Immunogenicity Assessment of Therapeutic Proteins:

Strategy of RMP

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Overview

- Immunogenicity is a specific risk for all therapeutic proteins
- Consequences range from nothing serious medical outcomes
- Pre-approval quality & clinical testing is important to exclude gross risks but does not allow quantification of full profile
- RMP needs to address specifically
  - Risk Identification & Characterisation (e.g. case definitions & antibody assays)
  - Risk minimisation & Mitigation (e.g. plans to restrict to IV use for epoetin alfa, actions proposed in response to detected risk)
  - Risk Monitoring (e.g. specific framework to associate risk with product)
  - Risk communication (e.g. minimisation & mitigation messages for patients & physicians)
- RMP should address product and reference product risks
- RMP needs to address risk with different populations & indications

Post Approval RMP

- Objective should be to characterise & quantify risk for novel compounds or reassure risk is no worse than reference product for biosimilar proteins
- Requires understanding of numbers needed to assess risks, particularly rare risks
- Important to consider how to identify immunogenicity (neutralizing ab related) risk
  - Secondary loss of effect in naïve patient
  - Any Loss of effect in non-naïve patient
  - Evidence of presence of neutralizing antibodies
  - Other important features of specific case-definition
- Framework should be proposed for ensuring attribution of detected risk to specific product
- A priori decision about relevant sample size

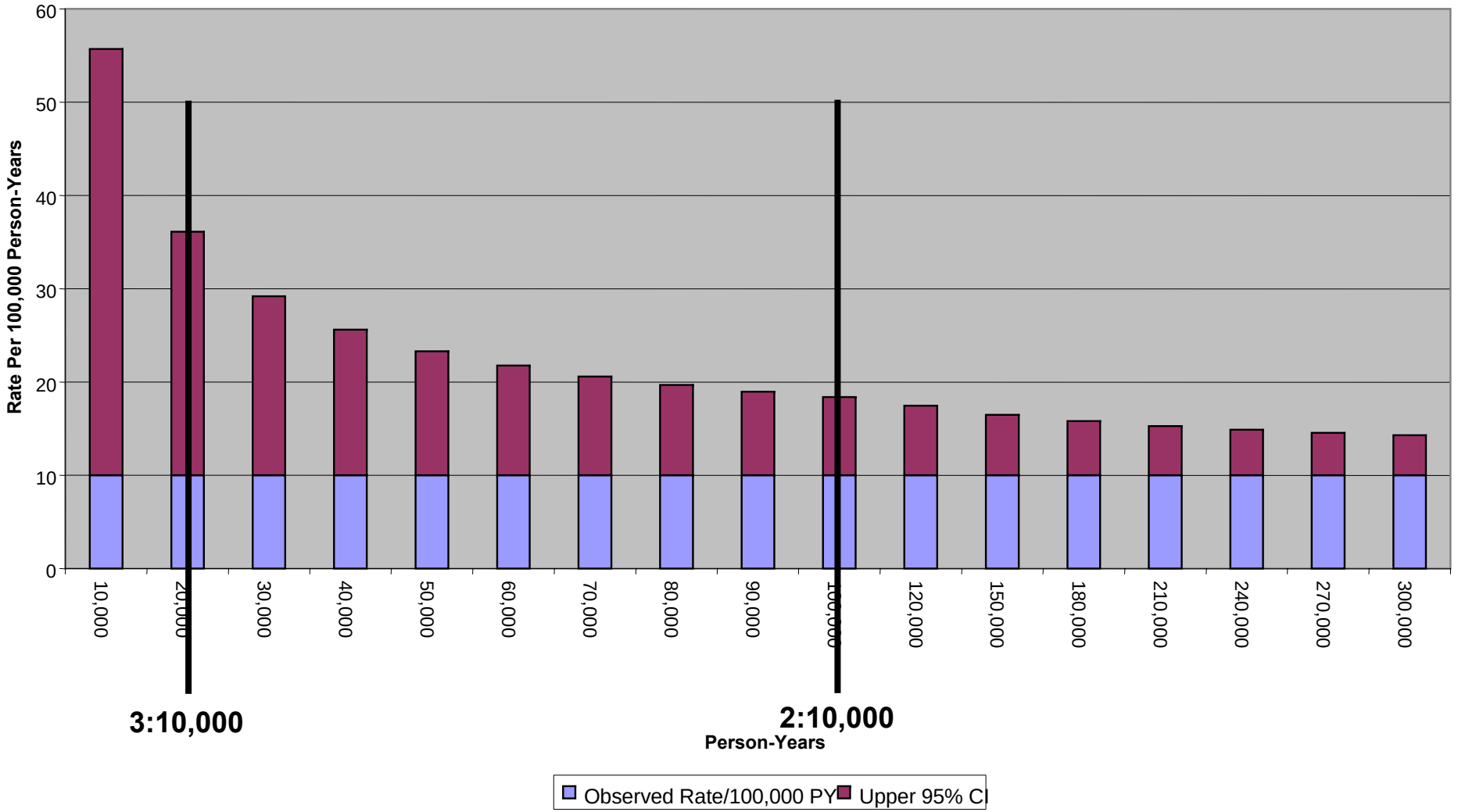
Sample Size Considerations

- We need to accept that risk is not as important as Benefit-Risk balance

- Excess risk should be defined as-
  - When frequency / severity outweighs benefits
  - When risk worse than alternative therapies
  - When severe risks cannot be mitigated

- Sample sizes will need to be considered based on predicted exposure, level of relevant risk & severity of risk

Difficulty In Excluding Rare Risks-
Upper 95% C.I. for observed rate of 10 per 100,000 PY



Risk Identification

- Well constructed and clinically relevant case definitions are critical
- In the post approval environment physicians need to know what they should report
  - Physicians see patients with loss of effect not antibodies
- RMP should describe the algorithm the company will follow to investigate all potential cases of loss of effect to derive cases that meet the agreed definitions
- Requires communication of how to access specific investigation tools to physicians and availability on request
  - E.g. antibody testing & product assays

Risk Minimisation & Mitigation

- Specific measures to control known risks must be clearly identified and communicated
- Monitoring to ensure effectiveness of risk minimisation is critical
- Example Risk Minimisation for known risk:
  - Epoetin Alfa & PRCA (renal indication)
  - Restriction of use to IV route
  - Communicated in label
  - Communicated actively by company to physicians
  - Effectiveness monitored by PRCA rate and also in-market surveys
  - Should be required for all products using EPREX as reference product

Risk Monitoring

- Specific framework proposed to estimate risk based on capturing index cases and accurate estimation of exposure
- Key Factors:
  - Degree of under-reporting or recognition by physician
  - Potential for product confusion
  - Estimated frequency of risk
  - Potential severity of risk
- Registry & Cohort studies may be required to study potentially rare but important risks where risk identification or product attribution is difficult

Risk Communication

- The label is not adequate to communicate specific risk minimisation activities or change behaviours
- Specifically-
  - How to avoid established risk (e.g. avoid SC route in renal failure for epoetin alfa products without data)
  - How to investigate for potential risk
    - Where to get antibody testing & product assay
    - What other causes should be considered
    - Where to report cases for accurate assessment
  - What to do when risk is confirmed
    - Duration of follow up & outcomes collection
    - Alternative therapies (may require non-company assistance)
- Critical to success of RMP

RMP:
Final Considerations

- Many, or most products will not require complex RMP
- Risk can be unpredictable and hence framework for robust risk detection and monitoring is important
- Risks may vary in different populations and indications hence the RMP should be dynamic

Case Example
RMP & EPREX Registry

EPREX Registry

- Implemented to assess and confirm that the EPREX specific increase in PRCA has been resolved following manufacturing changes

- Also designed to establish rate of PRCA attributable to EPREX in markets where product attribution is difficult
  - E.g. Thailand

- A pragmatic framework for studying large sample sizes

EPO Biosimilar Quality Evaluation (Singh, ASN 2006)

- Quality of biosimilar EPO products sold in Thailand were tested as well as same brands from other parts of the world:
  - Hemax: All 4 batches tested failed for aggregates (>4%) and isoforms (9-10)
  - Epokine: All 6 batches had batch to batch variability in quality
  - Eporon: 1 batch tested failed for aggregates and isoforms
  - Espogen: All 6 batches tested have additional isoforms of EPO
- "…these results point to unpredictable efficacy and the need for continuous PhV monitoring to ensure patient safety when using biosimilar epoetins."

Global Risk Management Plan

- **A Risk Management Plan has been implemented to stimulate reporting of cases *and* facilitate investigation and antibody testing**

  Key Components:

  1. **Guidance in the label**
  2. **Proactive pharmacovigilance**
     - **Provision of free antibody testing**
     - **Independent Safety Advisory Committee**
     - **Quarterly EPO Ab-mediated PRCA report**
     - **Prospective long-term follow-up of all PRCA cases**
  3. **Educational programs**
  4. **Registries and Clinical Studies**

Purpose of the Prospective Immunogenicity Surveillance (PRIMS) registry

- To estimate the incidence rate of erythropoietin antibody-mediated PRCA in patients with CRF (established CKD) after SC exposure to:
  - EPREX® (epoetin alfa)

PRIMS registry

- Multinational (EU and ASIA PACIFIC), multicentre
- Prospective cohort design
- Electronic data capture via web-based tool
- 3-year observation period post-enrolment
- No interventions or constraints
- Focused data collection
- Systematic approach if loss of effect is observed

Inclusion criteria

- CRF (established CKD)
- On dialysis, peritoneal dialysis, or haemodialysis
- Receiving, or about to receive (within 1 month), EPREX, Neorecormon or Aranesp by sc route
- Age ≥18 years
- Likely to remain on SC ESA for ≥1 year
- Informed consent where needed

Exclusion criteria

- >1 year since commencing sc ESA therapy
- Immunosuppressive medication or corticosteroids (equivalent to prednisolone ≥15 mg per day)
- History of PRCA or aplastic anaemia
- Experiencing loss of effect, ongoing at time of enrolment
- History of anti-erythropoietin antibodies prior to enrolment

Follow-up

- During normal healthcare visits quarterly recording of:
  - ESA exposure
  - Hb level
  - stage of disease
  - treatment modality
  - serious adverse events
    - possibly related to an ESA product
    - unexplained loss of effect
- Causes of unexplained loss of effect reported to sponsor
  - PRCA-specific questionnaire

Suggested approach to loss of effect

- **After usual underlying causes excluded:**
  - **if low reticulocyte count**

    and/or
  - **bone marrow examination suggests reduced erythropoiesis**
- **Test for antibodies**
  - **use validated test for detection of anti-erythropoietin antibodies**
  - **testing in an independent central lab is possible**

Independent case assessment and reporting

- **Case Adjudication Committee – PRIMS dataset**
  - 3 independent physicians
  - blinded to brand of ESA prescribed
- **Safety Advisory Committee – Global data**
  - 5 independent physicians
  - periodic review of unblinded patient data
  - make recommendation based on risk assessments
- **Progress reported to EU HA (part of Quarterly Report)**
  - 3 month (enrollment update)
  - 6 month (exposure update)

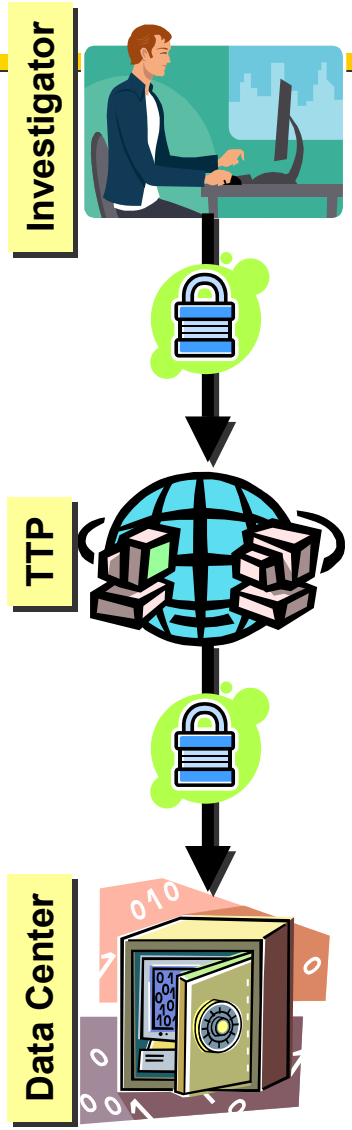
Sample size considerations

- Large numbers required to determine incidence rate of a very rare event
- Sample size of PRIMS registry
  - 20,000 person-years exposure to EPREX
  - 20,000 person-years exposure to comparators
- Triggers for review
  - PRCA rate with EPREX exceeds
    - comparator
    - historical rate
  - <10,000 patients could be recruited in 2 years

Privacy and data protection

- EU has implemented most strict privacy and data protection laws
- The use of encryption techniques by Trusted Third parties ensures patient privacy
- Encryption keys are destroyed after completion and reporting of the registry
- The PRIMS registry has been designed to meet those requirements

Electronic CRF



- Investigator enters data in the e-CRF
- Data are encrypted before they are sent to Trusted Third Party Provider (TTP) via the internet

- TTP filters patient identifiers (ex: patients initials) and encrypt them with another algorithm that cannot be decrypted by the Data Center
- Other patient data are encrypted by an algorithm that can be decrypted by the Data Center

- Patients data are decrypted and added to registry database identified by a unique patient number
- Patient identifiers cannot be decrypted and remains unreadable

Strengths of PRIMS registry

- Near 100% enrollment of eligible patients
- 100% follow-up for target adverse drug reactions
- Systematic approach to key adverse events
- Conform to ICH standards
- User friendly electronic data capture via web-based tool
- Data encryption by Trusted Third Party
- Patient identifiers cannot be decrypted by data center
- Case assessment by independent experts

Thank You