

**IABS Workshop, May 19-20, 2011, Baltimore
Adventitious Agents, New Technologies, Risk Assessment**

Assessing Risk When a Potential Adventitious Agent is Found

**Scientific Principles to Consider When a Potential
Adventitious Agent is Found in a Marketed Biological
Product**

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Outline

- Introduction and Background of the Document
- Scope and Purpose
- Regulatory considerations
 - Regulatory oversight
 - How was the agent found?
 - What exactly was found?
 - Where was it found?
- Re-evaluation and new benefit/risk assessment
- Further steps



Introduction

- Porcine circovirus DNA in rotavirus vaccines in 2010
- New technologies may detect agents that previous methods were not capable of, like:

New generation of massively parallel (deep) sequencing methods (MPS)

- A broad regulatory framework exist pre-licensure



Background (pre-licensure)

- Close control of the vaccine manufacturing environment
- Appropriate testing of the raw material, incl.:
 - **Cell substrates**
 - **Seed material**
 - **Other raw material (e.g. culture reagents, stabilizers)**
- Testing of intermediates and final product
- Among others specific requirements exist regarding:
 - **Viral safety evaluation**
 - **Risk associated to BSE/TSE**



Background

- ❑ But a few aspects associated with findings, discovered subsequent to marketing authorization are **not** well defined, in the sense of regulatory actions and decision-making
- The International Conference of Drug Regulatory Authorities (ICDRAs) recommended that WHO assist countries to develop risk management strategies to respond to scientific advances for detection of adventitious agents in biological products.
- The Expert Committee on Biological Standardization (ECBS) recommended that WHO lead the development of a risk assessment process subsequent to marketing authorization.



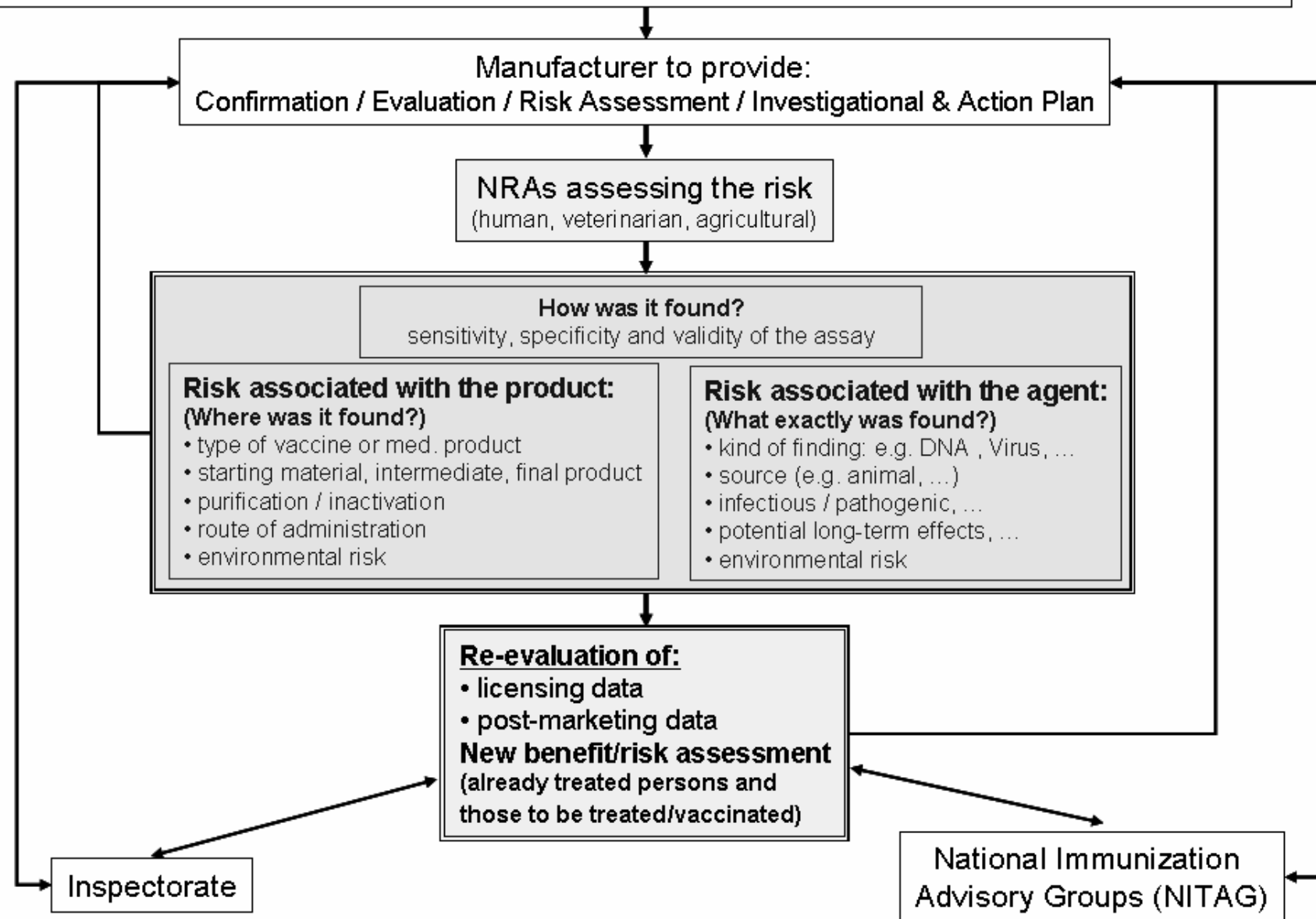
Scope and Purpose

- To provide an **overview of the principles** related to the scientific assessment of risk with any new finding of a potential adventitious agent in an **already registered** biological product.
- To **assist regulators** in the **considerations** they might include during the evaluation and decision-making process.
- It does **not** cover:
 - Risk assessments performed by the manufacturer
 - Guidance on the decisions taken by health care officials (National Immunization Advisory Groups, NITAGs)
 - Guidance on GMP compliance and subsequent decisions/actions



Regulatory Oversight

Any finding of a previously unrecognised adventitious agent coming from any source



NRAs assessing the risk

How was the agent found?

This question relates to:

- Sensitivity and specificity of the method used**
- Validity of the assay**
- Directly linked to the need for reliable confirmation of the finding by the manufacturer**



What exactly was found?

- Is the agent a known agent, a member of a known family or a novel agent?
- Are the nucleic acids that were found simply fragments or full/length intact genomes?
- Are they free or particle-associated?
- If associated with particles, are the particles infectious?
- Are the particles infectious for human cells?
- Is the agent known to be infectious for humans?
- Does the infectious agent cause disease in humans?
- Is the agent transmissible from human to human, animal to human or human to animal?
- Potential long term effects or other effects that can be linked to the agent need to be evaluated



Where was the agent found?

The type of product concerned has an important impact on the potential risk:

- How was the agent introduced?**
- Was the agent found in the starting materials, intermediates or the final product?**
- Are other products affected?**
- Impact of purification and/or inactivation processes, etc.**
- Route of administration**
- Risk to the environment is influenced by both: product & agent**



Re-evaluation & New Benefit / Risk

Re-evaluation of:

- Quality / non-clinical / clinical data
- Post-marketing data (phase IV, pharmacovigilance)
- Communication with the Inspectorate

➔ New benefit/risk assessment

Process which largely depends on:

- Type of adventitious Agent
- Type of product and Indication
- Communication with public health officials (NITAGs)



General comments

Title, Scope and Purpose

- Subsequent to marketing authorization
- Vaccines – Biologicals / biotechnology products?
- Viral contaminations – all kind of adventitious agents?
- Addressing an earlier step?
 - Evaluation of the significance of detecting nucleic acid sequences in vaccines and other biologicals?



Further Steps

- **First Draft sent out for comments, April 2011**
- **WHO discussion in Baltimore, 18 May 2011**
- **IABS Meeting on Adventitious Agents, new Technology and Risk Assessment, Baltimore, 19-20 May 2011**
- **Preparation of a second Draft & second round for comments**
- **Report to ECBS in October 2011**



Thank You

Adventitious Agents Sub Committee

WHO Drafting Group on the evaluation of cell substrates for
production of biologicals

Thank you for your attention

