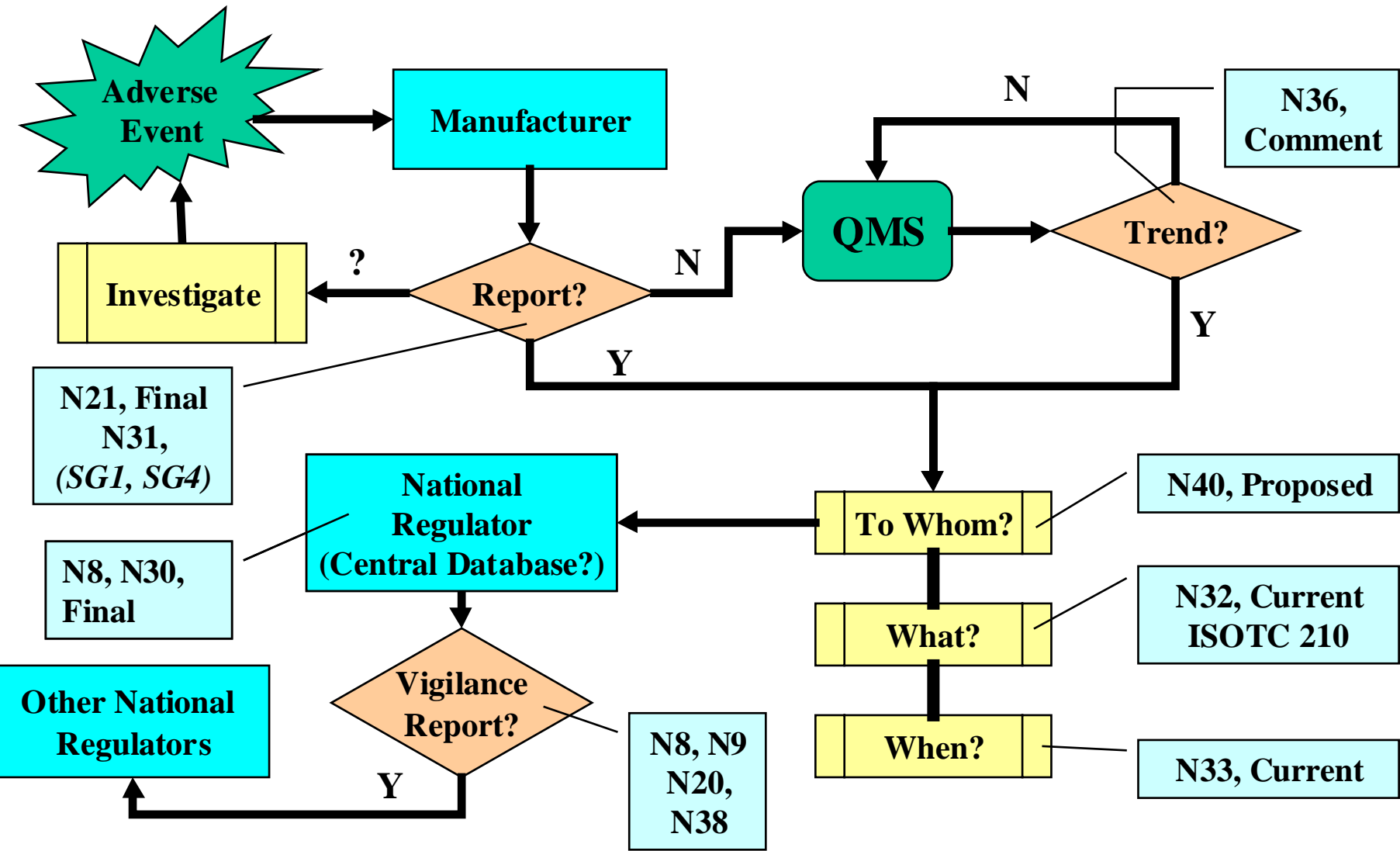
- Significant increase in observed incidence
 - a rapid and continuous increase in (i) over a limited number of time intervals for high volume products (e.g. over 1 - 3 months)
 - a slow and continuous increase in (i) over a larger number of time intervals for low volume products (e.g. over 3 - 6 months)



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Common & Well Characterized AEs

- SG2 document is for information only and is not a guidance or recommendations
 - Target audience – medical device regulators
 - Goals
 - Facilitate sharing of information on “what” and “where” alternative reporting options currently exist.
 - Provide resources for NCAs who want to implement alternative reporting options in lieu of individual reporting requirements.
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Common & Well Characterized AEs

- Currently only the United States FDA offers postmarket AE reporting alternatives.
 - Information is provided to assist other NCAs gain confidence to implement alternative summary reporting (ASR) programs.
 - NCAs interested in establishing ASR programs are welcome to contact FDA for assistance and support.
 - See <http://www.fda.gov/cdrh/osb/guidance/315.pdf> for more information on the ASR program.
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Common & Well Characterized AEs

- Basis for exemption:
 - AEs must be well known, well documented and characterized in the scientific and medical literature, and reported consistently.
 - In such cases, FDA has determined that it can continue to evaluate and monitor these AEs effectively and efficiently through the submission and evaluation of periodic reports.
 - Reduces work for both manufacturer and FDA.
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Common & Well Characterized AEs

- Requirements for alternative reporting:
 - Manufacturer must request to participate in the ASR program.
 - FDA provides manufacturer with written documentation defining the specifics of the ASR being granted.
 - Data is aggregated & submitted in a summary report to FDA on a defined periodic schedule.



Common & Well Characterized AEs

- Types of events *not* covered
 - 5-day report under FDA 21 CFR 803.53.
 - Death occurred, except mechanical heart valve.
 - Mechanical heart valve if implant < 5 years.
 - Permanent pacemaker electrode where manufacturer confirmed device failure.
 - Approved PMA device marketed < 2 years.
 - Multiple serious injuries due to a single event or device failure.
 - Explosion or fire.
 - Unusual, unique or uncommon events
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Common & Well Characterized AEs

- Devices included for all manufacturers
 - Endosseous Implant
 - Intravascular (I.V.) Administration Set
 - Intravascular Catheter (short-term)
 - Intravascular Diagnostic Catheter
 - Mechanical Heart Valve
 - Mechanical/Hydraulic Impotence Device
 - Permanent Pacemaker Electrode
 - Port and Catheter, Implanted, Subcutaneous, Intravascular
 - Saline Internal Inflatable Breast Prosthesis
 - Silicone Gel-filled Internal Inflatable Breast Prosthesis
 - Urological Catheter



When implemented, SG2 recommendations will:

- **Harmonize the definition of what is and what is not a reportable event**
 - **In that way, any manufacturer would have a single process for making decisions about whether or not to report**



Current concern:

- **Whether to have mandatory reporting of use errors to Competent Authority**
 - **Some countries already have such a requirement**
 - **Industry concern about reporting on their “customers”**
 - **Use error recognized as important and persuasive - disagreement how to resolve**



SG2 Working Drafts

Working Draft -

- **SG2-N31R7.2: Proposal for Reporting of Use Errors with Medical Devices**



GHTF Study Group 2

For more information regarding Medical Device Adverse Event Reporting please contact

<http://www.gh tf.org/>

