EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dose- and schedule determination and amendments of EU Centrally Approved Products (CAPs)

Dose finding workshop Dec 2014

Presented by Falk Ehmann MD, PhD

Deliverables Session 5

Define the impact of D-E-R information in regulatory submissions, approval and post authorisation development

→ To provide further evidence of the value of optimised dose and schedule determination during drug development and post authorisation

Analysis: 135 medicinal products containing new active substances (NAS) EU centrally approved between 2010 to 2014

→ **Major objections** related to **dose-finding and schedule** raised during the **evaluation** of these products

→ **Dose- and schedule related label (SmPC) changes** of **marketed** products (Variations)

Major objections related to dose-finding and schedule:

Results: 10% (12 out of 135) of centrally approved products (NAS) had a dose and/or schedule related MO been raised during their evaluation (2010 - August 2014):

- Unexplored impact of **(non)-fasted** state and **ethnicity** on dosing,
- **Inconsistency** of **extrapolation from PK** dose finding evidence to final recommended dose
- Unacceptable high Adverse Drug Reaction **(ADR) rates** linked to **proposed dose**
- Non accordance between **non-clinical dose-range curve** and dose-response **relationships**
- Insufficiently justified **extrapolation of dose-response curves** for dose selection
- **Inexplicable in vitro potency assay** relationship with clinical **dose selection**
- **Not established or justified** dosing regimen / recommendations (missing evidence)

Original Investigation | January 22/29, 2014

Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012 FREE

Leonard V. Sacks, MBBCh[1]; Hala H. Shamsuddin, MD[2]; Yuliya I. Yasinskaya, MD[2]; Khaled Bouri, PhD, MPH[3]; Michael L. Lanthier, BA[4]; Rachel E. Sherman, MD, MPH[1]

[+] Author Affiliations

JAMA. 2014;311(4):378-384. doi:10.1001/jama.2013.282542.

Results Of the 302 identified NME applications, 151 (50%) were approved when first submitted and 222 (73.5%) were ultimately approved. Seventy-one applications required 1 or more resubmissions before approval, with a median delay to approval of 435 days following the first unsuccessful submission. **Of the unsuccessful first-time applications, 24 (15.9%) included uncertainties related to dose selection**, 20 (13.2%) choice of study end points that failed to adequately reflect a clinically meaningful effect, 20 (13.2%) inconsistent results when different end points were tested, 17 (11.3%) inconsistent results when different trials or study sites were compared, and 20 (13.2%) poor efficacy when compared with the standard of care…

Conclusions and Relevance

Several potentially preventable deficiencies, **including failure to select optimal drug doses** and suitable study end points, accounted for significant delays in the approval of new drugs. Understanding the reasons for previous failures is helpful to improve the efficiency of clinical development for new drugs

Dose- and schedule label amendments **during marketing** phase:

10% (13 out of 135) of centrally approved medicinal products (NAS) had their dose and schedule SmPC (label) section amended during the covered marketing phase:

→ **7/13** products experienced **dose changes**

- 4x experienced **dose changes** in **special populations (renal- and hepatic impaired),**
- 3x experienced **dose changes** due to **drug drug interactions** (**DDI)**,

- 2x dose/schedule changes for **patients' convenience** and compliance,
- 4x amended label due to **safety signals** and

Dose de- / increase recommendations in special populations

renal impaired

→ **PK simulations** with **end-stage renal disease haemodialysis patients** demonstrated that an **additional single supplemental dose** should be taken immediately after haemodialysis

→ study results showed AUC_{inf} and Cmax increase by 79% and 34% in **severe renal impaired** → dose **decrease recommended**

→ **Simulations** to assess **PD time profile** in patients with end stage renal disease (ESRD) on haemodialysis resulted in a **revised starting dose** in these patients

hepatic impaired

→ PK study shows **not achievement of therapeutic plasma concentrations** in patients with **severe hepatic impairment** → not recommended in SHI pat.

Dose de- / increase recommendations due to Drug-Drug-Interaction

- → DDI study showed **amended dose** does **compensates for an inducing effect**
- → DDI in **vivo-in vitro (IVIV) extrapolation modelling** → with a strong **CYP1A2 inhibitor** → dose reduction is recommended

Patient convenience motivated **schedule** label changes

- → phase 3 study demonstrated **non - inferiority** of increased dose **twice daily** to previously recommended dose **every 8 hours**
- → dosage regimen using **different infusion volumes** and schedule exhibited linear and time-independent pharmacokinetics

Safety signal motivated label changes

→ Overdose due to **different expression of strength and dose** (base / salt) → **base only**

→ **overdose** following **administration- or medication errors** → improvement of description of the **product's reconstitution process**

→ Increased arterial and venous **thrombotic events** → **not to use** in **heart attack or stroke patients**

→ Increased rate of **acute rejection** → **cautious corticosteroid tapering** in **HLA mismatches**

Table 1: Dose and schedule label (SmPC) changes of EMA evaluated medicinal products during the marketing phase.

Medicinal product (INN)	**Label (SmPC) change under posology and administration (SmPC section 4.2)**	**Motivation for dose and schedule label (SmPC) change**
Trobalt (retigabine)	dose increase in dialysis patients	**Suboptimal dose in special populations and Drug-Drug-Interaction (DDI) motivated label change (dose in- or decrease)**
Edurant (rilpivirine) and Eviplera (emtricitabine / rilpivirine / tenofovir disoproxil)	dose increase due to DDI	**(3 renal-, 1 hepatic impaired and 3 DDI motivated label changes)**
Votrient (pazopanib)	dose reduction and CI in severe hepatic impaired patients	
Esbriet (pirfenidone)	dose reduction due to DDI (selective inhibitors CYPP1A2)	
Xalkori (crizotinib)	dose decrease in severe renal impaired patients not under dialysis	
Jakavi (ruxolitinib)	revised starting dose in end stage renal disease patients	
Jevtana (cabazitaxel)	medication errors (overdose) lead to improved description of product reconstitution process	**Safety signal motivated label changes**
Halaven (eribulin)	medication errors (overdose) due to the use of erbulin salt and base was resolved by expressing erbulin strength and dose consistently using erbulin base only	
Iclusig (ponatinib)	CT data suggested a higher cardiac ADR rate in Inclusig treated patients. Therefore Inclusig has been CI in patients with history of heart attack and stroke	
Nulojix (belatacept)	Postmarketing signal resulted in a recommendation to cautiousely taper corticoids	
Incivo (telaprevi)	Novel product administration of twice instead of trice daily lead to improved patient convenience	**Patient convenience/improvement motivated dose and schedule label changes**
Zinforo (ceftaroline fosamil)	Novel product administration using different infusion volumes lead to improved patient convenience	

submitted

Literature:

Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980–1999y; **Peck et al**, pharmacoepidemiology and drug safety 2002; 11: 439–446

KEY POINTS

***dose changes occurred in 21%** of indicated population

* **Postmarketing changes** to labelled dosage regimens may reflect **suboptimal drug development**

* **Dosage changes** occur frequently and appear overwhelmingly to be **safety motivated**

* The rate of these changes is greater for newer drugs than older drugs

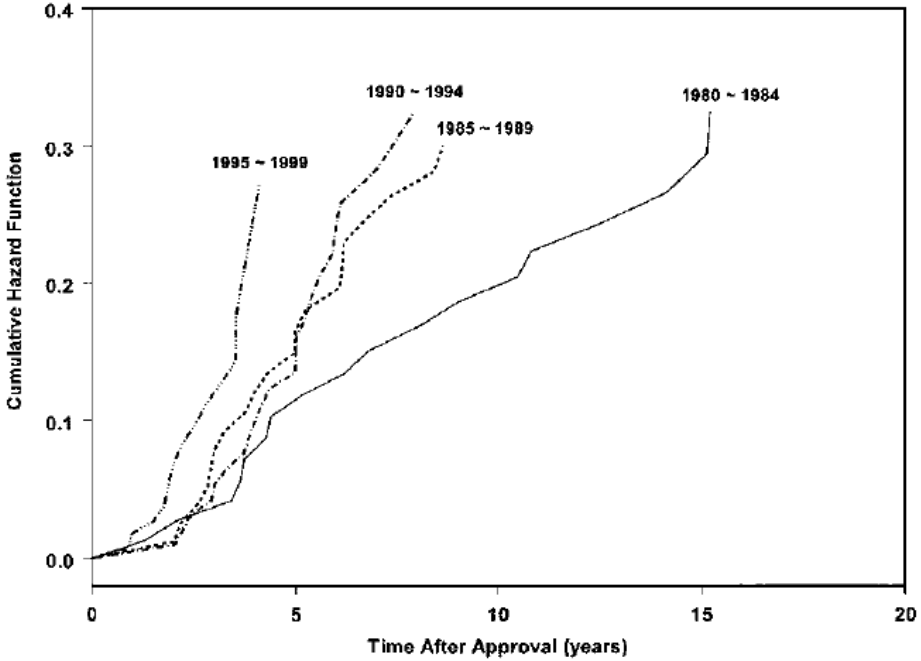


Figure 3. Cumulative hazard function for dosage change over time by epoch. The drugs of the most recent epoch were exposed to a 3.15 times greater risk of undergoing a dosage change (p¼0.003)

Summary conclusion:

- 4 / 13 label changes are **dose amendments** in **special populations** attributed to **renal and/or hepatic impaired** patients
  → need to intensify focus on this group during development?
- 3 / 13 label changes are dose amendments motivated by DDI
  → need to investigate earlier?
- 4 /13 products experiencing a post marketing dose- and schedule related label change triggered by **PhV and safety signals**
  → highlighting importance of close drug monitoring!

To consider:

- Only approved medicinal products have been analysed
- Observation period “only” 5 years (2010-2014 → average 2.5 years marketed)
- Dose and administration changes small fraction of all post-authorisation label changes during the product life-cycle → however high relevance to safe and efficacious use
- Consider / differentiate trigger for label/dose change i.e. MAH / Regulator / other
- Not accounted for are off-label dosage changes occurring in practice
- Stratification by therapeutic area or by product classes (biologicals vs. chemicals)
- Time of label/dose change (close to MAA?)
- Analysis by type of Marketing Authorisation (accelerated, exceptional circumstances, conditional approval)?

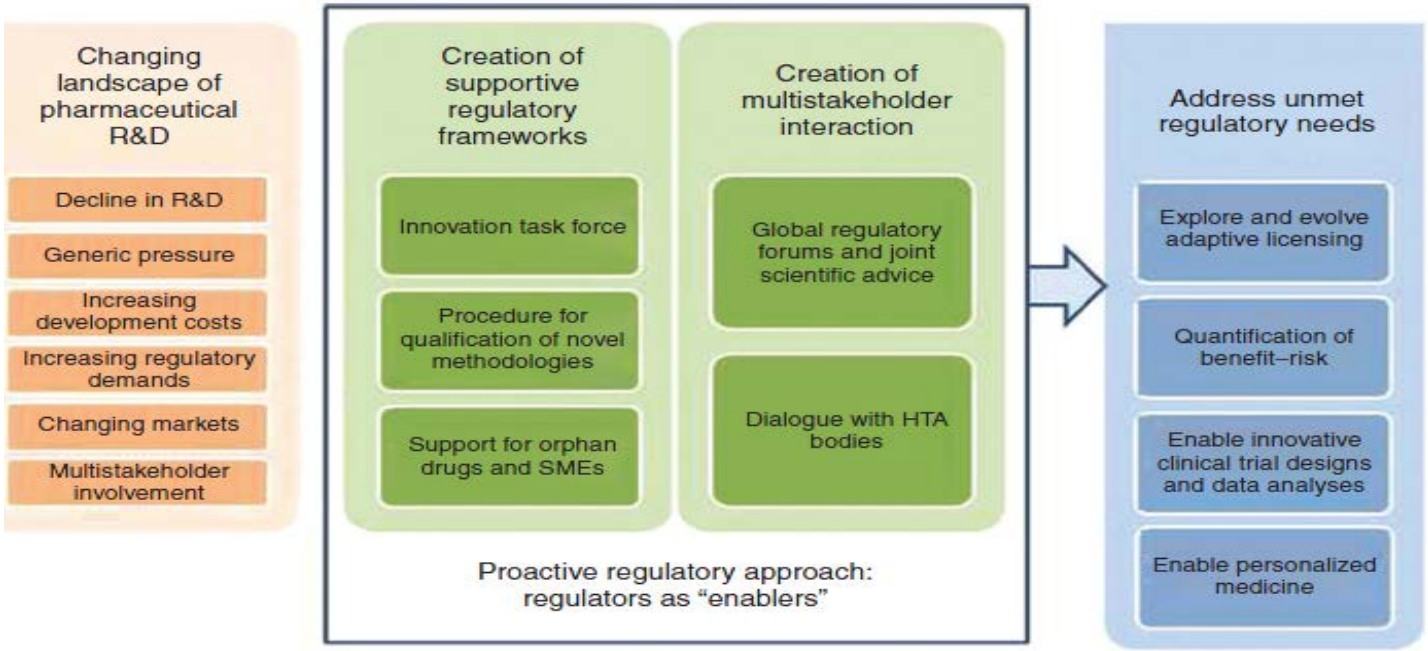
Regulatory tools:

- Conditions and **restrictions** for safe and effective use
- Recommended measures for safe use including Risk Minimisation Measures
- Post-approval **obligation** for PASS / PAES
  - Post-Authorisation Safety Studies (**PASS**)
  - Post-Authorisation Efficacy Studies (**PAES**)
- **Specific Obligations** in the framework of a MA under **exceptional circumstances** or of a **conditional MA**

Tools to further enable dose selection:

- Drug-Drug-Interaction (DDI) studies
- Modelling and Simulation
- Pharmacogenomics
- Population PK in Phase III drug development
- Physiologically-based pharmacokinetic (PBPK) models
- Population PK in post authorisation studies
- PK/PD and PG in safety databases and registries

Gatekeepers and Enablers: How Drug Regulators Respond to a Challenging and Changing Environment by Moving Toward a Proactive Attitude



Received 21 November 2012; accepted 17 January 2013; advance online publication 3 April 2013. doi:10.1038/clpt.2013.14

CLINICAL PHARMACOLOGY & THERAPEUTICS

Thank you for your attention

Comments or questions?

Follow-up questions: falk.ehmann@ema.europa.eu

Acknowledgements:
Francesca Di Giuseppe
Marisa Papaluca
Tomas Salmonson