Vaccine 34 (2016) 6617–6625

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Adventitious agents and live viral vectored vaccines: Considerations for archiving samples of biological materials for retrospective analysis☆

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ARTICLE INFO

Article history:
Available online 15 June 2016

Keywords:
Live viral vaccines
Vaccines
Adventitious agents
Traceability
Sample archiving
Vaccine manufacturing
Vaccine safety
Brighton Collaboration

ABSTRACT

Vaccines are one of the most effective public health medicinal products with an excellent safety record. As vaccines are produced using biological materials, there is a need to safeguard against potential contamination with adventitious agents. Adventitious agents could be inadvertently introduced into a vaccine through starting materials used for production. Therefore, extensive testing has been recommended at specific stages of vaccine manufacture to demonstrate the absence of adventitious agents. Additionally, the incorporation of viral clearance steps in the manufacturing process can aid in reducing the risk of adventitious agent contamination. However, for live viral vaccines, aside from possible purification of the virus or vector, extensive adventitious agent clearance may not be feasible.

In the event that an adventitious agent is detected in a vaccine, it is important to determine its origin, evaluate its potential for human infection and pathology, and discern which batches of vaccine may have been affected in order to take risk mitigation action. To achieve this, it is necessary to have archived samples of the vaccine and ancillary components, ideally from developmental through to current batches, as well as samples of the biological materials used in the manufacture of the vaccine, since these are the most likely sources of an adventitious agent. The need for formal guidance on such vaccine sample archiving has been recognized but not fulfilled. We summarize in this paper several prior major cases of vaccine contamination with adventitious agents and provide points for consideration on sample archiving of live recombinant viral vector vaccines for use in humans.

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http://dx.doi.org/10.1016/j.vaccine.2016.02.015
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1. The need for archiving vaccine samples and other biological materials

Vaccines are one of the most effective public health medicinal products with an excellent safety record. Well-planned and implemented immunization programs have profoundly reduced the morbidity and mortality of targeted diseases [1], such as the global eradication of smallpox [2] and the elimination of poliomyelitis [3] and measles [4] from many regions of the world. Since vaccines are usually administered to large populations of healthy people including children, frequently with the goal of near universal coverage (under legal mandate in some countries), their safety and quality are paramount for public health.

As vaccines are produced using biological materials, there is a need to safeguard against potential contamination with adventitious agents. Adventitious agents are defined by the World Health Organization (WHO) as microorganisms that may have been unintentionally introduced into the manufacturing process of a biological medicinal product [5]: these include bacteria, fungi, mycoplasma/spiroplasma, mycobacteria, rickettsia, protozoa, parasites, transmissible spongiform encephalopathy (TSE) agents and viruses. Adventitious agents could be inadvertently introduced into a vaccine through starting materials used for production, such as cell substrates, porcine trypsin, bovine serum, or any other source materials of animal or human origin [6]. Therefore, extensive testing is recommended at various stages during vaccine manufacture to demonstrate the absence of adventitious agents [5]. Additionally, the incorporation of viral clearance steps in the manufacturing process, which evaluate the capability of the manufacturing production process to inactivate and/or remove potential viral contaminants [7] can aid in reducing the risk of adventitious agent contamination in a biological product; however, for live viral vaccines, aside from possible purification of the virus or vector, extensive adventitious agent clearance may not be feasible. Hence, the issue of unknown contamination risks of live or vectored vaccines requires more stringent safety oversight [5].

In the event that an adventitious agent is detected in a current vaccine, it is important to determine its origin, evaluate its potential for human infection, and discern which batches of vaccine may have been affected for notification and in order to take risk management action plans. To achieve this, it is necessary to have archived samples of the vaccine and ancillary components, ideally from developmental through to current batches, as well as samples of the biological materials used in the manufacture of the vaccine, since these are the most likely sources of an adventitious agent.

Although currently recommended testing has a good record for demonstrating absence of adventitious agents in vaccines, there have been rare cases of adventitious agent detection in some licensed vaccines. A recent notable event was that of porcine circovirus 1 (PCV1) in a rotavirus vaccine [8–10]. Early episodes of contamination of biologicals (e.g., tetanus contamination of diphtheria anti-toxin) date back to the beginning of modern immunization and led to the establishment of regulatory oversight in the early 1900s [11]. The discovery that early polio vaccine was contaminated by simian virus 40 (SV40) due to infection of rhesus monkeys resulted in a major manufacturing change in the cell substrate from primary rhesus monkey kidney cells to African Green monkey kidney cultures [12]. The detection of bacteriophage was detected in measles and polio vaccines, reverse transcriptase in measles and mumps vaccines, and the emergence of bovine spongiform encephalopathy (BSE) commonly known as “mad cow disease” in the 1980s, and ultimately the human version variant Creutzfeldt–Jakob disease (vCJD) in the 1990s, led to considerable regulatory deliberations, and also guidance on the use of bovine (and other) materials that could transmit transmissible spongiform encephalopathies (TSE's) [12–15].

Viral vaccines are grown in cell cultures that may have been propagated in media containing bovine serum, and possibly used porcine trypsin for cell passage. Thus, in addition to archiving final released vaccine, there is also an argument for archiving the starting biological materials and of records that provide full traceability of biological materials used in vaccine manufacture. However, the issue of cell and serum archiving and their full traceability are not within the scope of this document at this point in time, and this paper will focus on the live recombinant viral vectored vaccine itself.

Laboratory testing is used to demonstrate the absence of adventitious agents in the vaccine. In the event that contamination is found in a released vaccine after it has been marketed, samples obtained from vaccinees (e.g. serum and PBMCs) may be used to evaluate whether the adventitious agent infected the vaccine recipient. Retrospective testing confirmed the presence of PCV1 DNA in Rotarix® since the initial stages of its development and in vaccine lots used in clinical studies conducted pre- and post-licensure [10]. Therefore, adventitious agents that fail detection using technologies available at the time a vaccine was originally produced and used, might at a later stage be detected by re-testing using emerging technology. In order for a new technology to be utilized to improve vaccine safety and detect past contamination events, samples of the vaccines and materials used in their production and samples from the vaccine recipients need to be collected and archived. Hitherto, the need for formal guidance on such vaccine sample archiving has been recognized but not fulfilled [15]. The Brighton Collaboration Viral Vector Vaccine Safety Working Group, formed in 2008 with voluntary representatives from academia, government and industry [16], has therefore summarized in this paper several prior major cases of vaccine contamination and provides points for consideration on sample archiving of live recombinant viral vector vaccines in humans. The Group recognizes that this document may be controversial, especially the cost implications, but feel it is important to stimulate the discussion on both the need for vaccine sample archiving and how this need might be met.

While this document focuses on live viral vector vaccines, relevant past experience with traditional viral vaccines are discussed and the lessons learnt may be usefully applied to novel vaccines, especially those that are live attenuated.

2. Historical context: past to future

History has shown that extensive testing for adventitious agents during manufacture of vaccines has prevented major contamination events and potential adverse clinical consequences. However, reports of product contamination have occurred periodically, mostly due to viruses present in biological reagents used for production (e.g. animal tissues or primary cell substrates, serum, or trypsin). The genomic and biotechnology revolution of the last decades has enabled the development, licensure, and production of many new vaccines and biologicals. The number of vaccine manufacturers who supply the global market has also been increasing, many of whom are from emerging economies [17]. While all vaccine manufacturers are regulated by their national health authorities, and those who supply UNICEF are pre-qualified by the WHO as meeting good manufacturing practice (GMP) standards [18], their capabilities differ and many need improved pharmacovigilance systems, such as standardization of safety reporting [19].

Since many if not most vaccines globally will likely continue to be made using biological reagents for the foreseeable future, the possibility of adventitious contamination cannot be totally

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