Safety of new products – do we have enough tools in place?

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Outline

- Safety surveillance and pre and post registration studies
- EMA requirements
- New drugs and long term safety observation

Safety surveillance

- Drug approval process should ensure efficacy and safety of new products

- Drug development is generally divided into phases

Pre clinical and clinical studies

Pre-registration				Post-registration
Preclinical testing	**Phase I**	**Phase II**	**Phase III**	**Phase IV Post-marketing**
Laboratory and animal studies	Healthy subjects	Patients	Patients	Patients
Assess biological activity and **safety.**	Assessment pharmacokinetic, dosage and **the most common side effects.**	Evaluate effectiveness and **adverse events and immunogenicity.**	Verify effectiveness and *monitor* ***adverse long-term use.***	Verify risk/ benefit ***in a real world setting.***

Regulatory requirements

- Viral safety
- Adverse events
- **Immunogenicity**

(http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109692.pdf)

Viral safety

- Viral contamination can be analysed by:
  - virus testing within the manufacturing process
  - implementation of virus inactivation and removal steps in manufacturing process

Adverse events

- vital signs (blood pressure, heart rate, temperature, respiratory rate, etc.)
- development of hypersensitivity/anaphylactic reactions (including against host cells proteins, excipients and residues used in manufacturing process)
- for recombinant products, the use of non-human cell-lines raises the possibility of different contaminants and altered immunogenic potential
- for FIX concentrates, thrombogenicity should also be considered a potential safety issue

Immunogenicity

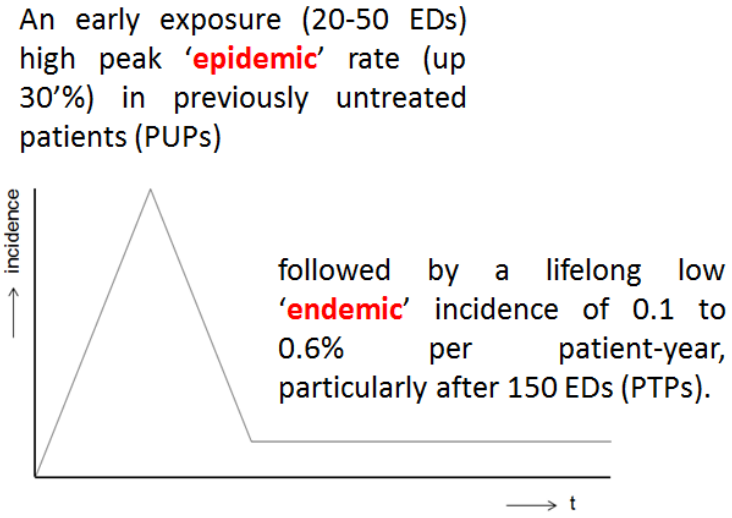
- Neutralising antibodies are the most important immunological concern
- Inhibitor development should be studied in:

Pre-authorisation

  - 50 previously treated patients (PTP≥12 years) with severe haemophilia A for 50 EDs
  - 50 children allocated in two cohorts of 25 PTPs (6- <12 years) and 25 (<6 years) for 50 EDs
  - Start of PUP study (50 PUPs for at least 50 EDs)
  - the modified Nijmegen method of the Bethesda assay should be used
  - in case of positive results for an inhibitor, an inhibitor retesting using a second separately drawn sample as confirmatory measurement should be performed.

Novel approach to clinical trial design: a biphasic nature

The 'epidemic' [≤ 35%; 20-50EDs] *vs* 'endemic' [0.1-0.6%/ patient-year] incidence of inhibitor development in PUPs and PTPs, and the potential to use known epidemiology to design **2-phase** studies in PTPs



(Dimichele DM, et al. Design of clinical trials for new products in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13:876-9)

Definition of post-marketing surveillance

- Procedure implemented after a drug has been licensed for public use, designed to provide information on use and on safety (occurrence of side effects, adverse effects, etc)
- It uses a number of approaches to monitor the safety of licensed drugs, including spontaneous reporting databases, prescription event monitoring, electronic health records, patient registries and record linkage between health databases
- Large-scale post-marketing pharmacovigilance studies are necessary to include sufficient numbers of patients for statistically valid assessments

(McNeil JJ, et al. Pharm Med 2010:24: 281–8)

Importance of post-marketing surveillance

- A landmark report from the Institute of Medicine of the National academy emphasized that:

  The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug – preapproval clinical trials do not obviate continuing formal evaluations after approval.

  (Institute of Medicine of the National Academies. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press; 2007).

- Safety monitoring of medicines (EMA):

  Some side effects or 'adverse reactions' may not be seen until a very large number of people have received the medicine and used it over longer time periods. The safety of all medicines is monitored throughout their use in healthcare practice.

  (http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000456.jsp&mid=WC0b01ac05801ae8fb)

Regulatory requirements

- **FDA**[1]:
  - post-marketing studies can be mandated if there is credible information to suggest potential issues with safety/efficacy of the licensed products (pharmaco epidemiologic studies/clinical trials with specific safety end-points)
  - specific requirements for long-acting products: no new guidance at the present time
- **EMA**[2]:
  - post-marketing investigations should be performed
  - number of HA patients is 200 (this sample size allow to observe antibodies in one or more patients with at least 95% probability in case inhibitors occur at an incidence of 1.5% or higher)
  - number of HB patients is 50
  - study participants should be PTPs (>150EDs) (patients from pre-authorization clinical trials can also be enrolled)
  - follow up: at least 100 EDs
  - specific requirements for long-acting products: no proposal to amend existing legislation

1. Guidance for Industry, Postmarketing Studies and Clinical Trials - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, 04/11
2. Pharmacovigilance legislation, http://www.ema.europa.eu/; Documents: EMA/CHMP/BPWP/144533/2009 and EMA/CHMP/BPWP/144552/2009

Longer acting Products

Technology	Target	Product	Status	Pediatric trials	PUP trials
PEGylation	FVIII	BAY94-9027	Phase III completed	Active, not recruiting (NCT01775618)	//
		N8-GP	Phase III completed	Active, not recruiting (NCT01731600)	Ongoing (NCT02137850)
		BAX 855	Phase III completed	Active, not recruiting (NCT02210091)	//
	FIX	N9-GP	Phase III completed	Active, not recruiting (NCT01467427)	Ongoing (NCT02141074)
Fc-Fusion	FVIII	Eloctate (rFVIIIFc)	**Approved by FDA at 2014**	Completed (NCT01458106)	Ongoing (NCT02234323)
	FIX	Alprolix (rFIXFc)	**Approved by FDA at 2014**	Completed (NCT01440946)	Ongoing (NCT02234310)
Albumin-fusion	FIX	CSL654	Phase III completed	Completed (NCT01662531)	Ongoing (NCT02053792)
Modification of amino acid sequence	FVIII	CSL627	Phase III	Active, not recruiting (NCT02093897)	//

Safety and toxicity of PEG

- Toxicity (short and long –term)
  - renal/hepatic toxicity
  - vacuolation
- Immunogenicity
  - anti-PEG antibodies

Toxicology of PEG

- The pharmacokinetic of PEGylated proteins is initially driven by the two major parts of the molecule, the **protein itself** and i**ts conjugated PEG part**.

- The usual study times, in toxicology studies, are not sufficient to clarify whether:

  - clearance of PEG from cell vacuoles is a consequence of the very long terminal elimination half-life

  - the disappearance of vacuoles is correlated to cell turnover, although some of the sites of vacuolation occur at site of very low cell turnover (e.g. choroid plexus ependymal cells).

(Baumann *et al.* Drg Discov Today 2014;10:1623–1631)

Longer acting coagulation products

- When the PEG is cleaved from the molecule resulting in the formation of metabolic PEG the biodistribution and pharmacokinetic are then governed by PEG-related mechanisms.

FVIII-PEG or FIX-PEG

→ Whether the **PEGylation site** is in **linker** region, upon activation the linker containing **the pegylation site is cleaved off.** ⇨ PEG molecules excreted by renal filtration (slow urinary clearance of high MW>30 kDa) or by cellular uptake.

→ Whether the PEGylation site is in A or C domains, **no cleaved upon activation.** ⇨ PEGylated proteins should be removed from the circulation via the same mechanisms as the parent protein.

→ Whether the epsilon-amino groups of lysine are Pegylated, and **almost** of the **PEG chains** are into the B-domain linker, **cleaved off** upon activation. ⇨ PEG molecules excreted by renal filtration, cellular uptake or removed from the circulation via the same mechanisms as the parent protein.

(Mei B, et al. Blood 2010;116:270-279; Thim L, et al. Haemophilia 2010;16(2):349-59; Negrier C, et al. Blood 2011;118:2695-2701; Turecek PL, et al. Hamostaseologie 2012;32(Suppl 1):S29-38)

Safety of PEG-protein conjugates

Consequences of chronic intravenous administration of PEGylated proteins:

- vacuolation of renal cortical tubular epithelium **in rats**
- vacuoles in the liver, kidney renal tubules and macrophages in the bone marrow of **monkeys**
- the vacuoles were transient and not correlated with any toxic effect (normal urinalysis parameters and any renal dysfunction)

(Bendele *et al.* Proteins. Toxicol Sci 1998;42:152–157)
(Young et al. Transl Res. 2007;149:333-342)

CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population

16 November 2012
EMA/CHMP/SWP/647258/2012

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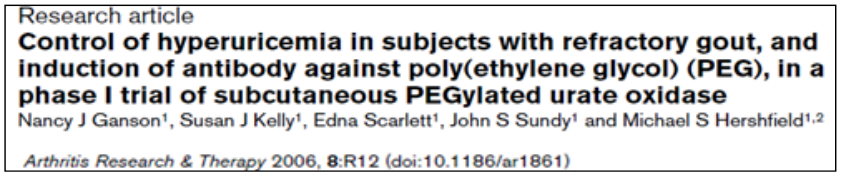
- In case ependymal vacuolation is observed in preclinical studies for a drug product intended for long-term treatment, paediatric development should only be initiated when there is a sufficiently large safety margin.

- It is recommended that before conducting clinical trials of more than 4 weeks duration with a PEGylated drug product, the applicant should address:
  - whether ependymal cell vacuolation has been observed in the preclinical studies
  - whether the PEGylated drug product may undergo active transport across the blood-CSF barrier
  - the biodistribution of the PEGylated drug product

anti-PEG antibodies

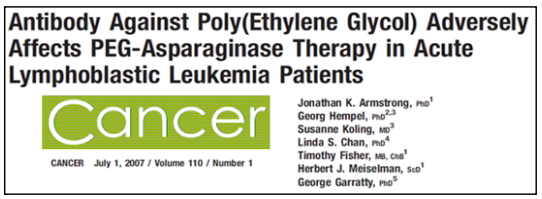
- Some studies have reported the development of anti-PEG antibodies
- Plasma half-life of PEG-asparaginase and PEG-uricase were dramatically shortened in some patients
- anti-PEG antibodies were detected in the patients plasma before the treatment
- The widespread use of PEG polymers in healthy-care products, cosmetics and foods could elicit anti-PEG antibodies in some individuals


Research article

Control of hyperuricemia in subjects with refractory gout, and induction of antibody against poly(ethylene glycol) (PEG), in a phase I trial of subcutaneous PEGylated urate oxidase

Nancy J Ganson[1], Susan J Kelly[1], Edna Scarlett[1], John S Sundy[1] and Michael S Hershfield[1,2]

Arthritis Research & Therapy 2006, **8**:R12 (doi:10.1186/ar1861)


Antibody Against Poly(Ethylene Glycol) Adversely Affects PEG-Asparaginase Therapy in Acute Lymphoblastic Leukemia Patients

Cancer

CANCER July 1, 2007 / Volume 110 / Number 1

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(Garay *et al.* Expert Opin. Drug Deliv. 2012;9:1319-1323)

Long term safety evaluation

- Long term observation using an standardised and homogeneous data collection system is necessary (ISTH recommendations)
- Each patient using a new drug needs to be registered in such a system which could become also the source of post-marketing surveillance
- Data collection needs to be mandatory and data storage could be at **National registries**