Compassionate Use Systems in the EU –
How to improve for early access to patients

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1. Early Access Schemes in the Member States – Heterogeneity
2. Experience with National & “Centralised” Compassionate Use Programmes – Case Study
3. Future Opportunities – Priorities for Improvement
1. Early Access Schemes in the Member States (MSs) - Heterogeneity
Early Access Programmes in EU
Implementation is based on applicable national laws

Named Patient Basis (NPP)
(Art. 5 - Directive 2001/83/EC)
Supply of unauthorised medicines in response to unsolicited requests for use by individual patients

Early Access Program
~ Clinical trial with primarily a safety endpoint (incl. extension studies)
Supply to eligible patients at specific sites only

Compassionate Use
Such as Art.83 – Regulation 726/2004 and corresponding programmes in line with local national laws:
Supply of unauthorised medicines to a group of patients with a chronically or seriously debilitating or a life-threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product.

Implementation
Art. 83:
5 times in 11 years for 2 indications; all in virology

Phase I

Phase II
Clinical Trials

Phase III

Licensing

Post-licensing

MA Authorisation
Access/Reimbursement

Regulatory Submission

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Specific Differences in MS Schemes

- **General system**
  - Approval or notification, dossier content, EC approval, timing, applicant, length of validity, protocol, safety reporting

- **Approval**
  - Allowed, required, safety, efficacy

- **Liability**
  - Necessary or not

- **Data collection**
  - IMP or commercial supply, labeling requirements, how long need/allowed to supply

- **Medicine**
  - Companies, hospitals, insurance or patients

- **Import process**
  - Physicians, company, hospital or applicant

- **Payment**
  - NPP, Cohort, Both, direct import, different terminology

EC – Ethics Committee

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2. Experience with National and “Centralised” Compassionate Use Programmes (CUPs) Case Study
BMS- Overall CUP Experience with Daclatasvir

Treatment of Hepatitis C in combination with Sofosbuvir +/- Ribavirin

**Combined & tailored approach:**
- Name Patient Programme (NPP)
- Compassionate Use Treatment Protocol – Cohort, in some EU countries

**Regulatory & Medical Implementation**

- Article 83 dossier: collaboration with EMA excellent in all steps
- Regulatory environment highly varied across MSs
- Not a ‘clinical trial’ but interest to maximise data collection via treatment protocol (incl. efficacy)
- “Real life” safety & efficacy data collected
- Interim data published & presented in international congresses (dissemination of knowledge)
- Opportunity for thousands of patients with no other treatment options and highest medical need
Timeline Overview – Daclatasvir
Art. 83 CHMP Opinion: November 2013

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- **Ph 2 Study AI444040:** DCV+SOF + RBV
  - Unmet medical need
  - EASL: compelling data presented

- **CHMP request art. 83**

- **CHMP Opinion art 83**

- **MAA Accelerated Assessment**

- **DCV MAA validated**

- **CHMP Opinion**

27 June 2014, EMA site:
“EMA recommends approval of Daklinza in chronic hepatitis C. First-in-class medicine to offer new treatment option for patients”. Authorised by European Commission on 22 Aug. 2014

CUP – Compassionate Use Programme
MAA – Marketing Authorisation Application
DCV - Daclatasvir
SOF - Sofosbuvir
RBV - Ribavirin
BMS Experience for Daclatasvir with MSs

🌟 Majority of MSs have national laws on CU:
- Named patient programme (NPP)
- Cohort compassionate use
- both or other mechanisms

🌟 Primary purpose: provide early access to patients in urgent need

🌟 BMS Experience:
- Tailoring implementation:
  - Cohort treatment in line with Art. 83: established in 7 MSs
    Opinion recommendation followed & adapted by MSs (with in some cases broader use)
  - NPP: several countries
- Challenges resulting from mutual lack of experience (company and MSs), since this provision of the EU law is rarely used, e.g:
  - Varied requirements, review of treatment protocol, varied approval timelines, lack of guidance templates (e.g as in ATU French system)
- Excellent interactions with MSs health authorities
CUP Daclatasvir and Real World Data

Some key efficacy data collected from the cohort program

- Situation mimicked the “real world setting” for the sickest patient population, for which clinical studies were not available in EU.
- Collection & reporting of safety data followed national & EU laws: varied.
- Patient population included patients with common co-morbidities - highest medical need. Welcomed by treating physicians.

Different mechanisms for collection of efficacy data needed to be implemented

- Further alignment across MSs on principles of implementation of CUP and collection of data (efficacy and safety) would be very beneficial given high interest by multiple stakeholders, including patients.
Patients’ Perspective

According to feedback heard:

• Expect to receive proper education/information via patient groups
• Expect to obtain equal chance across MSs for early access
• Need to decrease administrative burden and procedure time for early access
• Expect different approach of health authorities to risk-taking
• Very positive feedback on DCV Art. 83 implementation

“There is nothing worse for a patient, from a psychological and human standpoint, than being severely ill or even dying from a disease, when experimental treatments are out there, pending final evaluation.”

/BETTINA RYLL, Founder Melanoma Patient Network Europe DIA 2015, Paris/
3. Future Opportunities
Priorities for Improvement
Priorities for Improvements (1) Use/ Request of Art. 83

Problem Statement:
✶ It seems that very few MSs have requested Art. 83 opinions (according to available info):
   ✶ Ireland (1)
   ✶ Sweden (3)
   ✶ Finland (1)
✶ Lack of transparency on whether MSs notify EMA of “compassionate use” (Art. 83 (3))

Proposals:
✶ Research (survey/ study) needed on
   ✶ Overview on
      ✶ ongoing CU Programs in MSs
      ✶ functioning of reporting mechanisms to EMA (Art. 83(3))
   ✶ Root cause analysis why MSs are not requesting an Article 83 opinion
   ✶ Root cause why only few MSs established the framework to support cohort CUPs
Priorities for Improvements (2)

Article 83 Process

Problem Statements:

* **Request**: Currently only MS can request Art. 83 opinion

* **Guidelines**: Lacking considerations of real world/ efficacy data collection and clarification on timelines

Proposals:

* **Request**:
  
  * Consider how patient groups and industry can trigger requests (via MSs)
  
  * PRIME designation/ use of Adaptive Pathways could trigger (Co-) rapporteur MS to request Article 83 opinion after consultation with applicant (optional)

  → in case of unmet medical need and availability of adequate data

* **Guidelines**:

  * CUP to allow for critical real world data gathering

  * Guidelines for collection and more structured assessment of this first real world data could be developed for public benefit

  * Further clarification on timelines to be detailed and published by EMA/CHMP
Problem Statement:

- Current different approaches by Member States on compassionate use lead to
  - disparities in access to new innovative medicines by patients
  - high administrative efforts by all stakeholders

Proposals:

- Establishment of a framework for cohort CUPs across Member States is critical to allow full operation of Article 83
- Better alignment required between different national compassionate use systems in particular with respect to
  - scientific criteria
  - procedures (timelines)
  - standardised documents (e.g. CUP protocol templates)
Priorities for Improvements (4)
Integration of **Patient Perspectives**

**Problem Statements:**
- Disparities in patient access to innovative medicines across MSs
- Limited/ lack of patient involvement into set up of programmes/ current system

**Proposals:**
- Education/ info of patients on early access programs via patient groups
- Integration of patient perspectives into set-up of compassionate use programmes
- IMI projects may explore/identify opportunities and methodology for better patient involvement
Summary - Improve Current System

- **Application**: MSs to make more use of Art 83 and leverage the CHMP expertise.

- **Request**: Possibilities for patient groups and industry to request Art. 83 via MSs. (Co-) Rapporteur identified early in PRIME to allow for early request of Art. 83 opinions after consultation with applicant (optional).

- **Real world data**: Utilise CUPs to allow for critical real world data gathering and establish guidelines for collection and more structured assessment of this first real world data.

- **Alignment**: MSs to drive for stronger alignment between different national compassionate use systems in particular with respect to scientific criteria, procedures, standardised documents (e.g. CUP protocol templates).

- **IMI projects** may explore/identify opportunities and methodology to enhance patient perspectives into setup of CUPs and improve current systems.

- **National framework for cohort CUPs**: Systematic national implementation of a framework for cohort CUPs in all MSs to allow operation of Article 83 across all MSs.