Post Licensure Communication on Vaccine Safety among Regulator, Industry and Stakeholder

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Disclaimer

The information within this presentation is based on the presenter’s expertise and experience, and represents the views of the presenter for the purpose of this meeting.
TOPIC of DISCUSSION

1. Introduction
2. Regulatory Perspective on Vaccine Safety
4. Conclusion
Vaccination or Immunization is the top Public Health achievement of the 20th Century

MMWR 1999; 48:241

Vaccines are the most efficient public-health tools for promoting individual health and reducing the burden of infectious disease, +/- 6 million deaths are prevented each year by vaccines.
Strategic Issues

- Ensuring **consistent safety and quality** (pre-post market) of a vaccine long recognized as an essential element in any successful immunization/vaccination programme.

- **Local manufacturers in developing countries** are encouraged to involve in **new vaccine research and development**, e.g. new combo vaccine, pandemic influenza vaccine, rotavirus vaccine, meningitis vaccine, etc.

- **Safety of vaccines** is not absolute term but **risk/benefit assessment** e.g. Novel vaccines - how to evaluate safety; Long term safety (adventitious agents, genetic stability, GMOs).

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**the need for an Effective Communication on Vaccine Safety in the post Licensure phase**
Concept of Vaccine ‘safety’

- **Vaccine as biologicals**
  - Complex and variable, cannot separate product from process
  - Subject to contamination (esp adventitious agents)
  - Challenging to fully characterized (not highly purified, esp live vaccines)

- ‘Safe’ does not mean risk-free

Regulatory objective

- Ensure benefits outweigh foreseeable risks for defined indications and users
  - Benefit = the ratio of not to get a serious complication due to an infection
  - Risk = the risk to get a serious complication **due to vaccination**

- Regulatory decision must be **Risk-Based approach**
<table>
<thead>
<tr>
<th>Illnesses</th>
<th>Vaccine Safety</th>
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<tbody>
<tr>
<td><strong>Measles</strong></td>
<td>• <strong>Death:</strong> 1 in 3,000 cases in high income industrialized countries.</td>
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<td></td>
<td>• As much as 1 in 5 cases during outbreaks in low- to middle-income countries.</td>
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<tr>
<td><strong>Diphtheria</strong></td>
<td>Death: 1 in 20 cases.</td>
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<tr>
<td><strong>Tetanus</strong></td>
<td>Death: 25 – 70 in 100 cases overall (10 – 20 in 100 cases with good intensive care management.)</td>
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<tr>
<td><strong>Measles vaccine</strong></td>
<td>Encephalitis or severe allergic reaction: 1 in 1,000,000 cases.</td>
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<td><strong>DTP vaccine</strong></td>
<td>Continuous crying, then full recovery: 1 in 100 cases.</td>
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<td><strong>Tetanus toxoid vaccine</strong></td>
<td>• Convulsions or shock (full recovery): 1 in 1750 cases.</td>
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<tr>
<td></td>
<td>• Acute encephalopathy: 0 – 10.5 in 1,000,000 cases.</td>
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Safety Issue of Rotavirus Vaccine

- 1990’s: intussusception cases from rotavirus vaccine → Withdrawal of first rotavirus vaccine
- 2010: Porcine circovirus types 1 and 2 found in both licensed rotavirus vaccines
- Thorough investigation, incl contaminant testing were done by manufacturer, regulator (US FDA, EMA, TGA) and WHO (SAGE, GACVS)
- TGA on March 24, 2010 & EMA on March 26, 2010 in support of continuing use. Temporary suspension of GSK/Rotarix vaccine by the US FDA lifted May 14, 2010 → No adverse events related to these adventitious viruses

BUT..............
these raise Q about what else is out there.........
REGULATORY LIFE CYCLE OF VACCINE

1. **Discovery Phase**
   - Development and Selection of Candidate Vaccines and Technologies
   - Preclinical Studies (Chemical, Animal)
   - Immunogen Identification (e.g., protein, strain) and Proof of Concept

2. **Phase 1**
   - Human Studies

3. **Phase 2**
   - Clinical Studies (Human)

4. **Phase 3**
   - Manufacturing & Facility Assessment
   - Exploratory Development
   - 100s-1000s

5. **Exploratory Development**
   - General Investigational Plan
   - Laboratory and animal studies
   - Extensive safety studies
   - Development of Manufacturing processes, pilot lots assays

6. **Licensing/MA Process Development**
   - Licensing/MA Process
   - Post Licensure
   - Risk Communication among NRA, MA holder & other stakeholder
   - PMS/PV and or PHASE 4 Study

7. **MA & RMP**
Key Elements of Communicating Risk

All effective communications of risk contain the same key elements. The first element is: *The Risk is Defined for the Situation.*

Risk can generically be defined as the technical -- scientific -- assessment performed to determine the impact of a substance (or agent) on human health .... PLUS .... the perception of that hazard by those affected. Thus, defining risk is a result of ‘HAZARD’ + OUTRAGE.
## TYPE OF VACCINE RELATED EVENTS – POST LICENSURE

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Vaccine product-related reaction</strong></td>
<td>An AEFI that is caused or precipitated by a vaccine that is due to one or more inherent properties of the vaccine product.</td>
<td>Extensive limb swelling following DTP vaccination.</td>
</tr>
<tr>
<td><strong>2. Vaccine quality defect-related reaction</strong></td>
<td>An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.</td>
<td>Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.</td>
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<tr>
<td><strong>3. Immunization error-related reaction</strong></td>
<td>An AEFI that is caused by Inappropriate vaccine handling, prescribing or administration.</td>
<td>Transmission of infection by contaminated multidose vial.</td>
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<tr>
<td><strong>4. Immunization anxiety-related reaction</strong></td>
<td>An AEFI arising from anxiety about the immunization.</td>
<td>Vasovagal syncope in an adolescent following vaccination.</td>
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<tr>
<td><strong>5. Coincidental event</strong></td>
<td>An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.</td>
<td>A fever after vaccination (temporal association) and malarial parasite isolated from blood.</td>
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PM Vigilance activities are carried out to ensure that marketed vaccines continue to be safe.

**Process**

- **Risk Detection**
  - Monitoring AEFIs to detect risks and change in risk/benefit profile

- **Risk Assessment**
  - Assessing risk-benefit profile

- **Risk Minimization/Intervention**
  - Minimising risk by appropriate regulatory actions

- **Risk Communication**
  - Communicating information to optimise safe & effective use
EFFECTIVE COMMUNICATION:

Use Risk Management Principles

LEVEL of RISK IDENTIFIED

ESTIMATION of RISK MAGNITUDE

FOLLOW UP ACTION TO CONTROL RISK

INTERACTION & EXCHANGE OF RISK INFORMATION

INDUSTRY/MANUFACTURER

- HEALTH PROFESSIONALS
- PATIENTS/COMMUNITY/NGO CONSUMERS

&

- REGULATORS/NRA
- IMMUNIZATION PROGRAM

EFFECTIVE COMMUNICATION
**RISK COMMUNICATION**

- Effective communication: a successful risk communication which involves processes such as two-way dialogue, active listening and discussion among those who are involved, regulators, health workers, manufacturer and community.

- GOAL: Maintain confidence by properly responding to public/parent/community concerns, while increasing awareness (public and professional) about vaccine risks.

- Risk communication is an ongoing process that involves all stakeholders. It is essential in at least three situations, namely:
  - explaining properly the benefits and risks of a recommended vaccine;
  - addressing public concerns and upcoming or persistent rumours about vaccine safety;
  - preparing to address vaccine safety crises if and when they occur.

- To provide information rapidly, an effective AEFI monitoring & reporting system and PMV must be in place.
Vaccine Post Market Vigilance (PMV)

The speed with which data can be collected and provided following an AEFI or safety scare is critical in countering adverse publicity or manipulation.

Vaccine PMV relies on 3 steps:

**Signal detection**
- Detect signal that suggest an AEFI is related to a vaccine & does occur by chance
- One of the good sources is spontaneous reporting by health workers

**Development of Causality hypothesis**
Develop hypothesis on whether there is a possible causal association b/w an adverse event & vaccination based on the reported signal

**Testing of Causality Hypothesis**
Test hypothesis through the use of appropriate epidemiological methods, incl the study of available dataset
During the Marketing Application Approval process, a discussion with NRA on Post Marketing Risk Management Plan (RMP), to ensure the RMP includes certain key features, proposed strategies to manage various safety issues for Agency feedback.

Prior to submission of an application for Phase-IV clinical trials, a discussion on information that drives this application, the rationale and design of the further trial applications.

During and after the implementation of required Vaccine PMV

Anytime when there are critical and serious issues on Vaccine safety
CRITICAL FACTORS FOR PUBLIC RISK COMMUNICATION ON VACCINE SAFETY

- **Nature of Causation or Risk**
  unknown or uncertain; Serious, dreaded, dramatic, or memorable safety events

- **Type of Immunization**
  Are children or pregnant women involved? Is it part of a mass immunization campaign? Is it a new vaccine? Is the event relevant to the local situation (ie, vaccine already used)

- **Public Response**
  Could there be media attention? How large is the audience? Credibility and believability of rumour or media story. Does the event or information play on emotional fears?
CONCLUSION
How to Build up Public’s Confidence on Vaccine Safety (VS)

REGULATOR:
- Review & discuss Post Market RMP and Phase IV study
- Strengthen Regulatory requirement science based essential to ensure safety of vaccines
- Timely manage various VS issues
- Conduct an open, transparent - two way communication with all stakeholders

INDUSTRY:
- Provide scientific data
  - General issues in vaccine production and control
  - Design of studies critical issue to address safety in pre-clinical and clinical studies (RMP and Phase IV Study)
- Quality vs quantity of data on safety issues (PMV)

Timely manage VS issues with regulator
Thank you
Terima Kasih
Dhanyavad