



# **The role of safety monitoring to detect manufacturing quality issues: Experience at GSK Biologicals**

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# Safety and Manufacturing quality: A general framework

- Adverse events can be considered as:
- Inherent to vaccines:
  - Oral Polio and VAPP
  - Flu and GBS
  - Rotavirus vaccines and Intussusception
- Inherent to manufacturing:
  - Insufficient titers (Potential Lack of efficacy): Hib (PedVaxHib)
  - Related to adventitious agents
    - With known effects: HepB in yellow fever
    - Without known effects: SV40 in polio
    - Without expected effects: PCV in Rotavirus
  - A 'real' manufacturing problem:
    - Wild type virus not fully inactivated: Cutter
    - Toxin not completely inactivated
    - Other

# What do we look for?

- Any signal among the spontaneously reported adverse events that may suggest a relationship between the occurrence of these events and a particular manufacturing characteristic

= signal detection or hypothesis generation!

A signal does not mean the event is actually caused by the vaccine nor that there is a defect in the manufacturing process

# How do we detect signals?

- Perform Monthly Signal Detection
  - All reports of fatalities with a reported batch number
  - A significantly increased reporting rate of
    - Serious adverse events within a batch or bulk
    - Non-serious adverse events within a batch or bulk
    - 'Lack of Efficacy' reports within a batch or bulk
    - 'Lack of Sterility' reports within a batch or bulk
  - Technical complaints trends

# How do we validate signals?

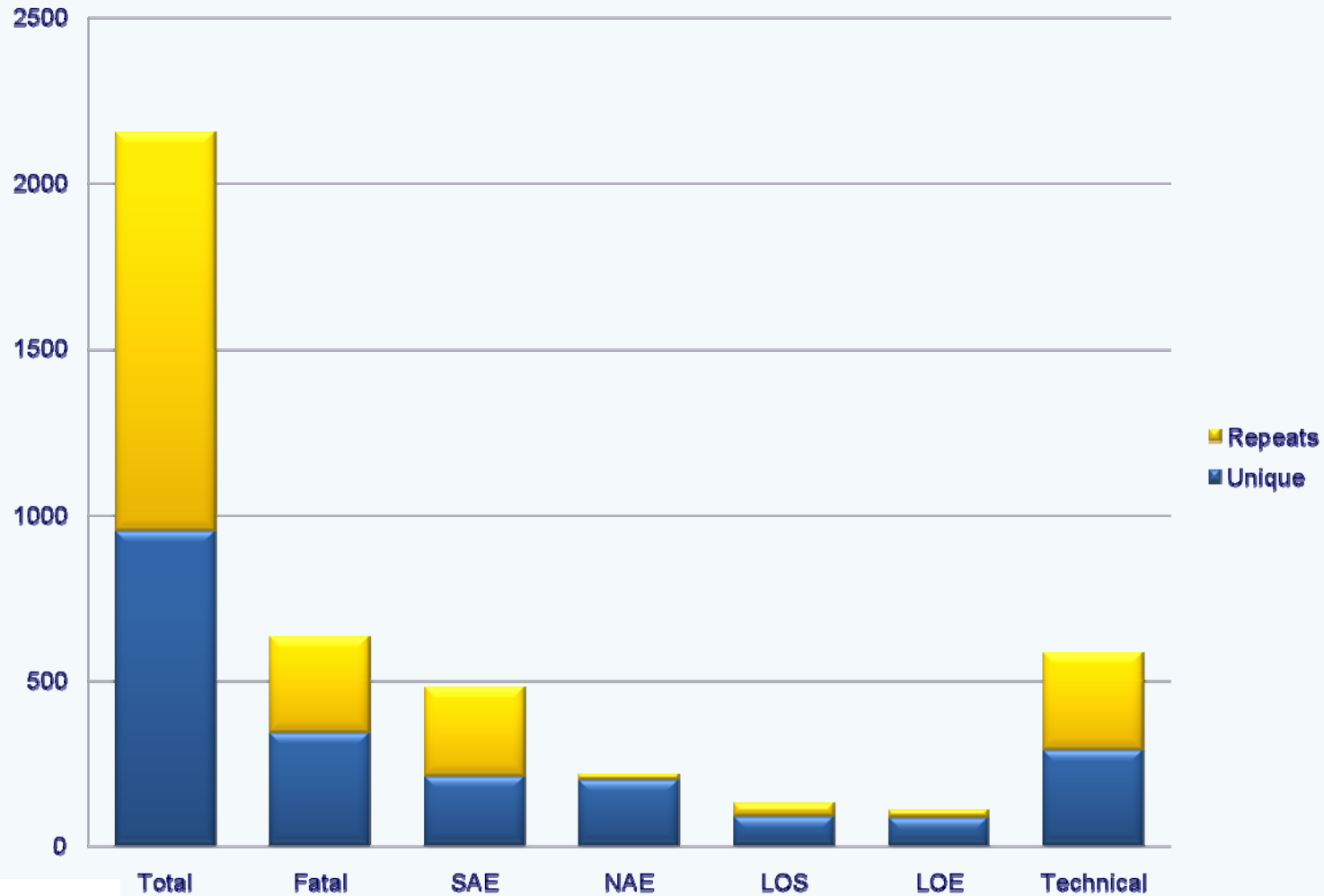
- Medical review, incl:
  - Type of events reported in the batch
  - Severity and seriousness
  - Reporter source
  - Background medical condition & other contributing factors
- Epidemiological review: Reporting rate of the events in the identified batch compared to rates for the same events in other final product batches and within same formulated bulk batches or vaccine in general

## Which signals are typically considered validated (selected for a manufacturing quality investigation)

- A concentration of a specific type of events for which an explanation other than a potential mfg deviation could not be identified
- First fatality report (within a batch) where the medical review cannot rule out the involvement of the vaccination as a contributing factor to the fatality

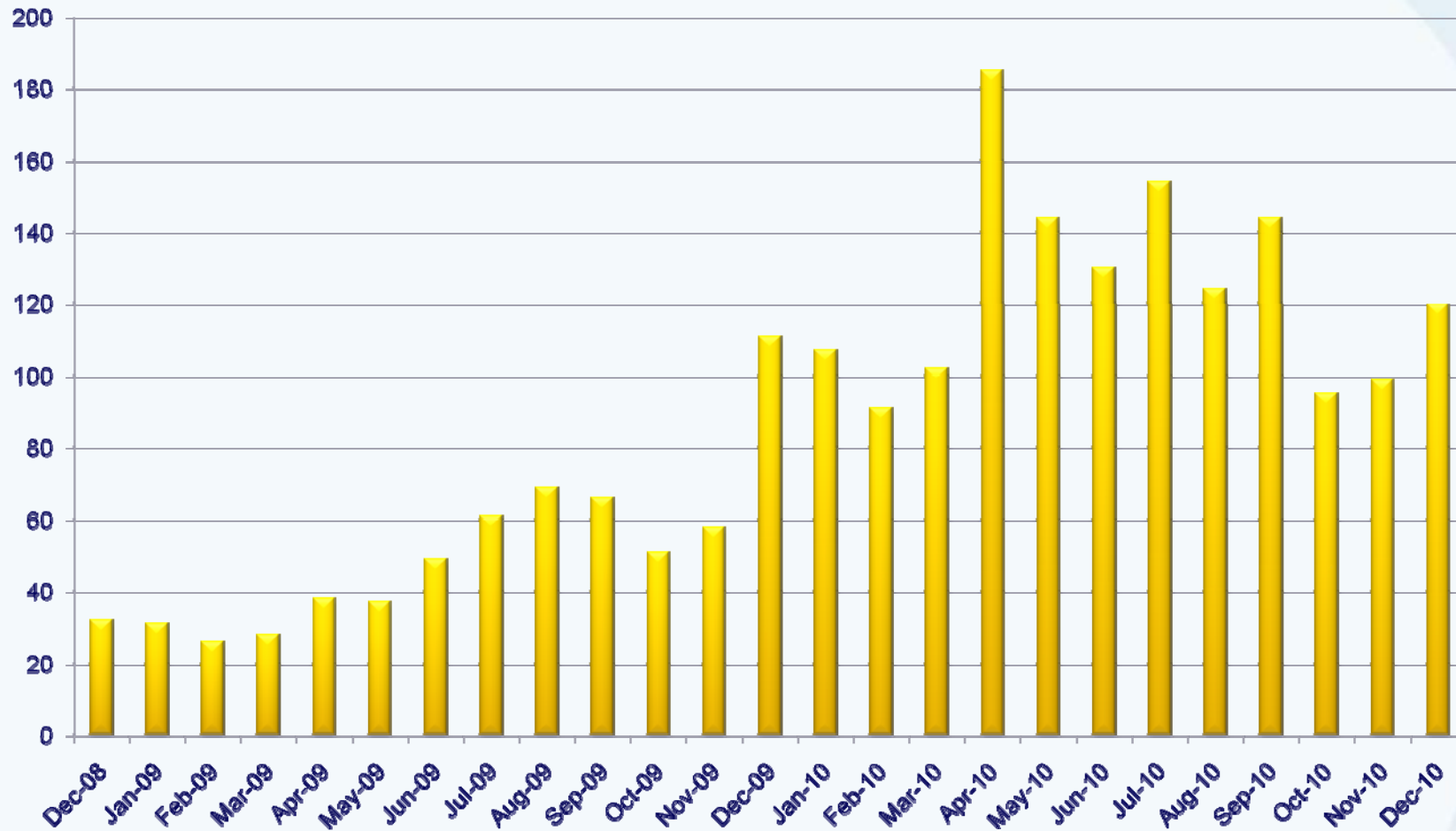
# Metrics by signal source

Number of signals reviewed per category (2 years)



# Metrics by calendar time

## Number of signals reviewed per month



# What have we learned?

- Positive:
  - A bridge between two worlds that were growing apart
  - Higher awareness of the potential impact of some manufacturing changes (and the value of batch numbers)
- Negative
  - Very resource intensive
  - Lack of guidance on what to actually look for
- Missing elements:
  - The potential link between the two types of events, eg:
    - Narcolepsy: what manufacturing deviation to look for?
    - Particles in the vials: what medical events to look for?

**THANK YOU**

# Flu vaccination and febrile convulsions in Australia

- **Summary:** To date, despite extensive analyses the biological basis for the excess cases of fever and febrile convulsions remains unclear.
- **Inspection of Manufacturing Facilities:** At this stage, based on findings from the two TGA audits and information from the US FDA audit, it has not been possible to identify a manufacturing deficiency that is causally linked to the occurrence of a higher than expected rate of febrile convulsions.
- **TGA Laboratory testing:** The TGA has undertaken an extensive range of testing of both retention and field samples of vaccine and this is continuing. To date no abnormalities in pharmacopoeial parameters (endotoxin and potency) have been identified in either retention or field samples. Additional testing has not shown ...

## Quality Investigation of Combo Lot Number A80CA007A of Arepanrix™ H1N1 (AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine) in Canada

- Results from thorough investigations conducted by both GlaxoSmithKline and Health Canada confirm that there was no link found between this vaccine lot and the anaphylaxis adverse events associated with this lot that had been reported.
- It is also important to note that Lot A80CA007A met all of the required specifications for the product, and that no significant differences were observed when Lot A80CA007A was compared to other lots.
- The investigations did not identify any specific quality or manufacturing attributes that would explain the observed higher anaphylactic reporting rate of Lot A80CA007A.
- It should be noted that the overall frequency of anaphylaxis following H1N1 immunization does not exceed the normal range observed after receiving seasonal influenza vaccine.