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GaBI Educational Workshops

First MENA Educational Workshop on
SIMILAR BIOTHERAPEUTIC PRODUCTS/BIOSIMILARS

1 September 2015, Le Meridien Dubai, United Arab Emirates

Clinical experience with EPO products approved via the generics pathway: the experience in Thailand

Morakot Papassiripan, PhD

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Introduction (1)

- In 1988, Erythropoiesis Stimulating Agent (ESA) was introduced and became the standard treatment for anemia in patients with Chronic Kidney Disease (CKD)
- In mid-1990s, a shift from the IV to the SC route of ESA occurred in many countries due to clinical and economic reasons
- In 2002, the Thai Health Product Vigillane Center received the 1st case of Pure Red Cell Aplasia (PRCA)
- In 1998, the original ESA product formulation using PS-80 as a stabilizer in stead of HAS

Introduction (2)

- In 1998–2003, the cases of EPO antibody-mediated PRCA were increased in CKD patients receiving one specific Eprex formulation [uncoated Polysorbate -80 (PS-80) PFS] by the SC route
- In March 2004, uncoated PS-80 PFS Eprex formulation was completely removed from the market
- The worldwide incidence rate of EPO Ab-mediated PRCA reports were decreased, except in Thailand
- October 2008, 85 patients were reported in lack of efficacy in relation to ESAs in Thailand

What are the issues in Thailand

- 15 brands of EPO Alfa and 1 brand of EPO Beta were registered in Thailand
- Poor people can receive EPO products because the cost is lower than the original product
- But, what problem does Thai FDA find?

"Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies"

Kidney Int. 2011 Jul;80(1):88-92.

- "Studied 30 patients with CKD treated by subcutaneous injection with biosimilar r-Hu-EPO and who developed a sudden loss of efficacy …"
- "Sera from 23 of these patients were positive for r-Hu-EPO neutralizing antibodies, and their bone marrow biopsies, indicated PRCA …"

"Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies"

Kidney Int. 2011 Jul;80(1):88-92.

- "Thus, subcutaneous injection of biosimilar r-Hu-EPO can cause largely adverse immunological effects a large …"
- "Long-term pharmacovigilance study is necessary to monitor and ensure patient safety for these agents"
- "Estimation risk for anti-r-Hu-EPO associated PRCA was 23/59,990"

"Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies"

Kidney Int. 2011 Jul;80(1):88-92.

- "An estimation of the actual cases using biosimilar r-Hu-EPO denominator with this complication was 1:2,608"
- "The results could not provide sufficient information to determine exactly which specific biosimilar products are directly responsible for causing anti-r-Hu-EPO associated PRCA …??" Interchangeability?
- "However, we can clearly state that repeated subcutaneous injection of biosimilar agents could result in the development of anti-r-Hu-EPO associated PRCA"

What are the solutions? (1)

- There are 16 EPO brands but none are biosimilar (even though Binocrit which was registered by the same pathway as the other EPO products) because of …

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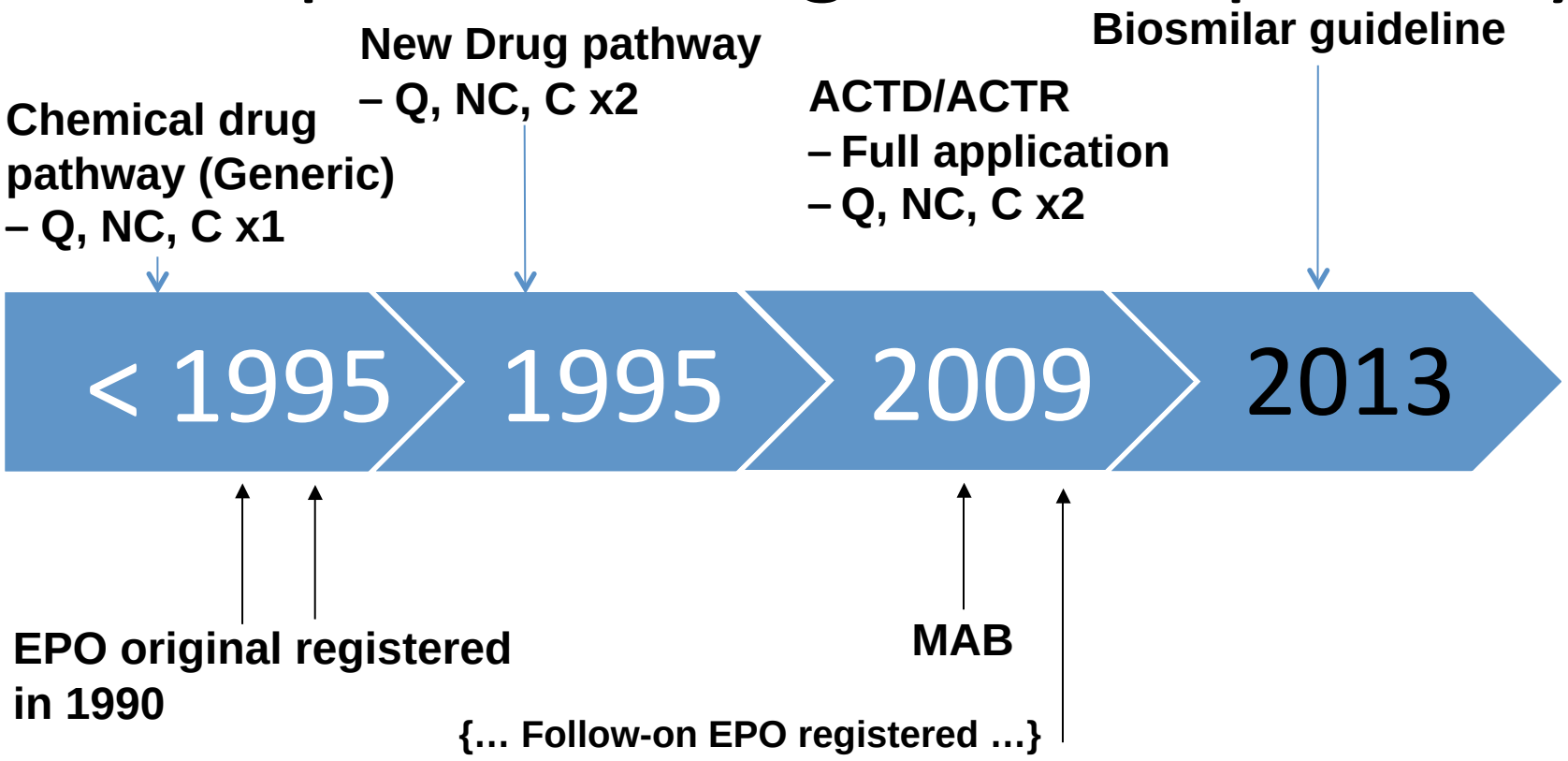
Development of registration pathway



What are the solutions? (2)

- Legal actions
  - Revised regulations
    - 2009 ASEAN Harmonization/ICH
    - 2013 Biosimilar registration pathway
  - New products of EPO will submit in the stand alone pathway (new biological product pathway) / the biosimilar pathway
  - Re-assessment process for the EPO products in the market
  - Pharmacovigillance system
- Non-legal actions
  - Dear doctor letter, Alert letter

Pharmacovigilance

Report
(mail, email, FAX,)
Online report, report form

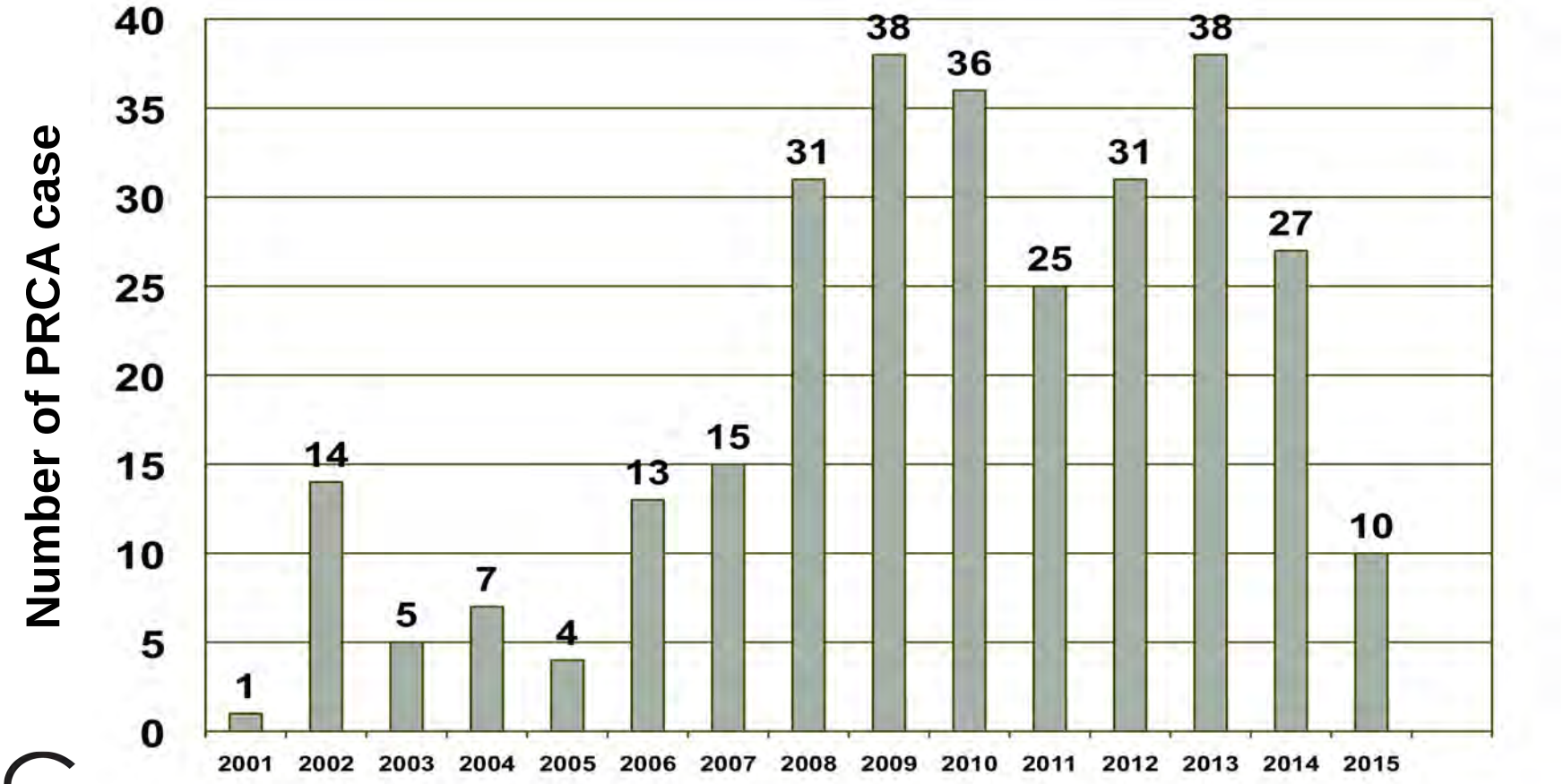
- Since 1983
  - Spontaneous passive surveillance
    - Safety drug monitoring program
  - Active surveillance
    - Intensive drug monitoring
    - Registry

Thai FDA : HPVC

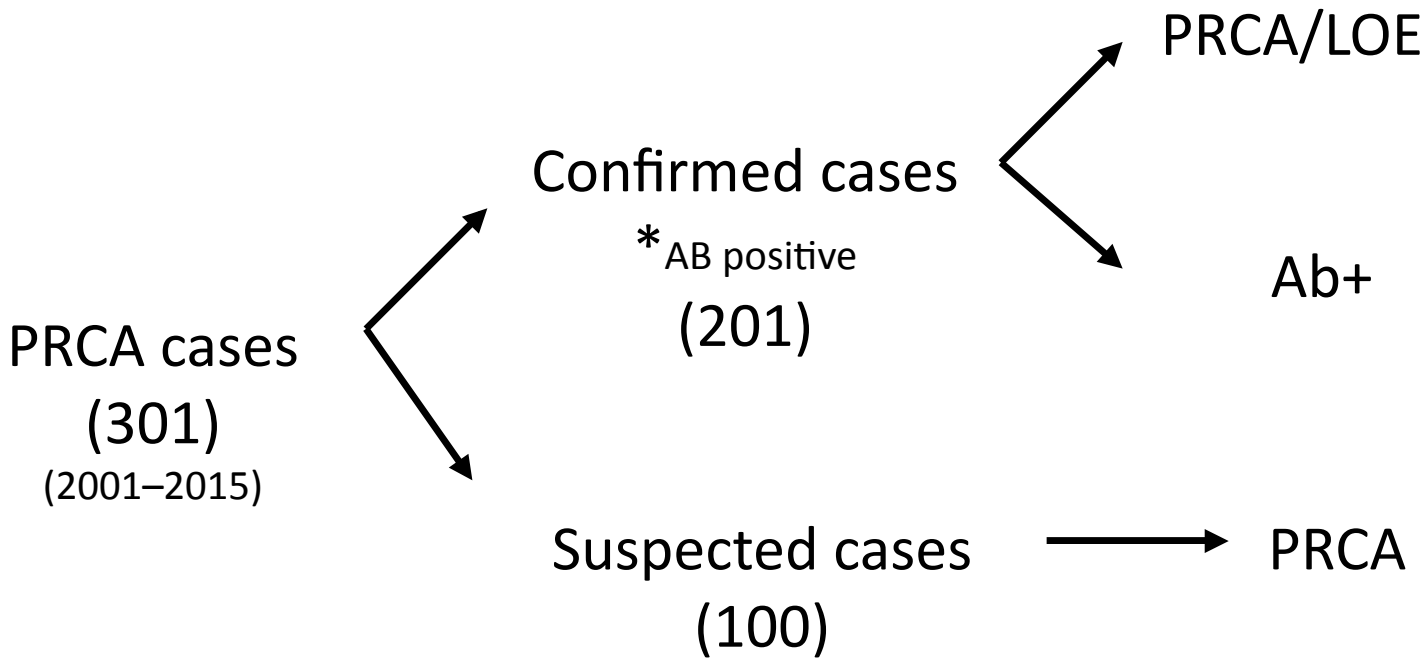
Dear doctor letter
Annual report
Bulletin

Sources of reports
(hospital, drugstore)
Marketing Authorization Holder

Current situation (1)



Current situation (2)



*Thai registry incidence = 1.7 : 1,000

Factors influencing immunogenicity

Product-related factors

- Protein (structure, primary sequence, novel epitopes, glycosylation, oxidation, deamidation)
- Product impurities, formulation, aggregation, degradation
- Protein properties, e.g. immunostimulatory, replacement therapy, physiologically important
- Administration: (dose, route (subcutaneous for EPO) , frequency of administration and duration of therapy
- Interchangeability

Patient-related factors

- Age
- Gender
- Genetic phenotype
- Ethnic sensitivity (IFN-alpha 2a more immunogenic in Chinese compared to Caucasian hepatitis patients 39% vs 14%)
- Immune status
- Disease

What are the possible causes for the high reporting rate of there events in Thailand?

- Product?
- Quality?
- Formulation?
- Storage and handling?
- Route of administration?
- Interchangeability of the products?
- Genetic phenotype?

Summary

Product

- How could Thai FDA solve this problem?
  - (Re-evaluation process, Biosimilar pathway)

Clinical practice

- Interchangeability
- Subcutaneous use
  - (Cooperate with the clinicians)

Consider

- Government's health budget supported
  - (If the price of product is over difference, the biosimilar product is necessary for use)
- Patient-related factors (in case of subcutaneous used)
  - Far and hard to go the hospital and receive drug

Acknowledgement

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