Regulatory Risk Assessment in the Case of Adventitious Agent Finding in a Marketed Vaccine

Scientific Principles to Consider

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed WHO document on Regulatory Risk Assessment in the Case of Adventitious Agent Finding in a Marketed Vaccine to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by 19 April 2013 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Quality Safety and Standards (QSS). Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at email: kangh@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (WHO/IMD/PUB/04.1).
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1. Introduction

The finding of an adventitious agent in a biological product has been of concern to regulatory agencies, manufacturers, and public health officials since the early 1900s when the issue first arose. Since then, there have been several instances where a new agent has been identified as a contaminant of a marketed product. The most recent example is the discovery of porcine circovirus DNA sequences in rotavirus vaccines in 2010. In response to this development, and recognizing the scientific advances for the detection of adventitious agents in biological products, the WHO Expert Committee on Biological Standardization (2010) and the International Conference of Drug Regulatory Authorities (ICDRA) recommended that WHO take a lead in providing guidance to its Member States on undertaking risk assessment strategies when an adventitious agent is detected in an already licensed vaccine.

Although the principles of drug regulation are generally consistent internationally, the legislation, duties, responsibilities and structure of institutions that have responsibility for translating the principles into laws, regulations, and guidance may vary substantially from country to country. Nevertheless, the following functions are generally considered essential for an acceptable regulatory system: marketing authorization and licensing; post-marketing surveillance, including for adverse events; lot release; laboratory access; Good Manufacturing Practice (GMP) inspections of manufacturing sites and distribution channels; and authorization and monitoring of clinical trials. Countries take this into consideration and adapt the principles to their structure. In addition to those regulatory functions, some countries have a National Immunization Technical Advisory Group (NITAG) that helps to guide national immunization policies, and usually works closely with the relevant regulatory agencies when safety issues arise.

This document is intended to provide guidance to regulators regarding the principles of risk evaluation and decision-making when a potential adventitious agent is found in an already licensed or registered vaccine.
It is taken as fact that manufacturers routinely assess risk to their products by the manufacturing procedures and environment as part of their compliance with GMP. In some countries, quality by design principles have also applied. It is taken as fact that public health officials make decisions on the basis of benefit/risk and often, cost/benefit balances. These established practices are assumed to remain in place when a potential new adventitious agent is found, and are beyond the scope of this document.

2. Background information

A variety of tests are required by National Regulatory Authorities (NRAs) and/or National Control Laboratories (NCLs) at various parts of the production process for biologicals that are intended to help assure that biological products and the biological starting materials from which they are manufactured are free of adventitious agents (i.e. viruses, bacteria, fungi, mollicutes, etc.). Further, it is important to ensure that the risk from potential agents, including transmissible spongiform encephalopathy agents (TSEs), that may be present is reduced by the choice of quality starting and source materials and by the production process (e.g. aseptic processing, viral and TSEs clearance and/or inactivation during purification processes). In addition to the traditional tests, new technologies for detecting adventitious agents are being developed and coming into use. These new detection technologies may have higher sensitivity than previously utilized methods and detect agents that previous methods were not capable of detecting. Up to now (2013), screening for adventitious agents has relied on the use of transmission electron microscopy, in vitro infectivity or biochemical assays, in vivo assays and specific polymerase chain reaction (PCR) tests. New methods and technologies, like like next generation sequencing (NGS), microarrays, or PCR paired with mass spectrometry, are powerful tools for the identification of viruses and other adventitious agents without having prior knowledge of the nature of the agent. Such new technologies might uncover the presence of other yet unrecognized adventitious agents in the future. Furthermore, new agents are emerging and being discovered. Therefore, the situation may arise where it is discovered, subsequent to marketing authorization, that a product, the cell substrate
from which it was produced, or source materials used in production are contaminated
with a previously undetected or unknown adventitious agent.

A broad regulatory framework exists with regard to adventitious agents and viral safety
of medicinal products pre-licensure, including evaluation by regulators of the
manufacturer’s control of the manufacturing environment; compliance with current GMP;
testing of source materials, intermediates and the final product; as well as requirements
for the validation of viral testing and removal procedures. Detailed WHO
recommendations and guidances are available concerning the use of animal cell
substrates for the manufacture of biological medicinal products (1). The risk associated
with TSEs in general and bovine spongiform encephalopathy (BSE) in particular is
addressed primarily through precautionary measures set out in WHO guidelines on
transmissible spongiform encephalopathies in relation to biological and pharmaceutical
products (2). The latest version of the WHO guidelines on tissue infectivity distribution in
transmissible spongiform encephalopathies should also be consulted (3). These tables are
periodically updated as new data become available. Nevertheless, there are aspects
associated with the discovery of a signal for a potential adventitious agent in a product
subsequent to marketing authorization, that are not well defined in the sense of
regulatory actions and decision-making. For example, how to handle the discovery of the
sequences of porcine circoviruses in rotavirus vaccines (4). Similar situations have
occurred in the past, including finding SV40 in Poliovirus Vaccines in the 1960’s (5) and
avian leukosis virus in Yellow Fever Vaccines (6,7). The development of the Product-
Enhanced Reverse Transcriptase (PERT) and related PCR-based RT assays led to finding
RT activity at levels not detectable by the conventional RT assay in avian cell-derived
vaccines in the mid-1990’s, which suggested the possible presence of a contaminating
retrovirus (8,9).

The above examples illustrate a situation in which either infectious agents were
discovered (by cell culture or by epidemiology) or in the last example, an enzymatic
activity was discovered using a much more sensitive assay. Recent advances in
technology have the potential for other types of findings to be made that are suggestive of
an adventitious agent contamination. These might include discovery of a structure
suggestive of a viral particle by visualization technologies, such as enhanced electron
microscopy; or discovering a partial nucleic acid sequence suggestive of an adventitious
agent by modern amplification or sequencing technologies. The sequencing technologies
may involve assessing genomes (free or encapsidated) or RNA transcripts. Further, they
may entail positive selection against an organized database of known sequences of
adventitious agents or negative selection to eliminate host cell sequences and analysis of
what remains. In either case, regulators may be faced with making risk assessments and
decisions about the safety of licensed vaccines on the market in their country on the basis
of incomplete data with regards to whether an actual adventitious agent is present or not.

3. Scope

This document is intended to provide information in the form of an overview of the
principles related to the scientific assessment of risk that could be considered with any
new finding of a potential adventitious agent in an already licensed or registered vaccine;
the same principles will apply to all biological products. The regulatory implications of
such a finding are also considered.

The document does not cover any aspect of the risk assessment and steps to be taken on
the part of manufacturers nor does it provide guidance on the decisions that might be
taken by public health officials, such as NITAGs. In the context of pharmaceutical
complaints and other incident-based risks to health, inspectorates usually have their own
risk assessment procedures, including a risk classification. This risk assessment, which is
sometimes referred to as health risk assessment, is also not included within the scope of
this document.

4. Regulatory considerations

Regulatory oversight is the responsibility of NRAs and/or NCLs.
Whenever new findings occur with the potential to have a negative impact on the quality,
safety or efficacy of a medicinal product, it is the responsibility of the manufacturer to
provide NRAs/NCLs with all relevant data and information currently available to inform regulatory decision-making. This should include confirmation and evaluation of the finding, the manufacturer’s own risk assessment and reduction strategy as well as an investigational and action plan, in order to facilitate any regulatory action that might be necessary.

Based on the manufacturer’s data and any other reliable, credible data available, the Regulatory Agency (NRA/NCL) will assess the risk of the potential adventitious agent. Some agencies may be in the position to perform their own independent investigations, which might help in assessing the risk. In any case, the risk assessment should be performed on the basis of current science and technology. Regulators should conduct an independent evaluation of the manufacturer’s new data in the context of the benefit/risk assessment of the licensed/marketed vaccine. The potential impact of regulatory decisions on public health should be discussed with public health officials, taking into account country-specific situations. This assessment should take into account the country specific benefit/risk assessment of public health officials, if available.

The main areas that should be considered in the risk assessment performed by the regulatory agencies can be headed by the following questions:

- How was the signal detected?
- Where was the signal identified?
- What exactly was identified?
Any signal suggesting a previously unrecognised adventitious agent coming from any source

Manufacturer to provide:
Confirmation / Evaluation / Risk Assessment / Investigational & Action Plan

NRAs/NCLs assessing the risk
(human, veterinary, agricultural)

How was the signal detected?
sensitivity, specificity and validity of the assay

What exactly was identified?
- kind of signal: e.g. DNA, Virus, ...  
- source (e.g. animal, ...)    
- infectious / pathogenic, ...  
- potential long-term effects, ...   
- environmental risk

Where was it identified?
- type of vaccine  
- starting material, intermediate, final product  
- purification / inactivation  
- route of administration  
- environmental risk

Re-evaluation of:
- licensing data
- post-marketing data

New benefit/risk assessment
(already treated persons and those to be treated/vaccinated)

Inspectorate

National Immunization Technical Advisory Groups (NITAG)

Diagram 1: Regulatory oversight

The above mentioned questions need to be considered for the evaluation of the manufacturer’s data relevant to the finding and the re-evaluation of the original data initially provided for marketing authorization. This is of particular interest if the type of agent or potential agent, newly identified, was likely to have been present at the time of marketing authorization. Special consideration also should be given to post-marketing data, if available. Details such as the characteristics of the recipient population, in terms of susceptibility to the agent and severity or complications from infection, may be useful considerations.

The whole evaluation and re-evaluation process should lead to an updated benefit/risk assessment, as a basis for any regulatory action that might be necessary. In addition, the
updated benefit/risk assessment is important to help public health officials to decide on current recommendations regarding use of the product in their country. Since the process is likely to be dynamic and new data for evaluation will continue to emerge during the process, the assessment includes feedback loops at each step, indicating the need for good communication practices between the NRA/NCL and the manufacturer and potentially between NRAs as well as other groups such as the NITAG and the Inspectorate.

Depending on national practices or due to the characteristics of the finding, it might also be necessary to include and/or facilitate direct communication between the manufacturer and public health officials, such as NITAGs.

5. Regulatory risk assessment

How was the signal detected?

This question addresses all the issues related to the sensitivity, specificity and validity of the test/assay that was used to detect and/or identify the potential agent and is directly linked to the need for reliable confirmatory data provided by the manufacturer. The actual assessment of risk includes two perspectives which are summarized by the following questions: What exactly was the signal, and where was it identified?

Where was the signal identified?

The type of vaccine or medicinal product concerned has an important impact on the potential risk. Directly linked to the type of product, there are other factors which should be considered, for example:

Was the signal found in the starting materials (cell substrate)/source materials, intermediates, or in the final product? Is there an impact, positive or negative, imparted by the purification and/or inactivation processes (on the starting/source materials or on the product), or any other manufacturing step? What is the route of administration of the product and how does it impact the risk to the product recipient from the potential agent?

Other parameters such as the dose, the route and schedule of administration, as well as
characteristics of the recipient population may be useful to consider in risk evaluation.

Finally, the potential risk to the environment is influenced by the product concerned (e.g. how it is excreted by the product recipients or how the manufacturing wastes are handled) as well as by the type of agent that was found.

Within this context, it would be appropriate to distinguish the characteristics of three main stages in the production of a biological medicinal product, i.e. starting materials, intermediates and the final product. The impact and applicability of the following questions vary within this context. The following questions are applicable once an adventitious agent has been identified or the finding is suggestive of an agent:

- How was the agent introduced (what are the results of the root-cause investigation)?
  - If the agent was introduced by the cell substrate, most/all lots would be implicated, representing a broader problem. If the agent was introduced by the environment, personnel, or specific batches of source materials, then a more limited number of lots may be implicated and a recall of those specific lots of the marketed product(s) could be an effective means to reduce risk to recipients. Assessment of whether those specific lots were used in humans, and clinical follow-up of humans exposed to the implicated lots, could provide valuable data regarding the actual risk to humans by the incident.

- Are other products affected?
  - If the agent was introduced in the cell substrate or source materials common to use by the manufacturer in more than the implicated product, more products may be contaminated. If the agent was introduced during production of a specific lot(s), other products made concurrently in the same facility at the time that lot was manufactured could be implicated. If, however, the affected cell substrate or source material batches are used for the sole purpose of producing one product, and/or if the facility is a dedicated facility, the risk to other products from that manufacturer may be limited. If product lots are infected by an upstream contamination, the frequency of the contamination should be addressed. Clinical lots used in product development may provide particularly useful information.
- Is it possible to remove the agent by purification?

  If the agent was found in the starting materials, or upstream intermediates, the purification process used in production of the implicated product(s) may be sufficient to remove the agent during routine production, thus, reducing the risks. Alternatively, it may be possible to change the production process to improve its ability to remove the agent from future lots of the product. Of course, any changes to manufacturing may have impacts on the established quality, purity, potency, safety, and efficacy of a licensed or registered product and must be approved by the relevant NRA/NCL prior to introduction of such process changes into the manufacturing procedures following the normal procedures for notifying the NRA/NCL regarding changes to approved manufacturing applications.

- Is it possible to inactivate the agent?

  If the agent was found in the starting materials, or upstream intermediates, it may be found that the inactivation process(es) used in production, if any, of the implicated product(s) may be sufficient to have inactivated the agent during routine production, thus reducing the risks. Alternatively, it may be possible to change the production process to improve its ability to inactivate the agent from future lots of the product. Of course, any changes to manufacturing may have impacts on the established quality, purity, potency, safety, and efficacy of a licensed or registered product and must be approved by the relevant NRA/NCL prior to introduction of such process changes into the manufacturing procedures following the normal procedures for notifying the NRA/NCL regarding changes to approved manufacturing applications.

- Especially for a live viral vaccine, what is the impact of the route of administration of the product?

  Viruses vary in their route of normal infection and may only establish productive infections when the host is exposed by a particular route. However, a product may be administered by other than the normal routes of viral exposure. Particularly, for parenteral products, which bypass the normal defense mechanisms of the host (skin, saliva, stomach acids, etc.), infection may occur more readily through this route of exposure. Of course, it may also be the case that exposure through an
abnormal route may preclude exposure of susceptible target cells, reducing risk.

Alternatively, if the product is delivered by a normal viral infection route (e.g. orally), then information about normal virus exposure, such as epidemiology data, may be more relevant to the situation.

- Is there a risk to the environment?

It may be determined that the agent does not pose a significant risk to the product recipients. However, the agent to which they were exposed may be shed by the product recipients through normal excretory processes. For example, oral poliovirus vaccine can replicate in the human gut and be shed in feces, thereby exposing close contacts of vaccinees through the fecal-oral route. It could be the case, if the agent were shed by the product recipients, that human and animal contacts of these recipients could be placed at risk of exposure to the agent.

- Is there a risk of dissemination at the manufacturing plant?

Even if the product itself is not contaminated, but an upstream material, such as a cell substrate is found to be contaminated, then there may be risk to the environment from the manufacturing process and disposal of manufacturing waste products, particularly in the case where the agent found is not already endemic to the geographic region of the manufacturer facility (facilities). It would be an expected aspect of current GMPs that wastes are decontaminated before release to the environment, but procedures should be reviewed regarding their effectiveness in consideration of the revealed contaminant.

**What exactly was identified?**

The risk associated with the agent primarily depends on the physical nature of the agent, e.g. whether what was found was nucleic acid or an intact virus, etc. In addition, the normal host species of the agent, whether it is animal-, plant- or human-derived as well as whether the finding has any potential to be infectious or even pathogenic to humans or animals needs to be considered thoroughly. In this sense, potential long-term effects or other effects that can be linked to the agent need to be evaluated. As already stated above,
the potential risk to the environment depends on both the characteristics of the agent and
the product concerned.

The text below leads decision-makers through a series of questions and potential answers
that should be considered in regard to the risks to humans associated with an adventitious
agent, the nucleic acid of which was discovered, through the use of new detection
technology, in a starting material or final product of a licensed biological medicinal
product. The series of questions may be modified for other types of findings, such as
structures suggestive of viral particles or enzymatic activities suggestive of the enzymes
encoded by viruses.

The questions that should be considered include the following:

- Is the agent a known agent, a member of a known family, or a novel agent?
- Are the nucleic acids that were found free or particle-associated?
- Are the nucleic acids that were found simply fragments or full-length intact
  genomes?
- If associated with particles, are the particles infectious?
- Are the infectious 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?

It should be borne in mind that like all scientific investigations, the evaluation is complex
and likely more complicated than answering a series of questions.

The finding of nucleic acids that might indicate the presence of an adventitious agent is
used to illustrate the general approach that might be taken:

If the viral nucleic acids are full-length and intact, but free (not particle-associated), they
still have the potential to be infectious if they are taken up by susceptible cells and thus,
they could still represent a risk, but only under the right set of conditions. These
conditions would include, but are not be limited to, whether the route of inoculation
would expose the free nucleic acids to nucleases (e.g. by oral administration) thus
eliminating them or fragmenting them before they could be taken up by cells. Further, the
route of administration could impact the availability of susceptible target cells to take up
free nucleic acids.
Likewise, if they are particle-associated, but fragmented, one must consider whether they
could infect cells in the recipient of the medicinal product. Also, when the nucleic acids
are uncoated in the cell, could they be repaired by natural cellular repair mechanisms, and
lead to a productive infection in the recipient despite having been fragmented inside the
viral particle?
In either of these cases or in the case of infectious particles that lead to only an abortive
infection in human cells, concern may still exist if the agent is one that is known to result
in pathology following abortive infection. Particularly, oncogenic viruses could still
represent a risk even if resulting in only an abortive infection.
For some viruses, it has been shown that while the host species does not display disease,
infection of humans (or another non-host species) by the virus may result in significant
morbidity or mortality. A significant example of this is simian Herpes B virus, which
usually does not cause disease in monkeys, which are the natural hosts, but which can
cause a fatal disease in humans.
Finally, if it is unknown whether an adventitious agent causes disease in humans but does
cause disease in the host species, this may represent a potential risk. In such a situation,
the post-marketing safety database, as well as the clinical trials database, should be
searched for signals from the clinical data reflective of the known pathology in the host
species, to determine if a similar disease syndrome might be occurring in product
recipients. However, symptoms and pathology may be quite different in humans, and this
must be kept in mind during the evaluation of databases.
One indicator that the agent may be able to infect humans, even in the absence of a well-
described disease syndrome or recognized zoonosis, would be the occurrence of
antibodies in exposed humans. One question that should be asked in addressing the
question of whether the agent infects humans is whether there is evidence of immunity in
humans, e.g. the presence of antibodies in veterinarians or individuals involved in the
husbandry of the animal species associated with the agent (e.g. pig farmers in the case of
the porcine circoviruses found in rotavirus vaccines). Further, if sera were saved from
human subjects in the clinical trials with the product, they could be screened for
antibodies to the suspected agent. If this is done, it may require review of the informed
consent forms from the original trial to determine if this additional use of the sera was
covered when the subject gave consent to participate. If additional studies, such as these,
were not covered by the original informed consent, it may require that subjects be
approached to give informed consent for their sera to be used for this purpose. Therefore,
consideration of such a potential future use of stored sera should be considered when
clinical trials are being designed to facilitate the most rapid and ethical future use of the
specimens.

**Re-evaluation**

All data provided by the manufacturer on the above mentioned questions and all other
reliable data available need to be assessed in the context of the original licensing data and
post-marketing surveillance data, if any. The re-evaluation of manufacturing and quality control data should be done in close
cooperation and communication with the responsible inspectorate. Especially important
are the assessment of potential GMP failures, strategies to avoid or mitigate the newly
identified agent and the root cause investigation.

In case the potential agent has been identified as a previously unrecognised adventitious
agent, nonclinical and clinical data including post-marketing data, if available, are
important for the evaluation of the safety and the potential risk of the agent and the
respective medicinal product. The assessment of these data should consider risks that
might be unique to a specific patient population, such as immunocompromised, infants,
or elderly, if they are included in the clinical indication for the product or often receive
the product off-label. Moreover, the epidemiology of the agent might inform the
assessment of the risk. The evaluation of potential long-term effects will depend on the
type and amount of data available.
New benefit/risk assessment

In principle, any time new data emerges on the previously unrecognized adventitious agent and/or the medicinal product, a new benefit/risk assessment is needed. This is consistent with the principles of risk assessment, that it be undertaken reiteritively.

Methods or principles for a systematic approach for benefit/risk assessments are given elsewhere and are not within the scope of this document (e.g. 10).

Within the health care professional community, there may be different perspectives of benefit and risk. In the case of GMP and/or pharmaceutical technical issues, the benefit/risk assessment falls within the responsibility of the inspectorate or the NRA/NCL. Each (new) benefit/risk assessment of a medicinal product may also have public health implications. Usually, the benefit/risk assessment of public health officials (NITAGs) is separate and might differ from the regulatory assessment due to additional considerations that should be taken into account (e.g. population vs. individual health considerations, cost/benefit analyses). As with the inspectorate, close collaboration and communication between the licensing authority and public health officials is considered to be crucial.

Benefit/risk assessments of medicinal products depend not only on scientific and biological considerations, but also on regional considerations and the particular circumstances (e.g. epidemiology, regulatory or legal framework) in those areas. Nevertheless, in a growing global environment, communication and the exchange of information on a global level is of utmost importance.

6. Summary and Conclusions

Regulatory risk assessment is a dynamic process both in terms of how it has evolved over the past 60 years and in the way in which information is accumulated and evaluated in any given instance. Much has been learned since the discovery of SV40 as a contaminant of polio vaccines in 1960, and it is hoped that the lessons of past instances of finding an adventitious agent in vaccines will provide useful guidance for the future. A central element of the risk evaluation process is that the assessment needs to be updated each time new data emerge; thus, it is an iterative process. Nevertheless, it is often the case that there is a need for immediate decisions at an early phase of the assessment when
many of the answers to the questions outlined in this document will not be available. This
presents particularly challenging situations for all interested and affected parties. Due to
the potential complexity of future events a simple guidance or a list of priorities to
consider can not be given. However, the four case studies in the accompanying
publication illustrate how this challenge was met in the past. Among the most important
lessons from the past is the desirability of transparency and communication. When all
parties with a vested interest in the outcome of a regulatory risk assessment are aware of
and understand the bases on which decisions are made, the probability of
miscommunication and error are minimized.

Glossary (alphabetical order)
The definitions given below apply to the terms used in this document. They may have
different meanings in other contexts.

Adventitious agent
Contaminating microorganisms of the cell culture or source materials including bacteria,
fungi, mycoplasmas/spiroplasmas, mycobacteria, rickettsia, protozoa, parasites,
transmissible spongiform encephalopathies (TSE) agents, and viruses that have been
unintentionally introduced into the manufacturing process of a biological product.
The source of these contaminants may be from the legacy of the cell line,
the source materials used in the culture medium to propagate the cells (in
banking, in production, or in their legacy), the environment, personnel,
equipment, or elsewhere.

Cell substrate
Cells used to manufacture a biological product.
The cells may be primary or cell lines, and may be grown in monolayer or
suspension culture conditions. Examples of cell substrates include primary
monkey kidney, MRC-5, CHO, and Vero cells.
Cells used to generate essential components of a final product, such as
Vero cells for the generation of “reverse genetics” virus for use in seeding
vaccine production, are considered to be “pre-production” cell substrates.
Whereas cells used to manufacture the bulk product (e.g. packaging cell
lines for gene therapy vectors; Vero cells for vaccine production; CHO
cells for recombinant protein expression) are considered to be
“production” cell substrates.

Dedicated facility
A manufacturing establishment or suite within the establishment that is used solely for
the production of one product and is not used to manufacture any other product at any
time. In contrast, a multi-use facility is one in which multiple products may be made
either on a campaign basis (one at a time) or simultaneously.

**Environmental risk**
The risk to public health and the environment. It does not assess the risk to the intended
recipient of the vaccine which is assessed through clinical studies of the vaccine. It does
not assess the risk to laboratory workers.

**Inspectorates**
A civil agency charged with inspecting and reporting on manufacturing facilities to
ensure compliance with regulatory requirements.

**Intermediates**
Partly processed product that must undergo further manufacturing steps before it becomes
a bulk product.

**Investigational and action plan**
A documented approach to undertake a risk reduction strategy through root cause
investigations and application of corrective and/or preventive actions.

**Marketing authorization**
An official document issued by the competent NRA for the purpose of marketing or free
distribution of a product after evaluation for safety, efficacy and quality. In some
countries, the term “licensing” or “registration” is used.

**Microarrays**
A collection of spots of nucleic acids attached to a solid surface. Each spot contains
picomoles of a specific nucleic acid sequence that serves as a probe. A sample may be
hybridized to the spots and detected by fluorophore-, silver-, or chemiluminescence-
labeling. The solid support may be in the form of a silicon or glass chip or as beads.
High-throughput approach to Southern or northern blotting.

**National Immunization Technical Advisory Group (NITAG)**
A technical resource providing guidance to national policy-makers and programme
managers to enable them to make evidence-based immunization-related policy and
programme decisions.

**Next generation sequencing (NGS)**
High through-put sequencing technology that processes sequences in parrallel, producing
thousands or millions of sequences at once from a sample. Methods include 454
pyrosequencing, Illumina, and several others. Each method has different attribute, such
as length of a typical sequence read, accuracy, number of reads per run, time for a run,
costs, etc. As a consequence, the method chosen should consider the purpose for which
the data are to be generated.

**Quality by design**
A systematic approach to product development or manufacturing that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. A means to build into a product or process the inherent set of characteristics needed to fulfil quality requirements.

**Regulatory risk assessment**
A systematic process of organizing information to support a risk/benefit decision to be made within a regulatory review and evaluation. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards, in balance with benefits associated with exposure to the medicinal product under review and evaluation.

**Risk**
The combination of the probability of occurrence of harm and the severity of that harm.

**Risk assessment**
A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

**Risk evaluation**
The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

**Risk reduction strategy**
A plan or method for attaining a decrease of the probability of occurrence of harm and/or the severity of that harm.

**Root-cause investigation**
A problem-solving method that involves systematic investigation of deviations or out-of-specification results in order to identify an underlying root cause of the faults or problems that caused them. Generally, the analysis aims to identify the factors that resulted in the nature, magnitude, location, and timing of hazards or adverse outcomes. In this manner, necessary behaviours, actions, inactions or conditions that require changing to prevent the deviation or OOS from recurring in future may be identified and corrected and/or prevented.

**Sensitivity**
The lower limit of quantitation (LLOQ) or limit of detection (LOD) of an assay. The LLOQ is the lowest amount of an analyte in a sample that can be quantitatively determined with suitable precision and accuracy. The LOD is the lowest amount of the analyte in a sample that can be reliably detected, but not necessarily quantitated as an exact value.

**Specificity**
The ability of the method to detect the required range of microorganisms that might be present in the test sample.

Starting/source material
Any substance of a defined quality used in the production of a vaccine product, but excluding packaging materials.

Test/assay
An analytical procedure or method, e.g. for identification of an analyte, for measuring impurities’ content or presence, or for quantitation of active ingredients.

Upstream
Activities that occur at or near the beginning of a process or manufacturing flow, e.g. cell culture and harvest or establishment of seeds or cell banks.

Validity
An expression of the degree to which a measurement performed actually measures the characteristic which the investigator wishes to measure.

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