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Vaccine Licensing and Safety

April 2013

Vaccine Licensing and Safety

- Licensing Process
- Vaccine Pharmacovigilance
- HPV Vaccine (Gardasil) Licensing and Safety
- Adverse Drug Reaction Reporting

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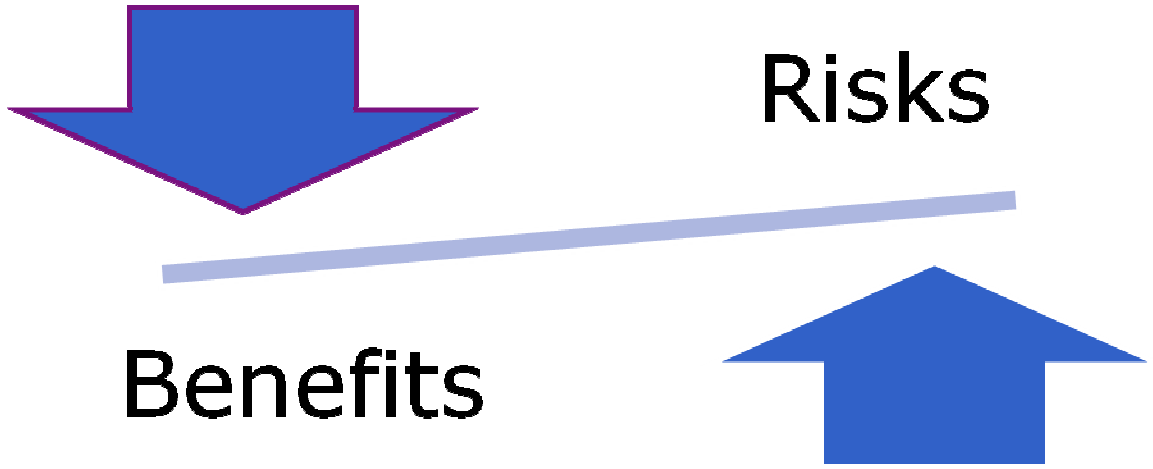
Vaccine Licensing and Safety

Dynamic Balance of Risks and Benefits

- Real
- Perceived



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- **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

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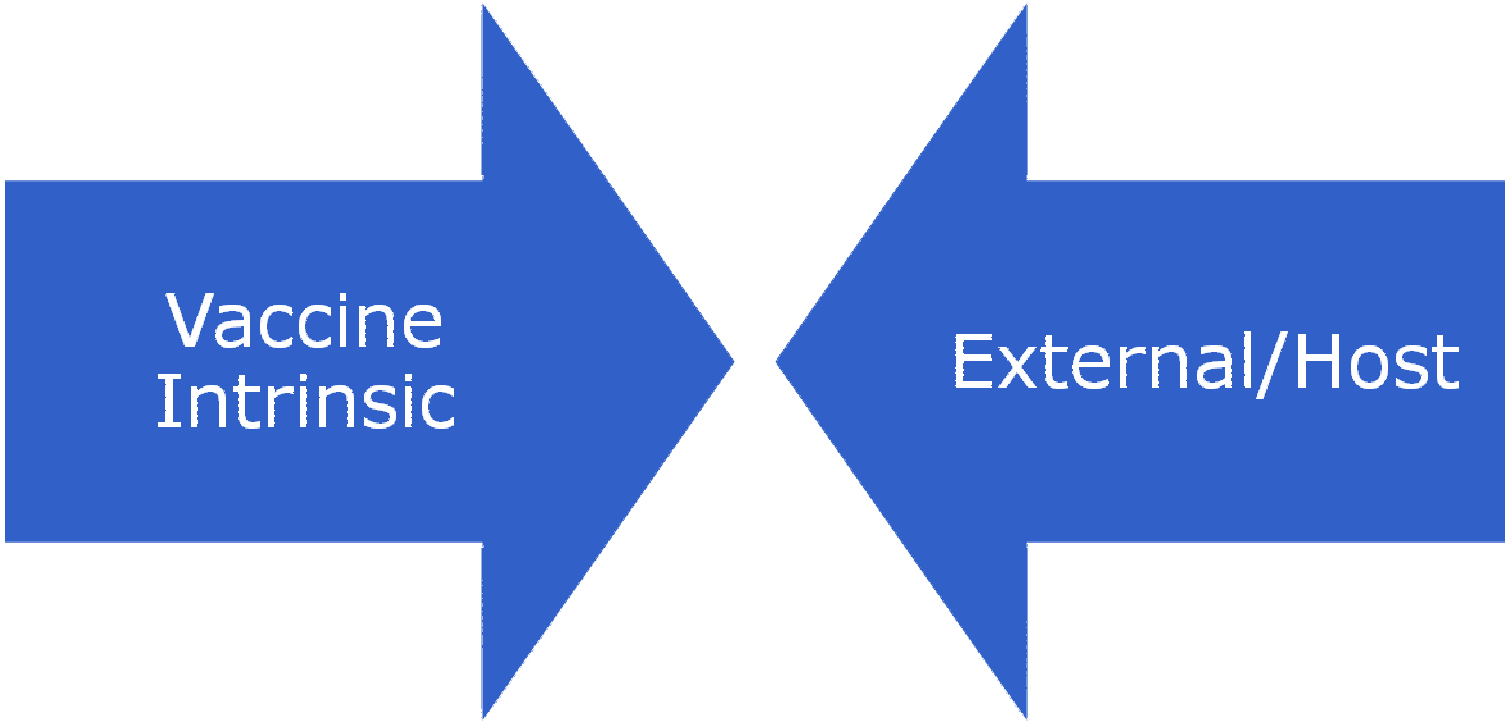
Factors Contributing to the Licensing and Safety of Vaccines



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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**

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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**

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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

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Licensing of Vaccines

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

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Vaccine Development/Life-Cycle

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**

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Vaccine Safety Stakeholders

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Pharmacovigilance of Medicines

- Legal Framework
  - **Directive 2010/84EU** amending, as regards pharmacovigilance, Directive 2001/83/EC
  - **Regulation (EU) No.1235/2010** amending as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004

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Adverse Reactions

- **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

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Adverse Events Following Immunisation

- **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

CIOMS/WHO Working Group on Vaccine Pharmacovigilance 2012

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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"*

CIOMS/WHO Working Group on Vaccine Pharmacovigilance 2012.

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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

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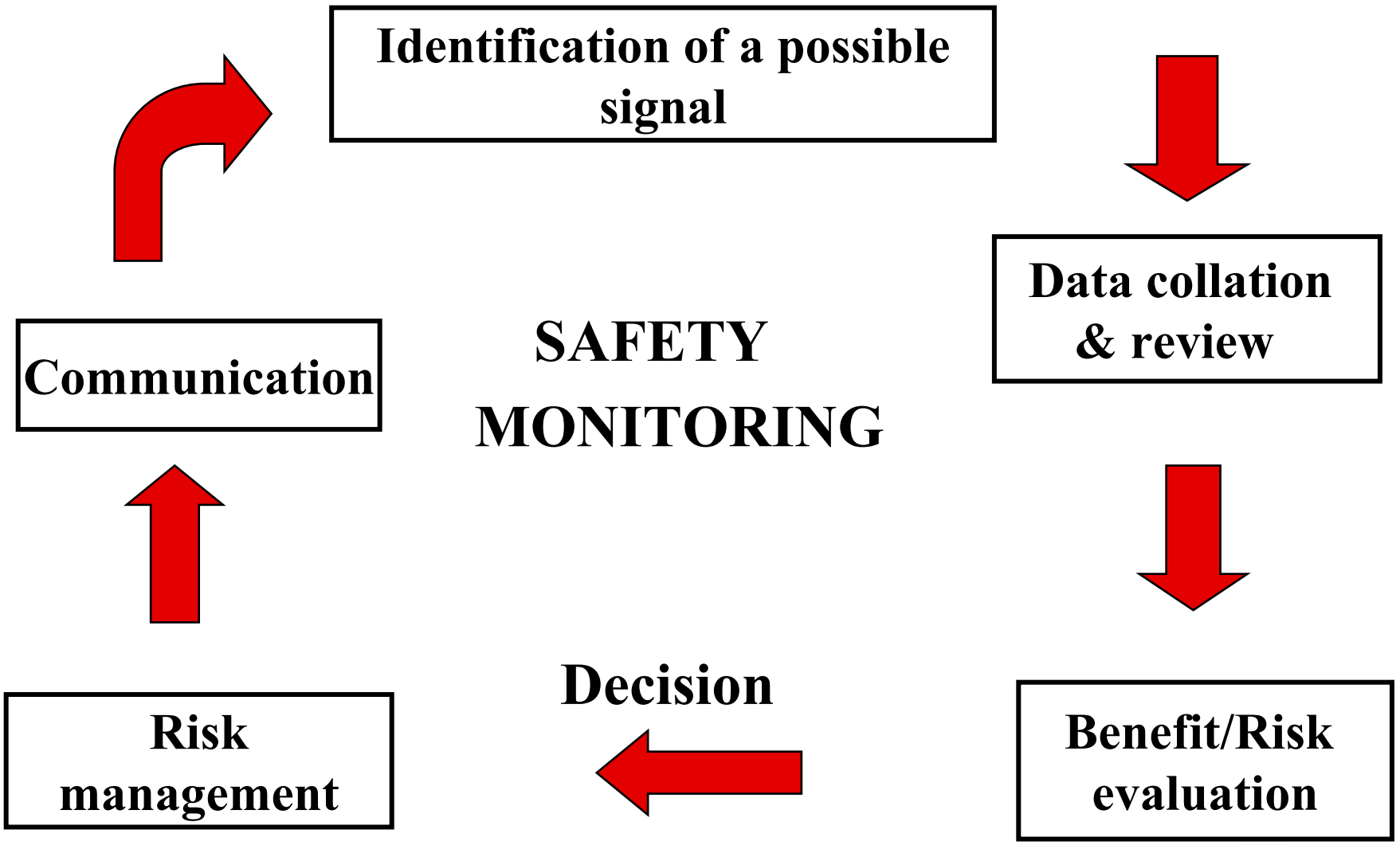
Evaluation of Pharmacovigilance Data



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)

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Post-Marketing Risk Evaluation

	Number of coincident events since a vaccine dose			Baseline rate used for estimate
	Within 1 day	Within 7 days	Within 6 weeks	
Guillain-Barré syndrome (per 10 million vaccinated people)	0·51	3·58	21·50	1·87 per 100 000 person-years (all ages; UK Health Protection Agency data)
Optic neuritis (per 10 million female vaccinees)	2·05	14·40	86·30	7·5 per 100 000 person-years in US females (table 2)[16]
Spontaneous abortions (per 1 million vaccinated pregnant women)	397	2780	16 684	Based on data from the UK (12% of pregnancies)[34]
Sudden death within 1 h of onset of any symptoms (per 10 million vaccinated people)	0·14	0·98	5·75	Based upon UK background rate of 0·5 per 100 000 person-years (table 2)[28]

Source: Black et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009;374:2115-2122.

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HPV Immunisation – Gardasil Summary of Product Characteristics (SmPC)

- 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

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Gardasil Summary of Product Characteristics

- 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

System Organ Class	Frequency	Adverse Events
Infections and infestations	Not known	Injection-site cellulitis *
Blood and lymphatic system disorders	Not known	Idiopathic thrombocytopenic purpura*, lymphadenopathy*
Immune system disorders	Not known	Hypersensitivity reactions including anaphylactic/anaphylactoid reactions*
Nervous system disorders	Very common	Headache
	Not known	Dizziness[1] *, Guillain-Barré syndrome*, syncope sometimes accompanied by tonic-clonic movements*
Gastrointestinal disorders	Common	Nausea
	Not known	Vomiting*
Musculoskeletal and Connective Tissue Disorders	Common	Pain in extremity
	Not known	Arthralgia*, Myalgia*
General disorders and administration site conditions	Very common	At the injection site: erythema, pain, swelling
	Common	Pyrexia At the injection site: hematoma, pruritus
	Not known	Asthenia*, chills*, fatigue*, malaise*

* Postmarketing Events

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Gardasil SmPC

- 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

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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

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Relevant IMB Gardasil Publications

- **Drug Safety Newsletter**
  - 37th Edition May 2010 (Insert) - HPV Immunisation Programme
  - 39th Edition November 2010 - Update on National Monitoring Experience
  - 43rd Edition August 2011 - Overview of National Monitoring Experience
- **Overview of National Monitoring Experience with Gardasil**
  - Published October, November, December 2010, February, July 2011

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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

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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.

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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

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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

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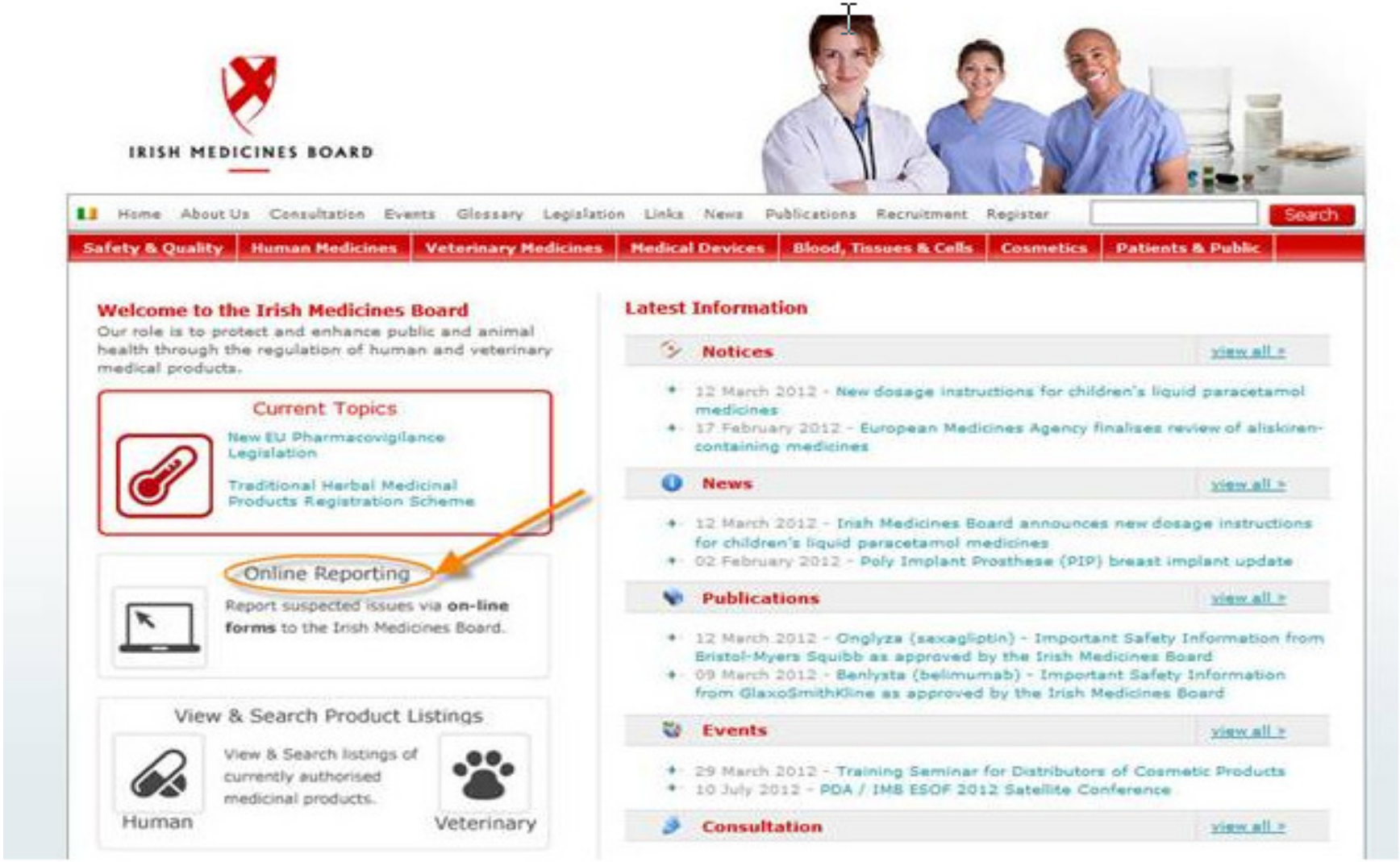
How to report?



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

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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

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References and Sources

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