Pharmacovigilance and HPV Vaccine

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Presentation Overview

• HPRA / EMA
• Licensing Process
• Vaccine Pharmacovigilance
• HPV Vaccine (Gardasil) Licensing and Safety
• Adverse Drug Reaction Reporting
Areas covered by the HPRA Regulatory Role

Legal frameworks have evolved and expanded the regulatory role across a range of areas over the past 20 years.
The European medicines regulatory network

~ 50 national regulatory authorities  European Commission  European Medicines Agency
EMA in the EU
Who do we work for?

over 500 million people living in the European Union
28 member states
27% of global sales of medicines
24 official languages
European Medicines Agency (EMA)

Scientific committees:
- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Paediatric Committee (PDCO)
- Committee for Advanced Therapies (CAT)

Working parties of Experts:
- Biologics Working Party (BWP)
- Patients' and Consumers' Working Party
- Quality Working Party (QWP)
- Safety Working Party (SWP)
- Scientific Advice Working Party (SAWP)
- Biomedical Medicinal Products Working Party
- Biostatistics Working Party
- Blood Products Working Party
- Cardiovascular Working Party
- Central Nervous System Working Party
- Infectious Diseases Working Party
- Oncology Working Party
- Pharmacogenomics Working Party
- Pharmacokinetics Working Party
- Rheumatology/Immunology Working Party
- Vaccines Working Party (VWP)
Centralised Licensing Process

- Application to EMA
- CHMP Rapporteur and Co-Rapporteur
- PRAC Rapporteur and Co-Rapporteur
- Peer Reviewer
- Assessments/recommendations CHMP/PRAC (210 days)
- Approval by EU Commission (SPC/PL)
- Post-market surveillance/Pharmacovigilance
Most common adverse reactions observed in Clinical Trials were injection site reactions and headache (mild to moderate).

### Table 1: Adverse Events Following Administration of Gardasil from Clinical Trials and Post-Marketing Surveillance

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Not known</td>
<td>Injection-site cellulitis *</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Not known</td>
<td>Idiopathic thrombocytopenic purpura*, lymphadenopathy*</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Hypersensitivity reactions including anaphylactic/anaphylactoid reactions*</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Dizziness*, Guillain-Barré syndrome*, syncope sometimes accompanied by tonic-clonic movements*</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Vomiting*</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Common</td>
<td>Pain in extremity</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Arthralgia*, Myalgia*</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>At the injection site: erythema, pain, swelling</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Pyrexia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Asthma*, chills*, fatigue*, malaise*</td>
</tr>
</tbody>
</table>
Licensing of Vaccines

- **Pre-Clinical Assessment**
- **Quality Assessment**
  - Formulation, Manufacturing Process
  - Compliance, Specifications
- **Clinical Assessment**
  - Immunogenicity
  - Efficacy
  - Safety
Vaccine Licensing and Safety

Dynamic Balance of Risks and Benefits

- Real
- Perceived
Factors Contributing to the Licensing and Safety of Vaccines

Vaccine Intrinsic

External/Host
Vaccine-Intrinsic Factors

• Type of Vaccine
  – e.g. Live attenuated, Inactive/Toxoid, Subunit, Recombinant

• Adjuvants, Stabilisers, Preservatives

• Combined Vaccines

• Vaccination dosing and schedule

• Route of administration
External/Host Factors

- Disease Epidemiology
- Age-groups
  - Paediatric/Adult/Elderly
- Sub-Populations
  - Pregnancy
    - Immunocompromised
- Medical/Vaccination History
  - e.g. previous vaccines and vaccination sites
- Vaccination Schedules
Vaccine Licensing and Safety

• High level of safety required and tolerance of risk low
  – Healthy population
  – Public perception of disease
  – Mass immunisation/Subpopulations

• Causality assessment of an adverse event may be difficult
  – Temporal association
  – Dechallenge/Rechallenge
  – Multiple Vaccines

• Complex biological products with complex manufacturing processes
  – Multiple antigens, live organisms, adjuvants, preservatives, stabilisers

• Communication
  – Media/Internet/Campaign Groups
Vaccine Safety
Anti-Compulsory Vaccination Hymn (Late 1800s)

Brothers in heart united/Raise we our voice today/Now let our vow be plighted/To sweep this law away./Say shall our little children/Suffer around us still,/Curs’d by a cruel custom/Doomed by a despot will. Brothers, we’re marching onward/Progress lies on before;/Fain would the hand of terror/Close up the burning door./Seizing our new-born infants,/Blighting their lives with pain;/Filling their veins with poison,/Tainting each tender brain Brothers, our fathers suffered,/Died that we might be free;/Died that a faith unfettered,/Right of each soul should be,/Yet doth a dark superstition/Peril the health of all;/Built on the sands of error,/Pray we it soon may fall!

‘Uninformed nonsense’ about HPV vaccine is endangering lives

HSE urges lifesaving vaccination
Court told of ‘horrendous adverse effects’ of HPV vaccine

Mother’s concerns over vaccination
Uptake of HPV vaccine down 15% in two years

Gardasil safety evidence is ‘overwhelming’

Cervical cancer vaccine has made my daughter ill
Vaccine Pharmacovigilance

• Vaccine Pharmacovigilance defined as “the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine or immunisation related issues and to the prevention of untoward effects of the vaccine or immunisation”

Legal Framework


Adverse Reaction: noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of marketing authorisation, including the misuse and abuse of the medicinal product.

There is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event.

Adverse event following Immunisation: any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.
Gardasil Safety Monitoring

- To end of April 2017, 1087 adverse reaction reports received by HPRA
- Majority of national reports have been non-serious and consistent with adverse events as described in the product information:
  - Including injection site reactions, headache, myalgia, fatigue, malaise, gastrointestinal symptoms and skin reactions.
  - Hypersensitivity reactions including a small number of anaphylactic-type reactions reported.
  - Vaccination related events of dizziness and syncope frequently reported
  - Some reports describe a range of symptoms: changes in menstrual cycle, concentration tiredness, joint pain, numbness, seizures, weight gain/loss
- National data pooled at a European database (Eudravigilance) with global reports data for signal detection activities.
Gardasil

- 1087 suspected Adverse Reaction Reports received

![Bar chart showing adverse reaction reports from 2007 to 2017]
Evaluation of Pharmacovigilance Data

Identification of a possible signal

Data collation & review

Benefit/Risk evaluation

Risk management

Communication

SAFETY MONITORING
Data Collection and Analysis

- **Data Collection**
  - Formal Studies
  - Routine Surveillance

- Standardised case definitions, reporting, investigation and assessment allows merging/comparison and exchange of data

- Background incidence rates - A critical aspect of the analysis of spontaneous reporting data and data from studies is the collection of background information on incidence of Adverse Events.

- Assessment of causality for events associated with vaccines aided by knowledge of their background incidence rates. (Observed vs. Expected analysis)
Regulatory history: Gardasil

Commission authorisation 20/9/2006

- Approximately 216,500,000 doses distributed and 72 million subjects vaccinated since market introduction
- Approved in 132 countries world-wide. No registration revoked or withdrawn for safety reasons

Post Marketing Evaluation:

- Cumulative safety data on all suspected adverse reaction reports included in the EV database,
- Published medical literature/Epidemiological studies and additional clinical trial results
- Assessments of Periodic Safety Update Reports (PSUR’s) which the company was required to submit to the competent authorities at defined intervals
<table>
<thead>
<tr>
<th>Incoming PSUR (Incoming Centralised)</th>
<th>Gardasil</th>
<th>19/01/2017</th>
<th>FINALISED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incoming PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>02/02/2016</td>
<td>FINALISED</td>
</tr>
<tr>
<td>Incoming Article 31 PRAC Referral</td>
<td>HPV vaccines</td>
<td>January 2016</td>
<td>FINALISED</td>
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<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>09/12/2014</td>
<td>FINALISED</td>
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<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>22/01/2014</td>
<td>FINALISED</td>
</tr>
<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>30/01/2013</td>
<td>FINALISED</td>
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<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>10/10/2011</td>
<td>FINALISED</td>
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<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>12/10/2010</td>
<td>FINALISED</td>
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<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>19/10/2009</td>
<td>FINALISED</td>
</tr>
<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>21/10/2008</td>
<td>FINALISED</td>
</tr>
<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>08/11/2007</td>
<td>FINALISED</td>
</tr>
<tr>
<td>PSUR (Incoming Centralised)</td>
<td>Gardasil</td>
<td>04/05/2007</td>
<td>FINALISED</td>
</tr>
</tbody>
</table>
EU Referral Procedure

July 2015: Focus on CRPS and POTS

Reviewed:

✓ All available data and analyses regarding CRPS and POTS from clinical trials and post-marketing safety data
✓ Scientific literature, data from Eudravigilance and studies submitted by Member States including Denmark, as well as information from Japan
✓ Detailed information submitted voluntarily by the public and patient groups, including those from Ireland
✓ Advice from the Scientific Advisory Group on vaccines, whose expertise was supplemented with additional European experts on these syndromes and in the areas of neurology, cardiology and pharmacoepidemiology
✓ Consensus PRAC → CHMP → EU Commission
EMA referral on Gardasil

EMA to further clarify safety profile of HPV vaccines

The European Medicines Agency (EMA) has started an evaluation of the safety profile of the human papillomavirus (HPV) vaccines. The agency’s Pharmacovigilance Risk Assessment Committee (PRAC) will review the available data and complete a detailed scientific review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), given human papillomavirus (HPV) vaccines. These vaccines are given to protect against cancer and other HPV-related cancers and precancerous conditions. This review concludes evidence does not support the vaccines cause CRPS or POTS.

Reports of CRPS and POTS after HPV vaccination are consistent with what would be expected in this age group.

HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS

On 12 November the EMA completed its review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), given HPV vaccines. These vaccines are given to protect against cancer and other HPV-related cancers and precancerous conditions. In line with its initial recommendations, EMA confirmed that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil, and Gardasil 9) and development of CRPS or POTS. Therefore, there is no reason to change the way the vaccines are used or used in the current product information.

CRPS is a chronic pain syndrome affecting a limb, while POTS is a condition where the heart rate increases abnormally on sitting or standing up, together with symptoms such as dizziness, weakness, as well as headache, chest pain, and fainting. There is no evidence to support that HPV vaccines cause these conditions.

Review of existing evidence suggests that CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. However, available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years also develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. Therefore, it is important to monitor the safety profile of these vaccines in conjunction with other conditions.
Human papillomavirus vaccines

Summary

Procedure started → Under evaluation → PRAC recommendation → CHMP opinion → European Commission final decision

HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS

Reports after HPV vaccination consistent with what would be expected in this age group

EMA has now completed its review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV) vaccines. These vaccines are given to protect them from cervical cancer and other HPV-related cancers and pre-cancerous conditions. In line with its initial recommendations, EMA confirms that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) and development of CRPS or POTS. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

CRPS is a chronic pain syndrome affecting a limb, while POTS is a condition where the heart rate increases abnormally on sitting or standing up, together with symptoms such as dizziness, fainting and weakness, as well as headache, aches and pains, nausea and fatigue. In some patients they can severely affect the quality of life. The syndromes are recognised to occur in the general population, including adolescents, regardless of vaccination.

Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. However, available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. The review found no evidence that the overall occurrence of these syndromes in vaccinated girls were different from expected occurrence in these age groups, even taking into account possible underreporting. The review noted that some symptoms of CRPS and POTS may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME).
EMA response to Nordic Cochrane Collaboration

26 May 2016

Complaint to the European Medicines Agency (EMA) over maladministration at the EMA

According to Article 6 of the EU Treaty and the Charter of Fundamental Rights of the EU (1), “Openness enables citizens to participate more closely in the decision-making process and guarantees that the administration enjoys greater legitimacy and is more effective and more accountable to the citizen in a democratic system. Openness contributes to strengthening the principle of democracy and respect for fundamental rights.”

On 26 November 2015, the European Medicines Agency (EMA) released a 40-page Adverse Event Report dated 11 November (2) on the safety of vaccines against human papilloma virus (HPV) to be used to decrease deaths from cervical cancer.

We are concerned about the EMA’s handling of this issue as reflected in its official response to the EMA to assess:

1. Whether the EMA has been open and accountable to the citizens and has respected the uncertainties related to the safety of the HPV vaccines.

2. Whether the EMA has lived up to the professional and scientific standards that mean the EMA has the right to guarantee that the administration enjoys legitimacy when evaluating and the data related to the safety of the HPV vaccines.

3. Whether the EMA has treated fairly - in a manner that guarantees that the administration enjoys legitimacy - a Danish whistleblower, PhD Louise Brinth, when she raised concerns about possible serious harms of the HPV vaccines.

4. Whether the EMA has treated fairly - in a manner that guarantees that the administration enjoys legitimacy - the observations and concerns the Danish Health and Medicines Authority (1) Uppsala Monitoring Centre had raised about possible serious harms of the HPV vaccines.

5. Whether the EMA’s procedures for evaluating the safety of medical interventions guarantees that the administration enjoys legitimacy. The EMA asked the manufacturer of the vaccines to stop.

Professor Peter C. Gøtsche
Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
1210 Copenhagen
Denmark
17 June 2016
EMA/ECA/14/2016
Deputy Executive Director

Dear Prof Gøtsche,

Subject: Your letter of complaint dated 26 May 2016 to the European Medicines Agency (EMA) over maladministration at the EMA.

I refer to your letter of complaint sent to Prof Rasi relating to maladministration at EMA. This reply only deals with point 4 of the section “Conflicts of interest” and a number of allegations on page 17 in the section “Final remarks” in your complaint letter. A reply to the other issues you have raised in your complaint letter is being finalized and will be provided to you within the next few days.

In your complaint you allege that Prof Rasi may have a conflict of interest, stemming from his previous contacts with industry, and which you claim he failed to declare. Without prejudice to any response and defence letter that Prof Rasi may wish to forward to you directly, EMA would like to reiterate its understandings and allegations in the strongest possible terms, for the sake of transparency owed to the general public and to the EU regulatory network of which EMA is an important member.

The Decision on rules relating to Articles 11, 14 and 13 of the Staff Regulations concerning the handling of declared interests of staff members of the European Medicines Agency and candidates before recruitment (EMA/62/2006/2013) describes the interests in pharmaceutical industry to be declared by the Agency’s staff. Amongst other things, EMA staff members are required to declare in their declaration of interests (DoI) any pecuniary interest of a person held for a period of 5 years prior to the start of employment with the Agency.

As you may be aware (see for instance European EMA Handbook), the inventor mentioned on a patent is the creator of the invention and is always entitled to be designated on the patent, regardless of who filed the patent application or owns the patent. An inventor remains an inventor throughout the term of a patent, but he is not necessarily the owner of the patent, e.g. the ownership rights may be vested originally upon, or subsequently assigned to, a subject other than the inventor/s. Only the owner of a patent can enjoy economic rights with regard to that particular invention. Therefore, neither the applicable rules, nor considerations of common sense oblige EMA staff to declare in their DoI any pecuniary interest for which they are the inventor/s, but not the owner/s, unless the inventor is entitled to
HPRA Website – www.hpра.ie

• Dedicated page on **HPV School Immunisation** programme.
• Includes links to HSE national immunisation guidelines, product information, publications, national monitoring experience, and EMA publications and assessment reports.
• Explains how to report side effects to the HPRA
Communications to Healthcare Professionals

Gardasil – update on national monitoring experience

The HSE human papillomavirus (HPV) schools immunisation programme commenced in May 2010 and it is estimated that since that time, up to 38,000 doses of Gardasil have been administered until the end of October 2010.

The Irish Medicines Board has received a total of 64 reports of adverse events associated with use of Gardasil up to the end of October 2010, 55 of which were received since the beginning of the school immunisation programme.

As a single patient may experience several reactions that will be included in a single report, the total number of reports will not be equal to the total number of patients vaccinated. In addition, as some patients have received two or three doses of the vaccine, the total number of doses administered is not necessarily equal to the total number of patients vaccinated.

The vast majority of reports received by the IMB to date have been consistent with the expected pattern of adverse effects for the vaccine, as described in the product information, and include injection site reactions, malaise, headache, myalgia, gastrointestinal symptoms and skin reactions (including pruritus). Reports of hypersensitivity reactions have also been received including reports of anaphylactic-type reactions in two patients, both of whom recovered without receiving appropriate treatment.

Anaphylaxis is a very rare event following vaccination. Appropriate medical supervision should always be in place in case of a serious allergic reaction or anaphylactic reaction to the vaccine.

Vaccination is recommended for all girls aged 12-15 years and boys aged 12-13 years. Parents and carers should be reminded that the vaccine is not recommended for use in persons who have had a previous allergic reaction to Gardasil or a previous severe allergic reaction to any component of the vaccine.

Adverse reactions may include various symptoms such as fever, headache, malaise, pain or tenderness at the injection site, localised swelling, pain, redness, itchiness and skin rash. However, these are not all the possible adverse reactions and other serious reactions may occur.

Appropriate medical treatment and supervision should always be in place in case of a serious allergic reaction or anaphylactic reaction to the vaccine.
Vaccine Safety Stakeholders

- Campaign Groups
- Media
- WHO/GAC VS
- European Commission
- ECDC/VAE SCO
- Vaccine Manufacturers/Scientists
- Regulatory Authorities/European Medicines Agency
- Healthcare Professionals
- Department of Health/Public Health Authorities/NIAC
- Vaccinees/Parents
- Media Campaign Groups
Conclusions

- Complex Biological Products
- Dynamic Benefit - Risk Balance
- European Collaboration (Global)
- Application of standardised pharmacovigilance standards and terminology in adverse event surveillance systems
- Importance of detailed Adverse Drug Reaction reports
- Effective communication and collaboration with stakeholders

*All essential in addressing the real and perceived Benefit / Risk Balance*
‘Avoiding risk is impossible, but managing it is critical to sustained success’
Thank You

Questions/Comments?
References and Sources

- www.hpра.ie
- European Medicines Agency www.ema.europa.eu
- www.historyofvaccines.org
- Gardasil Summary of Product Characteristics
- Gardasil Product Information Leaflet
- Brighton Collaboration https://brightoncollaboration.org