Review Article

REGULATIONS FOR TESTING AND LICENSING OF VACCINES IN UNITED KINGDOM

ABSTRACT

Vaccines are one of the most significant achievements of science and public health for prevention of infectious disease. Overall vaccination policies for HCP in should be periodically revaluated in order to provide optimal protection against vaccine preventable diseases and infection control with in healthcare. The guidelines address ethical issues that arise during a vaccine study. A network of Adverse Drug Reaction (ADR) monitoring centre alone with adverse event following immunisation (AEFI) provide the machinery for vaccine pharmacovigilance.

KEYWORDS: Vaccine pharmacovigilance, Adverse drug reaction, Adverse event following immunization, Vaccine preventable disease.

INTRODUCTION

Vaccines are generally given to healthy people especially children, old aged ones who have tolerance for adverse events. loss of confidence in vaccine safety threatens the continued success of immunisation programme. Vaccine's efficacy varies according to the type of vaccine and the manner in which the vaccine antigen is processed by the immune system

All government regulate the clinical development of vaccines. A thorough evaluation of vaccine safety must be performed before a government will grant a license to allow its use. After a vaccine license has been granted, almost all national immunisation programmes will continue to monitor the nature and frequency of adverse events following immunisation. [1]

Vaccine policy- makers use the information from adverse event reporting systems to guide vaccine policies, including policies to assess the benefit and risks of immunisation [1]

Before a vaccine is licensed, is carefully studied for all possible harm full effects. Testing proceeds in a step wise approach safety is first evaluated in animals. If there is no evidence of harm in animals, testing can begin in a small number of humans. If there is no evidence of harm in humans testing proceeds to increasing number of human subjects [1]

OBJECTIVES

1. To study about the vaccines regulation for reducing morbidity and mortality due to vaccine preventable diseases
2. To provide a proper licensed and monitored vaccine for human use

DISCUSSION

Before a vaccine can be approved in the EU, it has to undergo **rigorous testing** by its developer including the **scientific evaluation** by regulatory authorities. These include the European Medicines Agency (EMA) and other regulators in the EU/EEA countries.

Testing includes checking the vaccine's quality in terms of its purity, its ingredients, including its inactive ingredients and how it is manufactured. Then the vaccine developer evaluates the effect of vaccines. This involves tests in the laboratory and in animals.

The next step would be a **clinical testing programs in humans.** The vaccine developer tests the vaccine in three phases of clinical trials, with larger numbers of people in each phase. This program has to follow strict standards and protocols set by the regulators.

This can take around ten years from initial concept to final stages.

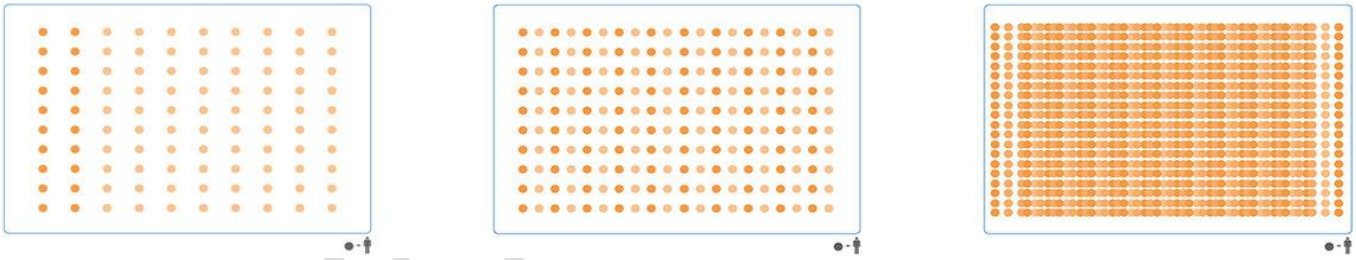

Figure 1: Stages of vaccine development-subject in clinical trials in different phases.

Vaccine evaluation

The important considerations during evaluation of vaccine include:

- Is the vaccine effective?
- What are the most common side effects?
- Is the vaccine safe?

At the end of the testing, the vaccine developer submits the results to the medicines regulatory authorities in United Kingdom as part of a 'marketing authorisation' application. The regulators can only approve the vaccine if its scientific evaluation of the tests results show that the vaccine's benefits are greater than its risks.

Medicines regulatory authorities can carry out inspections to make sure that the information the vaccine developer provides is trustworthy. They can also run tests to make sure that the batches of vaccines released onto the market are of the expected quality and have been manufactured correctly. The companies are required to conduct stringent testing, for which the acceptance criteria are pre-defined by the authorities, on each batch of vaccine released onto the EU market. [2]

Testing of vaccines, licensing, and monitoring:

a) Testing: People are often concerned to know how rigorously and extensively vaccines have been tested. This is especially true for new vaccines. This work will outline the process involved in developing and licensing a vaccine for use in the UK. The standard for testing and monitoring of vaccines is highly effective while considering to the few medical treatments given to healthy people (mainly healthy children). This means that the level of acceptable risk is much lower than it might be for a cancer treatment. It can take many years for a vaccine to pass through all the stages described below. In the case of the Men B vaccine, it took 15 years from the first idea to the vaccine being licensed for use.

These are some of the stages a vaccine will have gone through before use:

- Reviewing what has been done before.
- Theoretical development or innovation: Coming up with a new idea, or a variation on an existing idea.
- Laboratory testing and development: This involves '*in vitro*' testing using individual cells and '*in vivo*' testing, often using mice. The vaccine has to pass rigorous safety tests at this stage and demonstrate that it works in animals.
- Phase I study: An initial trial involving a small group of adult participants (up to 100 people). The drug is being trialed in human volunteers for the first time. This is carried out to make sure that the vaccine has major safety concerns in humans, and also to work out the most effective dose. Researchers start with small doses and only increase the dose if the volunteers do not experience any side effects, or if they only experience major side effects
- Phase II study: Trial in a larger group of participants (several hundred people). Phase II trials check that the vaccine works consistently and look at whether it generates an immune response. Researchers also start looking for potential side effects.
- Phase III study: Here trial takes place in larger group of people (usually several thousand). This is carried out on medicine or vaccines that have passed phases 1 and 2. Phase III trials gather statistically significant data on the vaccine's safety and efficacy (how well it works). This means looking at whether the vaccine generates a level of immunity that would prevent disease and provides evidence that the vaccine can actually reduce the number of cases. It also gives a better chance of identifying rarer side effects not seen in the phase II study.

- Licensing: Expert review of all trial data by the UK government (through MHRA). At this stage, the regulators check the products efficacy and safety levels. They also make sure that, for most people, the product's advantages far outweigh the disadvantages.
- Phase IV studies: Post marketing surveillance to monitor the effects of the vaccine after it has been used in the population. These may be requested by a regulatory body or carried out by the pharmaceutical industry.

The vaccine and the trials used to test must meet the regulations laid down by the following authorities:

- ICH-GCP (International Conference on Harmonization of Good Clinical Practice) - international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
- Declaration of Helsinki (1964; 2008) - Ethical principles for medical research involving human subjects
- EU Clinical Trials Directive - Enshrined in UK law by the Medicines for Human Use (Clinical Trials) Regulations (2004)
- RCPCH Guidelines for the ethical conduct of medical research involving children (2000) [3]

In addition, for trials in the UK, the vaccine and the trial must receive individual approval from the MHRA, while the trial itself must be approved from the following authorities:

- An NHS Research Ethics Committee
- The local NHS Research and Development office, who support and advise researchers in meeting the requirements of the UK regulatory framework
- The Health and Safety Executive (HSE), for certain types of trials

In the European Union, the European Medicines Agency (EMA) supervises the regulation of vaccines, along with other drugs.
At an international level, the World Health Organization (WHO) makes recommendations via a committee for biological products. Many countries adopt such standards set out by the WHO.

b) Licensing

Expert scientists and clinicians review data from the laboratory pre-clinical studies, clinical trials, manufacturing and quality controls, and also consider the conditions for its safe supply and distribution before licensing. The MHRA is responsible for regulating all medicines and medical device in the UK by

ensuring they work and are acceptably safe. They undertake robust and fact-based on judgment ensure that the benefits justify any risks.

Rolling review

A ‘rolling review’ is a regulatory process used to assess a promising medicine or vaccine during a public health emergency.

c) Approval

Regulation 174 of the Human Medicine Regulations 2012 enables rapid temporary regulatory approvals to address significant public health issues such as a pandemic. This regulation is an EU provision introduced in national law that allows for the authorization of a medicine in response to a public health need. Instead of going through the centralized licensing route of the EMA (which is the normal route until the end of the Brexit transition period), the MHRA authorized the supply of the vaccine based on public health need, provided the batches of vaccine meet specific standards.

d) Monitoring

After a vaccine is licensed, it continues to be monitored as part of a post-licensure monitoring of vaccines. The manufacturer of the vaccine may continue to test for safety, efficacy, and other potential uses (called Phase IV Trials). Also, the UK regulator, MHRA monitors vaccines to detect any possible signals of adverse events. [4]

Who is responsible for monitoring vaccine safety?

Although vaccines undergo rigorous testing before they are licensed for use, it is important that the safety of vaccines is monitored on an ongoing basis, as with all licensed drugs. In the UK, this is undertaken by the MHRA through the Yellow Card Scheme.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)

The MHRA is the government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe.

Improving public health by encouraging and facilitating development in products that will benefit people

Assessing the safety, quality, and efficacy of medicines, and authorizing their supply in the UK for human use. [5]

MHRA REGULATES

- Medicine
- Licensing of medicines

- Medicines for children
- Inspection and standards
- Importing and exporting medicines
- Best practice guidance on labeling and packing of medicines

ROLE OF MHRA

- Assess application for marketing medicinal products
- Assess application to undertake clinical trials
- Undertaking post marketing surveillance including
    - Pharmacovigilance
    - Quality defect monitoring
    - Sampling and testing
    - Product recall [5]

UK vaccination programme:

Vaccination programs against specific diseases began in the UK in the nineteenth century, though modern, nationwide programs took off following the establishment of the National Health Service in 1948. The timeline below, produced by Public Health England (PHE), sets out both the history of vaccine development and the introduction of routine vaccine programs in the UK. Multiple Vaccination Acts were passed during the nineteenth century which placed a duty on local authorities to provide vaccination free of charge. Vaccination against smallpox was made compulsory under the Vaccination Act of 1853 for all infants under three months old in England and Wales. All the nineteenth century Vaccination Acts (including the 1853 Act) were subsequently repealed by the National Health Service [6]

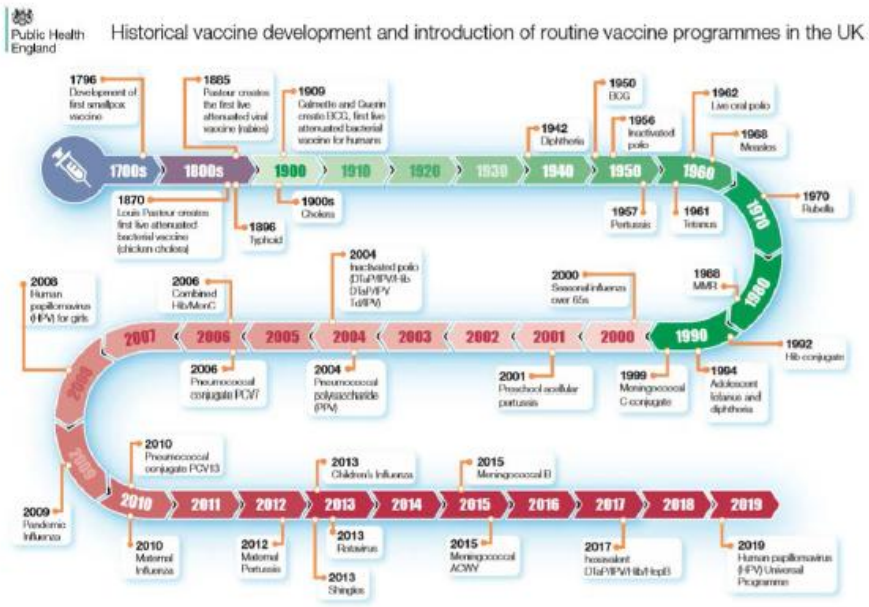

Figure 2: Historical vaccine development and introduction of routine vaccine programmes in the UK

UK immunization schedule*:*

The overall aim of the UK's current immunization schedule is to provide protection against the following vaccine-preventable infections:

- Haemophilus influenzae type b (Hib)
- Pertussis (whooping cough)
- Hepatitis B
- Pneumococcal disease
- Human papillomavirus
- Polio
- Influenza
- Rotavirus [7]

Age due	Vaccine given	How it is given[1]
Eight weeks old	Diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type b (Hib) and hepatitis B (DTaP/IPV/Hib/HepB) Meningococcal B (MenB) Rotavirus	One injection One injection One oral application
Twelve weeks old	Diphtheria, tetanus, pertussis, polio, Hib and hepatitis B (DTaP/IPV/Hib/HepB) Rotavirus Pneumococcal conjugate vaccine (PCV13)	One injection One oral application One injection
Sixteen weeks old	Diphtheria, tetanus, pertussis, polio, Hib and hepatitis B (DTaP/IPV/Hib/HepB) Meningococcal B (MenB)	One injection One injection
One year old (on or after the child's first birthday)	Hib/MenC Pneumococcal conjugate vaccine (PCV13) Meningococcal B (MenB) Measles, mumps and rubella (MMR)	One injection[2] One injection[2] One injection[2] One injection[2]
Primary school age children (school years reception to six) Chapter 19)	Live attenuated influenza vaccine (LAIV)	Nasal spray, single application in each nostril (if LAIV is contraindicated and child is in a clinical risk group, give inactivated flu vaccine; see Chapter 19)
Three years four months old or soon after	Diphtheria, tetanus, pertussis and polio (dTaP/IPV) Measles, mumps and rubella (MMR)	One injection One injection
Twelve to thirteen years old	Human papillomavirus (HPV)	Course of two injections at least six months apart
Fourteen years old (school year 9)	Tetanus, diphtheria and polio (Td/IPV) Meningococcal ACWY conjugate (MenACWY)	One injection One injection
65 years old	Pneumococcal polysaccharide vaccine (PPV)	One injection
65 years of age and older	Inactivated influenza vaccine	One injection annually
70 years old	Shingles vaccine	One injection

Figure 3: The schedule for routine immunizations, The Green Book [8]

Adverse Events Following Immunisation (AEFI)

All vaccinations offered on the national routine immunization schedule are available free of charge. No immunizations are compulsory. For childhood immunizations, parents or guardians make the decisions about whether a child is immunized and consent on their behalf. In the UK, 16- and 17-year-olds are presumed in law to be able to consent to medical treatment. Some children aged under sixteen many also have the capacity to consent to medical treatment themselves – this is called Gillick competence. The majority of vaccinations listed above are given during childhood. While newborn babies initially have immunity to some diseases due to antibodies passed to the child from its mother, this immunity is temporary and declines during the child's first year. The childhood immunization schedule is thus "designed to provide early protection against infections that are most dangerous for the very young". Additional

vaccinations that are not on the routine immunization schedule are offered to babies and children in specific high-risk groups.

For example, the BCG vaccine, which protects against tuberculosis (TB) is targeted at those babies up to age 1 who are born in areas of the UK where the rates of TB are high; have a parent or grandparent who

was born in a country where there is a high rate of TB. Similarly, the chickenpox vaccine is not part of the routine childhood vaccination schedule; but it is recommended for certain individuals, such as non-immune healthcare workers.

Surveillance and monitoring for vaccine safety

The agency has process of vaccine safety monitoring in the UK and the reporting of adverse events following immunisation (AEFIs). It also describes the mechanism for the reporting of suspected defects in vaccines or in the devices used for the administration of vaccines. All vaccines are extensively tested for quality, safety, and immunogenicity and/or efficacy before being licensed and used routinely. As not all side effects may have been identified prior to licensing, particularly if they occur very rarely, careful surveillance is required throughout their use. Important information on vaccine safety is routinely collected through the 'Yellow Card' scheme and from other sources, including medical literature, post-marketing safety studies, epidemiological databases, and other worldwide organisations. The MHRA has responsibility for monitoring the safety of all marketed medicines (including vaccines) and medical devices. Suspected adverse events following the use of vaccines, medicines and medical devices should be reported to the MHRA. [9]

The 'Yellow Card' scheme

The Yellow Card scheme is a voluntary reporting system for suspected adverse reactions (ADRs) to medicines, which includes vaccines. AEFIs that are suspected to be vaccine-induced should be reported as ADRs via the Yellow Card scheme. An ADR is an unwanted or harmful reaction following the administration of a medicine, vaccine, or combination of vaccines. The ADR may be a known AEFI, or it may be previously unrecognised. Spontaneous reports of suspected ADRs are received from UK doctors, pharmacists, dentists, coroners, nurses, midwives, health visitors and patients. There is also a statutory requirement for pharmaceutical companies to report to the MHRA serious suspected ADRs associated with their products. Spontaneous reports of suspected ADRs are received from UK doctors, pharmacists, dentists, coroners, nurses, midwives, health visitors and patients.

Reports of suspected ADRs submitted through the Yellow Card scheme are entered onto a computer database operated by the MHRA. The reporter receives an acknowledgement and is supplied with a unique registration number. Reports of suspected ADRs are regularly reviewed, and appropriate investigation and action is initiated if a possible problem is identified. The five regional monitoring centre of the Commission on Human Medicines (CHM) work in conjunction with the MHRA in collecting data on ADRs and facilitating local ADR reporting.

Which ADRs to report

The success of the Yellow Card scheme depends on early, complete, and accurate reporting of suspected ADRs. A Yellow Card should be submitted when a causal association is suspected between the product administered and the condition experienced by the patient. The MHRA encourages reporting of suspected ADRs even if there is uncertainty as to whether the vaccine played a causal role. All

suspected ADRs occurring in children should be reported. Newly licensed vaccine products are subject to enhanced surveillance and are given 'black triangle' status (indicated by an inverted triangle 't' on the product information). For such products, all serious and non-serious suspected ADRs should be reported, for both adults and children. For vaccines that have been marketed for two years or more, only serious suspected ADRs should be reported. This applies to all serious reactions, whether or not such reactions have previously been recognized with the suspected vaccine. Serious reactions that should be reported include those that are fatal. are life- threatening, are disabling, or incapacitating, result in or prolong hospitalization, are medically significant, lead to congenital abnormalities.

Deciding whether to report a suspected ADR

It is a matter of clinical judgment whether a suspected ADR should be reported or not. Although a reaction might occur in close temporal association with an immunization, often it can be very difficult to assess whether there is a causal link. If there is any suspicion that the reaction is vaccine-induced, an ADR should be reported. Many suspected ADRs are actually medical conditions that have occurred spontaneously and coincidentally.

The probability that a vaccine has caused an ADR may be increased if there is biological plausibility for the event. For instance, pyrexial illness occurring five to ten days or parotid swelling occurring three weeks after measles, mumps and rubella (MMR) immunization would be consistent with the incubation periods for measles or mumps viruses. On the other hand, pyrexia occurring less than three days after MMR vaccination is unlikely to be caused by the immunization, and an underlying infection is a more likely explanation. [10]

Conclusion

Vaccines are developed, tested, and regulated in a very similar manner to other drugs. In general vaccines are even more thoroughly tested than non- vaccine drugs because the number of human subject vaccine trial is usually greater.

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