Vaccine Licensing and Safety

April 2013
• Licensing Process
• Vaccine Pharmacovigilance
• HPV Vaccine (Gardasil) Licensing and Safety
• Adverse Drug Reaction Reporting
Dynamic Balance of Risks and Benefits

• Real
• Perceived
Vaccine Licensing and Safety

- High level of safety required and tolerance of risk low
  - Healthy population
  - Public perception of disease
  - Mass immunisation/Subpopulations
  - Mandatory
- 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
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 - EU Regulatory Framework

- Licensing of Vaccines - **Directive 2001/83/EC**
  1. Centralised Procedure - A single application is sent to the European Medicines Agency (EMA) and evaluated. The European Commission issues a marketing authorisation
  2. Mutual Recognition Procedure
  3. National Procedure
Licensing of Vaccines

• Pre-Clinical Assessment
• Quality Assessment
  • Formulation, Manufacturing Process
  • Compliance, Specifications
• Clinical Assessment
  • Immunogenicity
  • Efficacy
  • Safety
1. Exploratory Phase
2. Pre-Clinical Trials
   • Safety and ability to provoke an immune response
3. Phase I Clinical Trials
   • Safety, Initial dose data
4. Phase II Clinical Trials
   • Safety, Immunogenicity, Dosing and Scheduling
5. Phase III Clinical Trials
   • Safety and Efficacy
6. Phase IV (Post-Authorisation)/Pharmacovigilance
Pharmacovigilance of Medicines

• Legal Framework
  • Directive 2010/84EU amending, as regards pharmacovigilance, Directive 2001/83/EC
Adverse reactions which are “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

Directive 2010/84/EU
• **Adverse event following immunisation (AEFI):** “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”

1. Vaccine Product-Related AEFI
2. Vaccine Quality Defect-Related AEFI
3. Immunisation Error-Related Reaction AEFI
4. Immunisation Anxiety-Related Reaction AEFI
5. Coincidental Event AEFI
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”

Evaluation of Pharmacovigilance Data

- Signal Detection
- Signal Evaluation
- Signal Conclusion
- Action – Risk Management
  - Product Information Update/Vaccination Guides
  - Further Study
- Collaboration/Communication
  - Stable links and clear roles between stakeholders to ensure optimum information
Evaluation of Pharmacovigilance Data

Identification of a possible signal

Communication

SAFETY MONITORING

Risk management

Data collation & review

Decision

Benefit/Risk evaluation
Data Collection and Analysis

- **Data Collection**
  - Formal Studies
  - Routine Surveillance
- Standardising 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)
• Gardasil is an adjuvanted, recombinant, quadrivalent vaccine containing purified proteins of human papillomavirus (Types 6, 11, 16 and 18)
• Authorised in EU for use from 9 years for prevention of:
  • Premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types
  • Genital warts (condyloma acuminata) causally related to specific HPV types.
• Gardasil has been authorised for use since 2006 in the Europe and is authorised in at least 130 countries worldwide
• Contraindications – hypersensitivity, acute severe febrile illness
• Warnings include anaphylactic reactions, syncope, use in sub-populations
Most common adverse reactions observed in Clinical Trials were injection site reactions and headache (mild to moderate)

<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>Dizziness¹ <em>, Guillain-Barré syndrome</em>, 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></td>
<td>At the injection site: hematoma, pruritus</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Asthenia*, chills*, fatigue*, malaise*</td>
</tr>
</tbody>
</table>

* Postmarketing Events
- In addition bronchospasm reported very rarely and urticaria rarely.
- During Clinical Studies follow-up 24/15,706 Gardasil recipients and 15/13,617 placebo recipients reported non-specific arthritis/arthropathy
- More injection site swelling and headache reported with concomitant administration of DTP/Polio booster (mild to moderate in majority)
- Safety Profile summarised in Package Leaflet in accordance with SmPC
- Similar safety profile with bivalent vaccine (HPV 16 and 18) Cervarix
Gardasil Safety Monitoring

• To end of November 2012, 650 adverse reaction reports received by IMB
• Majority of these reports received from the school immunisation programme
• 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.
  • Vaccination related events of dizziness and syncope frequently reported
  • Hypersensitivity reactions including a small number of anaphylactic-type reactions reported.
• No new risks identified from national use of Gardasil
• National data pooled with European and Global data for safety evaluation
Relevant IMB Gardasil Publications

• **Drug Safety Newsletter**
  • 37\textsuperscript{th} Edition May 2010 (Insert) - HPV Immunisation Programme
  • 39\textsuperscript{th} Edition November 2010 - Update on National Monitoring Experience
  • 43\textsuperscript{rd} Edition August 2011 - Overview of National Monitoring Experience

• **Overview of National Monitoring Experience with Gardasil**
  • Published October, November, December 2010, February, July 2011
Adverse Reaction Reporting

• **Spontaneous reporting:** Cornerstone of safety monitoring, in particular with regard to rare, serious adverse reactions with a low background event rate.

• Adverse Events Following Immunization (AEFI) may be causally related or happen coincidentally. Prioritise reporting of those considered to be causally associated i.e. those which constitute suspected adverse reactions

• **Ideally provide:** Comprehensive information:
  - date of vaccination, brand of vaccine administered*, batch number*, site and route of administration, detailed description, medical history, concomitant drugs, course of the adverse event/reaction, therapeutic interventions and outcome

    (*In accordance with the revised pharmacovigilance legislation, the brand name and batch number for vaccines should be provided in the reports*)

• Details about the event in question help to determine whether it meets a case definition such as those developed by the Brighton Collaboration
Brighton Collaboration

- Scientific global vaccine research partnership network to enhance the science of vaccine research by providing standardised, validated and objective methods for continuous monitoring of safety profiles and by assessing benefit-risk
- Publishes AEFI case definitions based on systematic review of current evidence, consensus formation, structured peer review and scientific publication
- Case definitions endorsed by WHO and UN Council for International Organisations of Medical Sciences (CIOMS)
- Provides levels of diagnostic certainty based on major/minor criteria.

- Includes anaphylaxis, induration/cellulitis at injection sites, Guillain Barré/Miller Fisher Syndrome, narcolepsy, persistent crying, hypotonic hyporesponsive episode, viscerotropic disease etc.
What to report?

- Any suspected adverse reaction, but in particular:
  - Serious, suspected reactions
  - Any suspected increase in the frequency of non-serious reactions
  - Adverse reactions associated with medication error
How to report?

• On-line reporting system at www.imb.ie

• Adverse Reaction Forms:
  • Downloaded from IMB website and sent freepost to IMB
  • Available on request from IMB Pharmacovigilance Section 01 - 676 4971
How to report?

Welcome to the Irish Medicines Board

Our role is to protect and enhance public and animal health through the regulation of human and veterinary medical products.

Current Topics
- New EU Pharmacovigilance Legislation
- Traditional Herbal Medicinal Products Registration Scheme

Online Reporting
Report suspected issues via on-line forms to the Irish Medicines Board.

Latest Information
- 12 March 2012 - New dosage instructions for children’s liquid paracetamol medicines
- 17 February 2012 - European Medicines Agency finalises review of aliskiren-containing medicines
- 12 March 2012 - Irish Medicines Board announces new dosage instructions for children’s liquid paracetamol medicines
- 02 February 2012 - Poly Implant Prothese (PIP) breast implant update
- 12 March 2012 - Onglyza (saxagliptin) - Important Safety Information from Bristol-Myers Squibb as approved by the Irish Medicines Board
- 09 March 2012 - Benlysta (belimumab) - Important Safety Information from GlaxoSmithKline as approved by the Irish Medicines Board
- 29 March 2012 - Training Seminar for Distributors of Cosmetics Products
- 10 July 2012 - PDA / IMB ESOF 2012 Satellite Conference

Consultation

View & Search Product Listings
- Human
- Veterinary
What happens your report?

- Assessed in IMB and follow-up information sought as necessary
- Reports forwarded to European pharmacovigilance database **EudraVigilance** which is a data management system for reporting, continuous evaluation of suspected adverse reactions and supports signal detection.
- Reports evaluated in the context of other reports from National, European and Global experience and other relevant data
- Communication
  - Product Information
  - Drug Safety Newsletters/Dear Healthcare Professional Letters
  - Immunisation Guidelines/Healthcare Professional Guides
  - Information Leaflets/Information for Parents
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
References and Sources

- www.imb.ie
- European Medicines Agency www.ema.europa.eu
- Definition and Application of Terms for Vaccine Pharmacovigilance - Report of CIOMS/Working Group on Vaccine Pharmacovigilance 2012
- www.historyofvaccines.org
- Gardasil Summary of Product Characteristics
- Brighton Collaboration https://brightoncollaboration.org