

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 reevaluated 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 programmes. Vaccine effectiveness varies depending on the type of vaccine and how the immune system processes the vaccine antigen.

Vaccine clinical development is overseen by all levels of government. Before a government will grant permission to use a vaccine, it must be properly assessed for safety. After a vaccine licence has been granted, almost all national immunisation programmes will continue to investigate the kind and incidence of adverse events that occur 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 licenced, it is thoroughly tested for any potential side effects. Animals are employed to check safety as part of the testing method. If there is no indication of animal damage, testing on a small number of humans can commence. If no indication of human harm is discovered, the experiment will be expanded to include more human volunteers. [1]

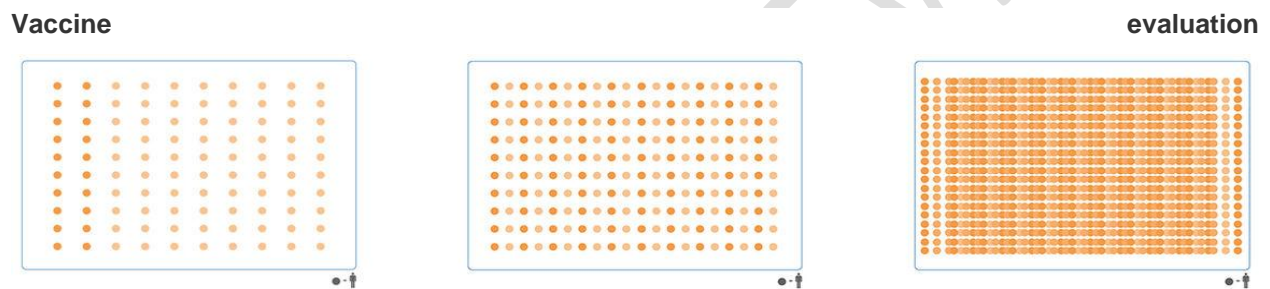
To study about the vaccines regulation for reducing morbidity and mortality due to vaccine preventable diseases.To provide a proper licensedand monitored vaccine for human use.

Vaccine before gets approved in EU, Vaccine undergoes arduous testing by regulatory authority team of scientific evaluation, which includes regulators in EEA countries/EU and also includes EMA(European Medicines Agency).

Vaccine is mainly assessed for its eminence in terms of Ingredients, purity along with the ingredients used in vaccine like inactive ingredients and how it'smanufactured. The vaccine effect is evaluated by vaccine developer, this is evaluated by testing Vaccine in laboratory animals.

The next step would be a testing vaccine in humans(Clinical Testing). Developer checks vaccine effectiveness in clinical trials which is comprised of three phases and involvement of large population in each phase of testing. Clinical trials will follow stringent protocols and standards laid down by regulators.

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



The important considerations during evaluation of vaccine include:

- Vaccine effective?
- Common side effects?
- Vaccine safe?

At end of vaccine testing, after all testing competes developer surrender results regulatory authorities in UK for 'Marketing Authorisation Application'. Regulatory authorities approves vaccine if anticipated risks justified by benefits.

Regulatory authority will conduct an inspection to check whether the information regarding vaccine provided by the developer is reliable. Medicine regulatory authorities will conduct tests of vaccines which are release to market to see they up to the anticipated quality and manufactured decorously. Companies having well designed stringent testing for vaccines to which criteria's are well defined by regulatory authorities.[2]

Testing of vaccines, licensing, and monitoring:

a) Testing:People expect to what extinct vaccines have underwent for testing and moreover for the newly developed vaccine. This work will provide an overview involved in authorizing and development of

vaccine in UK. Vaccine testing standard and checking is highly effective when they are treated on healthy people (Especially Children). Vaccines take years for passing all stages. Example: Men-B vaccine licensing took about 15 years.

Stages recommended for vaccines should undergo before using:

- Review has been done before.
- New idea for validation on previously existing.
- Laboratory development and testing: In vitro testing usually includes the use of cells whereas in vivo testing is done by using mice. The vaccine has to go through more stringent safety tests while it's demonstrating its effectiveness and how it works in animals
- Phase I study: This phase involves a minimum group of roughly 100 persons from the population. For the first time, the medicine is being tested on human participants. This is done to ensure that the vaccination has no serious safety issues in humans, as well as to determine the most effective dose. Researchers begin with low dosages and only raise the dose if the volunteers have no side effects or only have serious negative effects.
- Phase II: This phase of the clinical trial involves a population in thousands. In this phase vaccine immune generating ability and consistency performance is checked. Also, researcher identifies possible side effects.
- Phase III study: The trial includes the population in large numbers (More than a thousand). This is carried out on medicine or vaccines that have passed phases 1 and 2. Phase III studies provide statistically meaningful data on the safety and efficacy of the vaccination (how well it works). Which includes determining if the vaccine induces a degree of immunity sufficient to prevent disease and providing proof that the vaccination can really lower the number of instances. It also increases the likelihood of detecting uncommon adverse effects not identified in the phase II research.
- Licensing: All trial data was expertly evaluated by the UK government (through MHRA). The regulators now assess the product's effectiveness and safety. They ensure that vaccinations replace drawbacks with public benefits.
- Phase IV studies: This phase is called Post Marketing Surveillance where side effects of the vaccine after vaccine approved. This phase conducted by industry and required for regulatory authorities.

The trials used for vaccine testing and test conducted for vaccines should comply with regulations as per regulatory authorities.

- ICH-GCP (International Conference on Harmonization of Good Clinical Practice) - an international ethical and scientific quality standard for planning, conducting, documenting, and reporting human subject studies..

- Helsinki Declaration (1964; 2008) - Ethical guidelines for human subjects medical research.
- The European Clinical Trials Directive is enshrined in UK legislation through the Medicines for Human Use (Clinical Trials) Regulations (2004)

Furthermore, for studies in the United Kingdom, the MHRA must approve both the vaccine and the experiment, while the trial itself must be authorised by the following authorities:

- An NHS Research Ethics Committee 5.
- The local NHS Research and Development office, who support and advise researchers in meeting the requirements of the UK regulatory framework
- Then Health and Safety Executive (HSE), for certain types of trials.

EMA(European Medical Agency) manages the vaccine regulation and other drugs also.

WHO sends recommendations through committees for biological products. All countries adopt WHO standards.

b) Licensing

Clinicians and experts examine the clinical trials, quality controls, and manufacturing, pre-clinical studies, and they also look over the consideration of supply and distribution of vaccines before getting approval. IN the UK Medicines and Healthcare Regulatory Agency regulate all medical device, medicine by considering the safety before getting approval for licensing. They take facts based judgement and they also ensure benefit justify the risks.

Rolling review

A 'rolling review' is phenomenon ensuring public to get promising biological product while health emergency.

c) Approval

According to Regulation 174 of the Human Medicine Regulations 2012 which gives approve for the emergency use of vaccine during pandemic time. E.g.: Covid-19. This is regulation of EU introduced in national law which allows for authorization of medicines.

d) Monitoring

Once vaccine is approved and come into public use, biological product is monitored as post-licensure monitoring. In phase four trial manufacture will continue testing of biological product regarding efficacy, safety and along with other potential use. Medicine and Healthcare regulatory agency in UK they screen any signals of AE that occurred. [4]

Vaccine safety monitoring?

Vaccine undergone meticulous testing before they get approval for marketing. Vaccine safety is assessed by ongoing basis after given approval. Vaccine safety is carried out through Yellow Card Scheme in UK.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA)

The MHRA is the government organisation in charge of ensuring that medicines and medical equipment perform properly and are safe.

Improving public health by promoting and supporting product creation that benefits people. Evaluating the safety, quality, and effectiveness of medications and approving their supply for human use in the United Kingdom. [5]

MHRA REGULATES

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

ROLE OF MHRA

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

Vaccination programme in UK:

Vaccination programme against particular illness implemented in the United Kingdom in the nineteenth century, followed by the foundation of the National Health Service in 1948. The flowchart below depicts the usual process of vaccine development and introduction provided by PHE (Public Health England) in the United Kingdom. Many vaccination programmes were planned and established during the nineteenth century, and local governments were responsible for providing free immunisation to everybody. The Vaccination Act of 1853 made smallpox vaccination mandatory for all infants aged three months and under in England and Wales. Vaccination Acts were superseded by the National Health Service. [6]

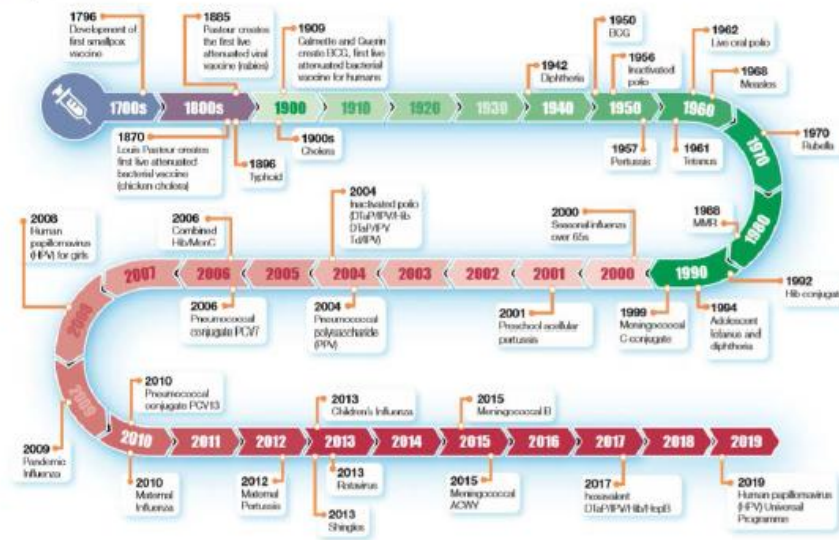


Figure 2: Vaccine development and introducing process.

UK immunization schedule:

Main objective of present UK's immunization to render protection against the infections which are prevented by vaccine:

- Hepatitis B
 - Pertussis
 - Pneumococcal infection
 - Polio
 - Rotavirus
 - Influenza
 - Hib
 - Human Papillomavirus
- [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)	One injection
	Meningococcal B (MenB)	One injection
	Rotavirus	One oral application
Twelve weeks old	Diphtheria, tetanus, pertussis, polio, Hib and hepatitis B (DTaP/IPV/Hib/HepB)	One injection
	Rotavirus	One oral application
	Pneumococcal conjugate vaccine (PCV13)	One injection
Sixteen weeks old	Diphtheria, tetanus, pertussis, polio, Hib and hepatitis B (DTaP/IPV/Hib/HepB)	One injection
	Meningococcal B (MenB)	One injection
One year old (on or after the child's first birthday)	Hib/MenC	One injection ²
	Pneumococcal conjugate vaccine (PCV13)	One injection ²
	Meningococcal B (MenB)	One injection ²
	Measles, mumps and rubella (MMR)	One injection ²
Primary school age children (school years reception to six) Chapter 19)	Live attenuated influenza vaccine (LAV)	Nasal spray, single application in each nostril (if LAV 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)	One injection
	Measles, mumps and rubella (MMR)	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)	One injection
	Meningococcal ACWY conjugate (MenACWY)	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)

Vaccines offered by national routine immunization are freely offered. Immunizations routine are not compulsory. Childhood immunization decisions are made by parents' or guardians' decisions on whether a child gets a vaccine or not. In United Kingdom sixteen year under children have right to have medical treatment on their own consent which is called Gillick competence. Vaccinations list given above. Initially new-born is resistant to some disease because antibodies that passed from mother to its child, inherited immunity is not temporary and it gets decline in child's first year. As a result, the paediatric immunisation schedule is "intended to provide early protection against infections that pose the greatest risk to very young infants."

Additional immunizations are not advised for all groups of newborns and children, but only for those at high risk.

For example, the BCG vaccine, given 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.

Surveillance and monitoring for vaccine safety

The agency in the United Kingdom has a technique for monitoring vaccine safety and reporting AEFI(Adverse event following immunization). It explains how to report any problems with vaccines or vaccine delivery equipment. Before they are licenced and widely used, all vaccinations are thoroughly examined for quality, safety, immunogenicity, and/or effectiveness. Because not all negative effects were found prior to licensure, especially if they occur infrequently, they must be carefully monitored during usage. The "Yellow Card" approach, as well as other sources such as medical literature, post-marketing safety studies, epidemiology databases, and other worldwide organisations, is frequently used to acquire important vaccination safety data. In the United Kingdom, the Medications and Healthcare Product Regulatory Agency is in charge of monitoring the sale of medical devices and medications. [9]

The 'Yellow Card' scheme

This scheme is based on reporting suspected adverse reactions of all medicines which also includes biological products also. AFEI also reported under yellow card scheme only. ADR is defined as unwanted or untoward reaction occurred through a vaccine/biological product. ADR may be not known previously. ADRs received from pharmacists, nurses, patients, doctors and also from the health visitor. Pharma industries should also report to MHRA(Medicine and Healthcare Product Agency) regarding serious adverse reactions regarding their products. Doctors, pharmacists, dentists, coroners, nurses, midwives, health visitors, and patients in the United Kingdom report suspected ADRs on the spur of the moment.

Suspected ADR reports filed under the Yellow Card programme are recorded into a computer database run by the MHRA. The reporter is given an acknowledgment and a unique registration number. Reports of suspected ADRs are evaluated on a regular basis, and if a probable issue is detected, a suitable inquiry and action is started. The Commission on Human Medicines' (CHM) five regional monitoring centres collaborate with the MHRA to gather ADR data and facilitate local ADR reporting.

Which ADRs to report

The yellow card scheme is successful in accurate and early reporting of suspected ADR at an early stage. It's submitted as a casual form that is associated between patients by administering the product. Medicines and Healthcare products regulatory agency (MHRA) supports reporting of adverse reactions and whether vaccine played their role. Adverse reactions seen in children are should be reported. Newley-approved biological products are given an inverted triangle with the symbol 't' on the product (black triangle), for such products non serious and serious adverse reactions should be reported in both adults as well as in children too. Only serious suspected adverse reactions (ADR) are reported for biological products which are been on market for two years and more than two years either the reactions are recorded previously or suspected. Hospitalization, medically significant, disabling, life-threatening, fatal, and congenital abnormalities are all reported under serious reactions.

Deciding whether to report a suspected ADR

Suspected adverse reaction reporting is a clinical judgment on whether to be reported or not. Some reactions will occur during immunization and it's very difficult to assess or find a link. Adverse reactions of vaccines that are likely to be suspicious are reported. Most of the adverse reactions are medical conditions that have occurred either coincidentally or spontaneously.

Vaccines caused adverse reactions are more due to biological plausibility for that event. For example, pyrexial illness occurred for about five to ten days after mumps and measles and rubella immunization. Where pyrexial fever also occurs for three days due to immunization and infection likely to be more explanation. [10]

Vaccination importance on Emergency Base: Emergency use authorization (EUA) is defined as permitting the use of vaccines during emergencies. E.g.: Pandemic like Covid-19. Under EUA unapproved medical products are allowed to use during emergency times by FDA to diagnose, prevent or treat life-threatening diseases.

Considering criteria been met and considering input from the FDA manufacturing industries will decide whether and at what time they can submit EUA requests to FDA.

Once the EUA has been applied FDA will scrutinize the Emergency Use Authorization (EUA) by checking criteria are met and along with the scientific data of the vaccine also.[11]

FDA Guideline: After submitting BLA to FDA, the company waiting for permission to market and distribute vaccines in the market. Once BLA is submitted FDA will scrutinize for safety data and

effectiveness and they look after facility information and manufacturing information which assures the quality of the product.

After verifying the details submitted by the company FDA will decide whether to give permission or not. If FDA approves company can market vaccines.

FDA take decisions based on the risk and benefits for those who received vaccines and as well as disease.

The scientific team of the FDA is comprised of pharmacologists/toxicologists,physicians, chemists, statisticians,experts in post-marketing safety,manufacturing and facility inspectors,clinical study site inspectors, and labelling and communications experts. This team verifies all the scientific data provided in BLA and makes decision whether to approve or not. If provided data met required criteria then FDA approves vaccine.[12]

Conclusion

Vaccines are created, evaluated, and controlled in the same way as other medications are. Vaccines are generally tested more thoroughly than non-vaccine drugs because the number of human subject vaccine trials is usually greater.

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