Erfahrung mit PAES, PASS und RMP - Sicht der Industrie

Science For A Better Life

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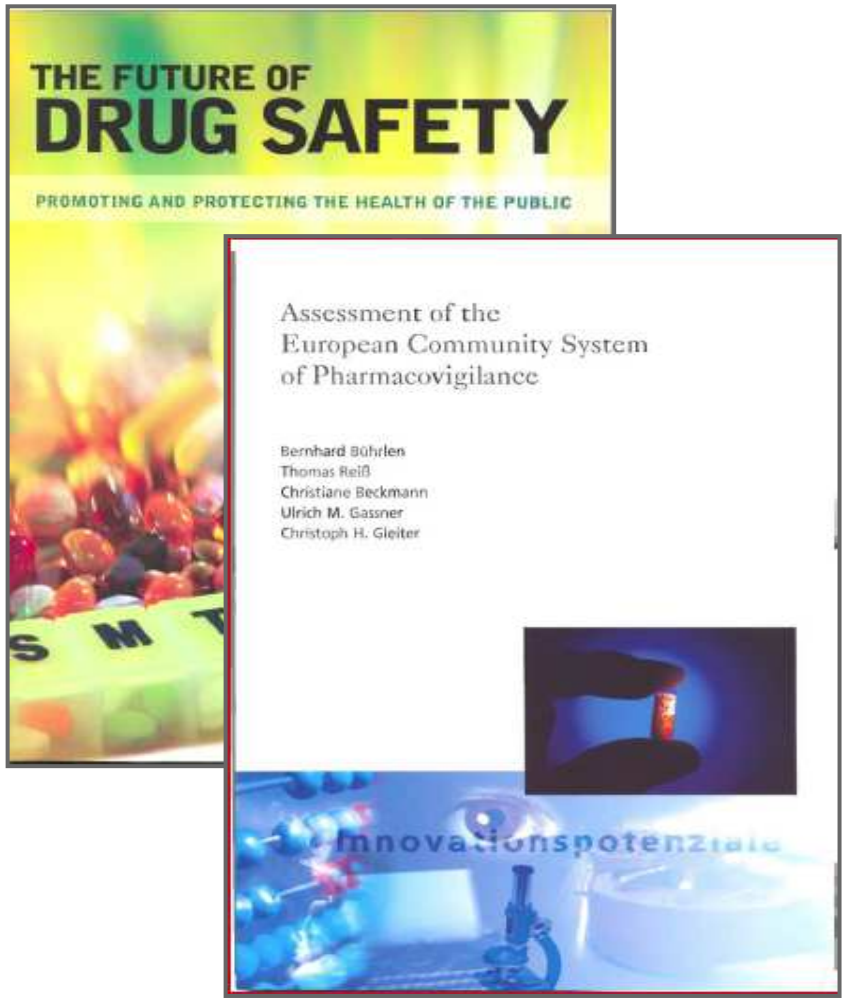
Pharmacovigilance needs to ensure patient safety in a rapidly changing environment



Evolving regulations and initiatives

(e.g., revised PV legislation, Report of the EU Commission on PV, IOM Report on the US Drug Safety System, FDAAA, Sentinel initiative)

- **Safety risk management from development to end of lifecycle**
- **Proactive Data mining, Signal detection and management + response from external databases for from HA authority databases**
- **Post-authorization safety and efficacy studies**
- **Transparency on safety matters**
- **Increased number of inspections, penalties & fines**

2007 legislation in the US has increased the focus on Safety Risk Management (FDAAA)

Section 901 of FDAAA grants the FDA sweeping new authority to require:

- Post marketing studies and clinical trials
- Safety labelling changes
- The concept of ‘Risk Evaluation and Mitigation Strategies’ (REMS) replaces that of RiskMAPs

Though limitations exist on the FDA’s authority to demand these actions, large penalties will be in place for non-compliance with legitimate demands

Risk Evaluation and Mitigation Strategy (REMS)

FDA may require manufacturers to establish risk management programs (REMS) for new therapeutics

So far, more than 50 drugs required explicit distribution restrictions under risk-management plans, primarily for risk of birth defects (i.e.accutane and isotretinoin generics), anaphylaxis, abuse and addiction (opioid analgesics), or other toxicity.

Recently, a growing number of existing pharmaceuticals have been subjected to REMS requirements

REMS program now a common requirement for new drug approvals, mostly requests for Medication Guide

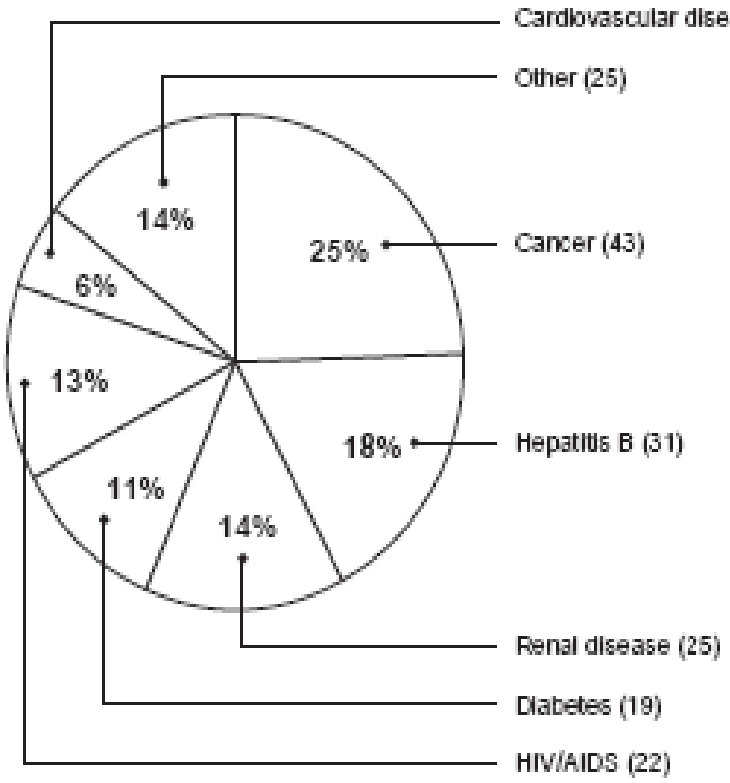
EU-RMP Broader Scope
REMS Focuses on Specific Risks

	REMS	EU-RMP
EU-RMP Part I		
Safety specification		√
Pharmacovigilance plan		√
Part II – Risk Minimization Assessments		
Medication guide / patient brochure	√	√
Education programs	√	√
Required training or certification	√	√
Restricted access, distribution, etc.	√	√
Monitoring of use, patient registries, etc.	√	√

Rachael L. DiSantostefano, Ph.D. Associate Director, Worldwide Epidemiology
GlaxoSmithKline, DIA San Diego June 2009

Post-Approval Commitments

Figure 7: Percentage of Postmarketing Studies Requested under the Traditional Process, by Disease, January 1, 1998–June 30, 2008



Source: GAO analysis of FDA data.

New PV Legislation

- Revised PV legislation adopted December 2010
  - Regulation EU 1235/2010, Directive 2010/84/EU
  - Date of coming into operation: July 2nd, 2012 and July 21, 2012
- Wave 1 and Wave 2
  - Deliverables further prioritized (public health – transparency/communication – process simplification)
- Legislation requires implementing instructions/guidance
  - EuComm issued draft implementing measures Oct 11
  - Modular Good Pharmacovigilance Practice Guideline
- **The legislation is the biggest change to the EU human medicines legislation since 1995**

Good Vigilance Practice Guide

GVP will be developed in a **modular approach** to facilitate its maintenance

Will replace Volume 9a

Final 'Wave 1" modules to be published <u>in July 2012</u>

- *Consultation Feb/March 2012*
- Module I: PV Systems and their Quality Systems
- Module II: PV System Master File
- Module V: Risk Management Systems
- Module VI: Data Management of Imdividual Case Safety Reports
- Module VII: PSURs
- Module VIII: PASSs
- Module IX: Detection and Management of Signals and information

Good Vigilance Practice Guide

Second wave:

9 modules (drafts expected Q3), final documents expected: December 2012

Module III:	Pharmacovigilance Inspections
Module IV:	Audits
Module X:	Post-Authorisation Efficacy Studies
Module XI:	Public Participation in Pharmacovigilance
Module XII:	Continuous PV, Ongoing Benefit-Risk Evaluation, Regulatory Action and Planning of Public Communication
Module XIII:	Incident Management
Module XIV:	Educational and Communication Tools and Materials for Pharmacovigilance and Risk Minimisation
Module XV:	Effectiveness of Risk Minimisation
Module NR:	Referral Procedures for Safety Reasons

What‘s new? (1)

- Legislation applicable to medicinal products at any point in their lifecycle
- Risk management systems will be required for all new authorized medicines
    - New line extensions or established products
    - What is new medicines ? Generics?, new forms ? New products ? Etc.
- New RMP considered to be pre- and post authorization ***risk-benefit management and planning***
    - ❖ Main purpose of PSUR is integrated, post-authorization ***risk benefit assessment***

What‘s new? (2)

- There are recognized differences in indication and healthcare system
  - Target population may be different across the world
  - Risk and benefit may be different in subsets of populations
  - Differences in disease prevalence and severity; benefit may vary across regions
  - Different RMPs may be required by region
  - Some RMP modules will be interchangeable with PSUR modules
  - Public posting of RMP summaries
- New modular structure for EU risk management plan will come into operation July 2012
- Transition allowed

What‘s new? (3)

- Pharmacovigilance Master File to be kept by MA holder
  - Contains PV system, all PV measures to be taken for all new products and should be available upon request within 7 days
  - Inspections will be performed regularly by the HA of country where PSMF is located

- Urgent Union Procedure (art 107i, 107j, 107k of 2001/83 as amended
  - Designed to assess significant emerging safety issues registered by any EU procedure
  - Issues leading to procedure through
    - Single case, PAES, PASS, Epi study etc.

What‘s new? (4) – PAES and PASS

- PAES and PASS can both be part of the RMP
- Are legal requirements coming with a registration and have to be performed and reported
- Designed to qualify potential efficacy and safety issues following approval

All risks that are judged to be important are characterised following a facilitated approach

Each important risk is characterized across five categories:

- Facts
- Ideas
- Knowledge gaps
- 'Homework' actions
- Risk management actions

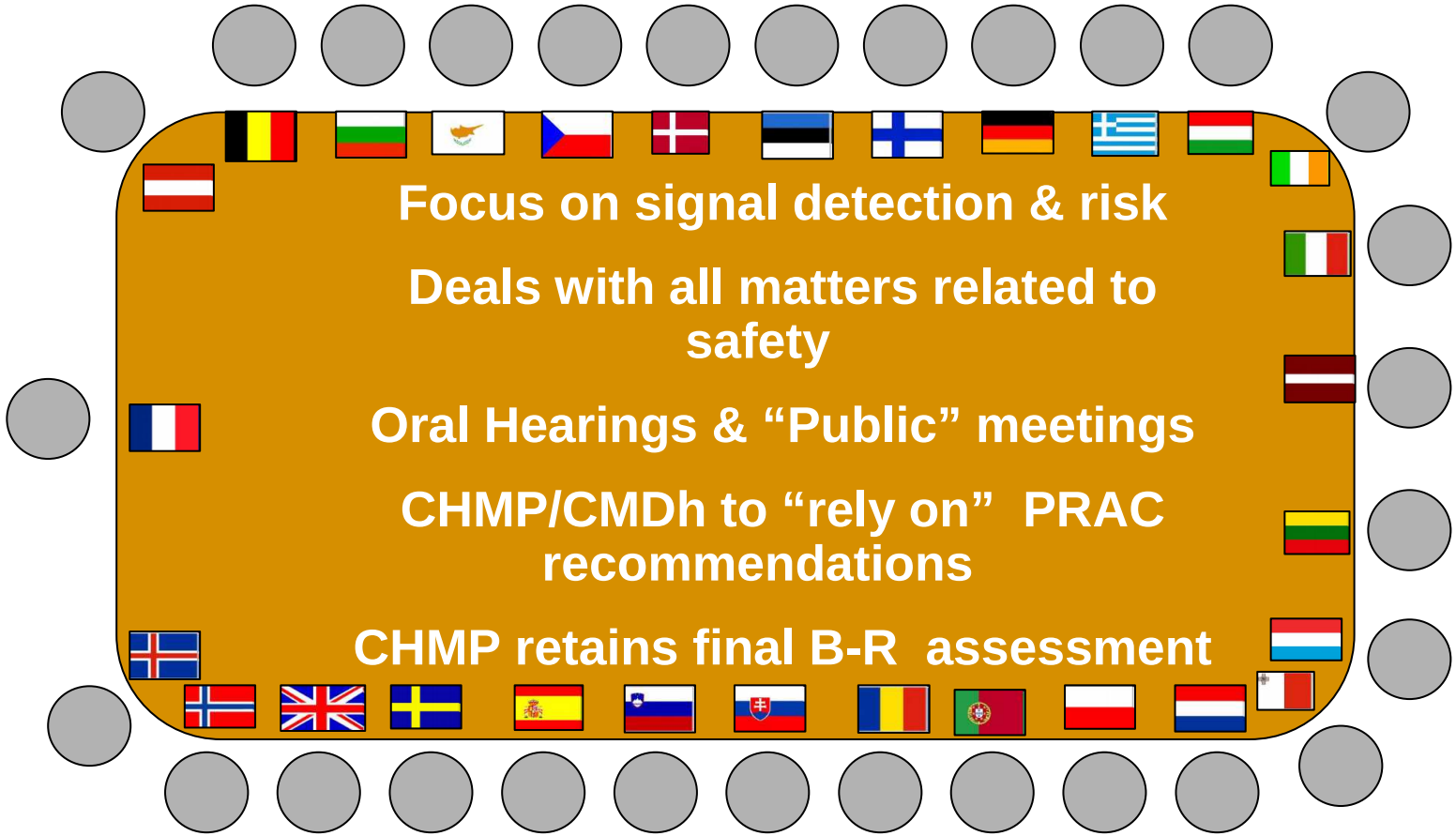
It is agreed on:

- A list of important risks
- Actions to be completed to close knowledge gaps
- Risk management action related to the important risks

PRAC – July, then monthly from Sept 2012

- The Pharmacovigilance Risk assessment Committee shall be responsible for
    - Pharmacovigilance activities for medicinal products
    - Risk management systems
    - Monitoring of the effectiveness of RMSs
- Provides recommendation to the CHMP
    - Deletion of an indication
    - Addition of CI, AE, warning
    - Change in dosing, duration of treatment, etc.

PRAC – July, then monthly from Sept 2012



+ 6 specific experts, one healthcare professional, one patient member rep

Taken from CHMP 2011 and just for visualisation

PRAC – Consequences for Industry

The PRAC has great influence and the power to recommend

- change the label
- ask for conducting PAES, PASS, Epi studies
- withdraw a product

Final decision by CHMP for CP and CMDh for MP/DC, and MS for NP

RMPs will become standard to all new applications / approvals


Worth1000.com

Example
Challenge: how to deal with EU RMP – for two new indications- : 2 separate plans

Time	Event	Indication 2	Indication 3	Comments
	RMP for approved Ind 1	Version 1		
xxx	Submission Ind 2	Version 2		
xxx	Submission Ind 3		Version 3	
xxx	Response to List of Questions Ind 2	Changes to RMP committed in responses		Some confusion with the two separate RMPs, comments received also for the (previously approved) text for Ind 1
	Response to List of Questions Ind 3		Changes to RMP committed in responses	
	Shortly before CHMP Opinion (day 181) Ind 2&3	Version 4, combined version		**New version of RMP, combines both RMPs-** (very long document) Includes all changes for Ind 2 and Ind 3
	With next PSUR	**Version 5, consolidated version**		Consolidated (shortened) version including all changes for Ind 2&3

Some quotes….

Yann le Cam (patients organisation EURORDIS) at DIA March 2012

You have all the tools already in hand so you can do it today if you just set this out as new EMA policy

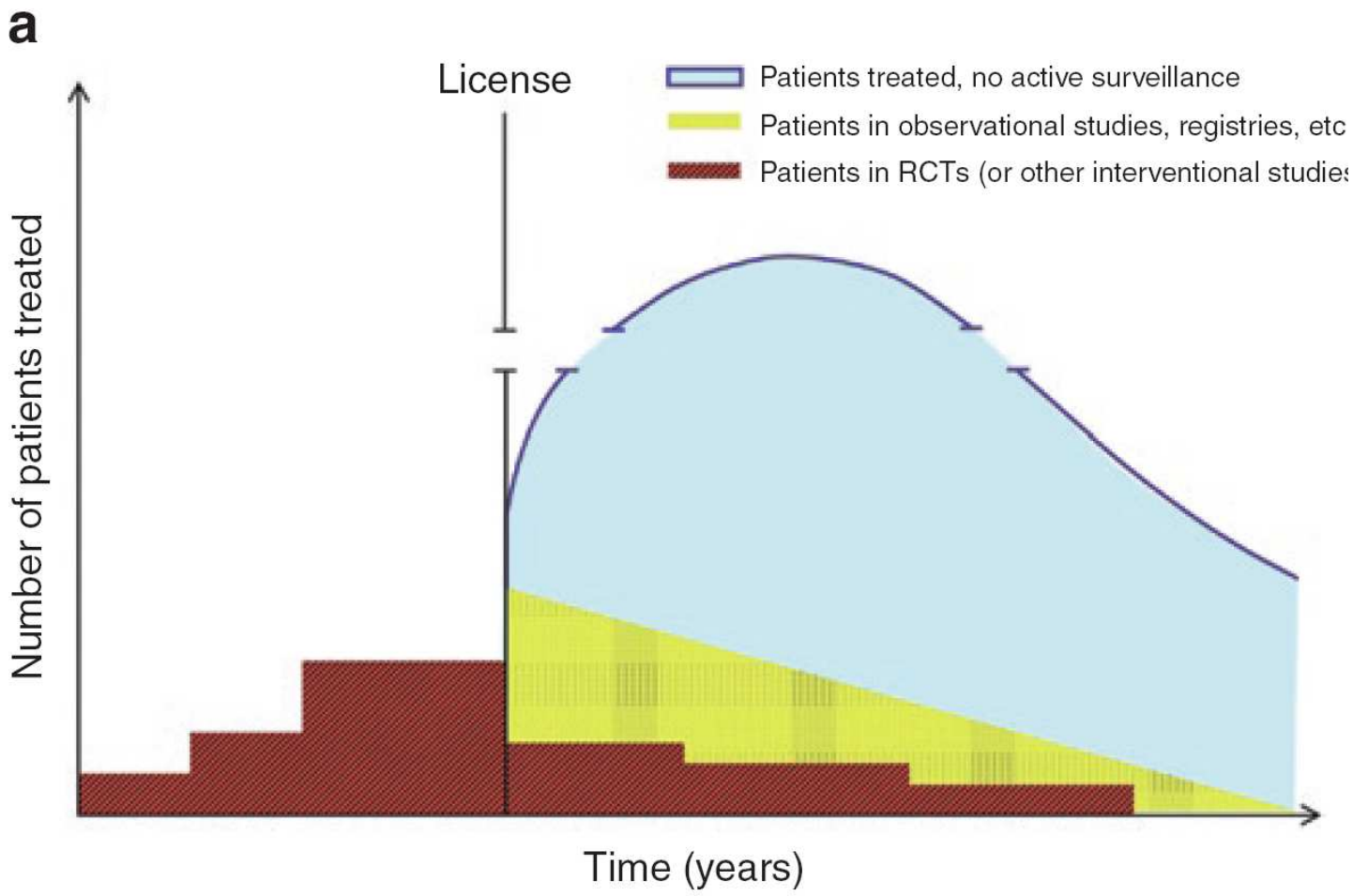
Eichler at DIA March 2012

New PV tools (Benefit Risk Evaluation update report, new RMP format, RMP actions, PAES study, automated signal generation) will hopefully lower the hurdle for Regulators to accept more uncertainties at time of initial approval

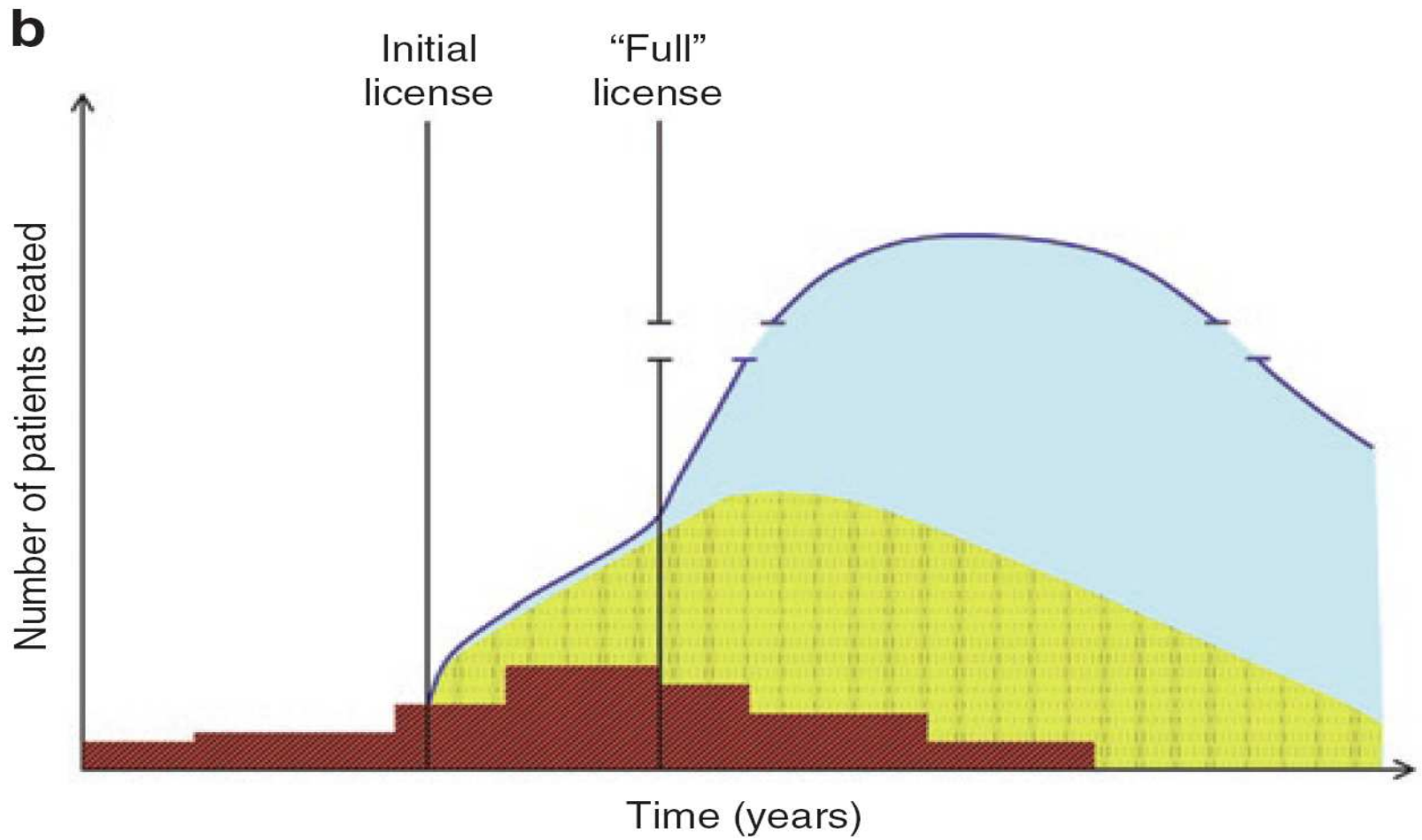
Schneider at DIA March 2012:

Training of assessor on operational level, shift of mindset is not yet there

Old model – EU regulators view



New model – impact on submission / approval ?



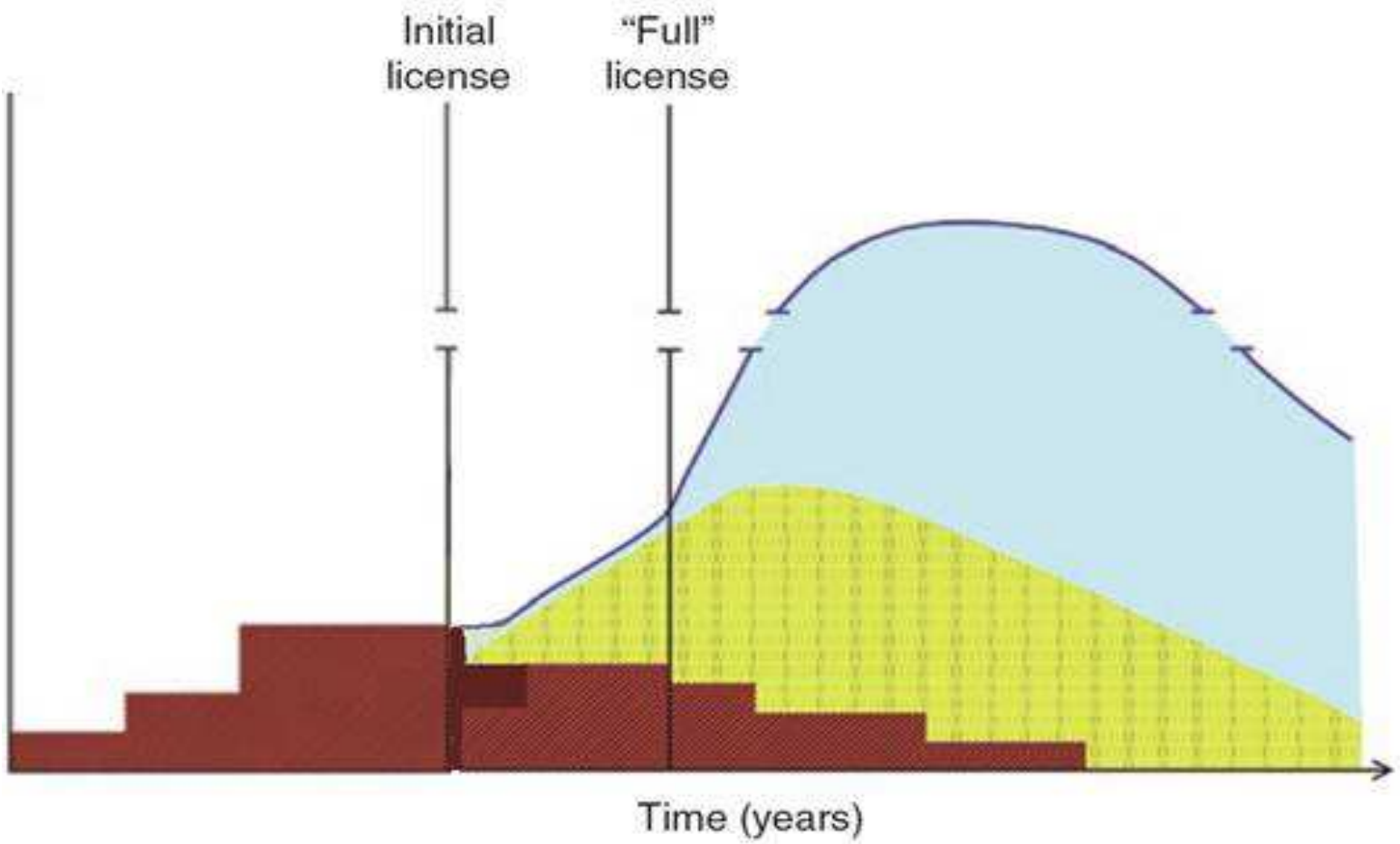
What is in it from an Industry perspective

Pros	Cons
• Early access • Early start of Return of Investment • Less investment prior to first license (postponement) • Allows flexible reaction to new technologies (studies in late stage of development) • Better initial price by payers for restricted group of patients • Using the new system to learn how it works • No legal change required – could be used today for pilots, actively request conditional approval	• Loss of IP • Less initial uptake, less initial sales due to restricted initial use • Hen or egg: a solid Benefit risk decision making framework will be needed and Regulators on operational level are not yet ready to take more risks • Higher costs for managing restricted uptake (PASS, observational studies, registries, informed consent) • Higher costs at late stage (PAES) • Manage customers expectations: ie Physicians/Patient who want the new drug for other indications – need to involve their perspectives early • Loose patients for controlled Clinical trials

Challenges that will be impacting industry

- Impact on epi studies, epi databases and analysis in data from the industry becoming available through increased transparency?
- Need for unique identifier per patient to avoid AE fraud ?
- Biosimilar AE reporting with batch number. Is this realistic?
- Do we need more physician training in what we need as info to make better Benefit-Risk decisions?

How do we make sure it does not end up like that?



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Thank you!