BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Possible Consequences of DSM-V or ICD-11 for Licensing of Psychopharmacological Products

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Disclaimer

- Personal views are presented
- Expressions cannot be regarded as official positions of EMA or BfArM
- Based on experience from applications and scientific advice procedures

Medicinal Products are approved for ...

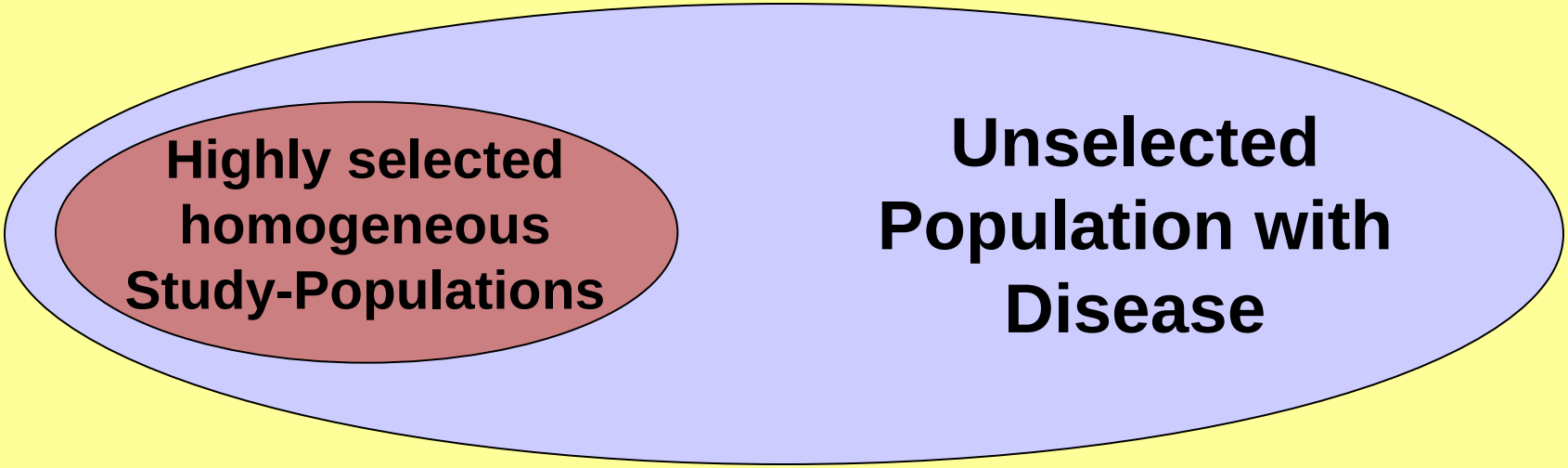
- **Distinct disease entities**
- **With positive Benefit-Risk-Assessment based on data for**
  - **Efficacy**
  - **Safety**
  - **Quality**

Current Diagnostic Systems: Categorial DSM-IV-TR / ICD-10

- Bridging between
  - Science and basic research
  - Health care professionals
  - **Applicable to the Community**

- Allows **development of medicinal products** in accordance to
  - Diagnostic criteria and etiologic assumptions
  - Standardized clinical decision making
  - Experience with effect sizes, responder rates ...
  - Choice of different treatment options

Study Populations in Clinical Trials



- Specificity >>Sensitivity
- Generalisability ?
- Labeling ?

Guidelines for Drug Development in Psychiatric Conditions

- Schizophrenia (CPMP/EWP/559/95 + Add.)
- Bipolar Disorder (CPMP/EWP/567/98)
- Depression (CPMP/EWP/518/97 Rev. 1)
- Panic Disorder (CHMP/EWP/4280/02)
- Generalised Anxiety Disorder (CPMP/EWP/4284/02)
- Obsessive Compulsive Disorder (CHMP/EWP/4279/02)
- Social Anxiety (CHMP/EWP/3635/03)
- Post-Traumatic Stress Disorder (PTSD) (CHMP/EWP/358650/06)
- Alzheimer‘s Disease (CPMP/EWP/553/95 Rev.1)
- Insomnia (CHMP/EWP/310566/07)
- Attention Deficit Hyperactivity Disorder (ADHD) (CHMP/EWP/431734/08)
- Smoking and nicotine dependence (CHMP/EWP/369963/05)
- Alcohol dependence
- PMDD

http://www.ema.europa.eu

„dimensional approach“

- **Pro‘s**
  - Avoidance of preassumptions
    - e.g. causal hypothesis
  - Increased validity of diagnostic criteria
  - Multidimensional holistic assessment of patients
    - Severity, functional level, patient related quality of life
- **Con‘s**
  - Loss of comparability to traditional criteria and decision-making
  - Heterogeneous patient populations
  - New complex assessment tools necessary
  - Increased polypharmacy

New Diagnostic Criteria for Alzheimer's Disease
Dubois B, Feldman HH, Jucova C et al. 2007

- **Core diagnostic Criterion:**
  Early and significant episodic memory impairment
- **At least one supportive criterion of**
  - **MTL atrophy shown with MRI**
  - **Abnormal CSF (amyloid-ß, tau, phospho-tau)**
  - **Specific pattern shown with PET**
  - **Proven DAT mutation**
- **Validation studies promising !!!**

NfG Major Depressive Disorder (1)

- **Introduction**
  - Description of newer research results
  - Placebo issue
  - Critique from evidenced based medicine
    - HTA assessment
  - Experience with children and young adults
  - Differential diagnosis
- **Scope**:
    - Antidepressants
    - Antipsychotics
    - Augmentation

NfG Major Depressive Disorder (2)

- **Confirmatory Studies**
  - New assessment tools / endpoints
  - Responder criteria
  - Patient related outcomes (for HTA)
  - Choice of control group (placebo + active control)
  - Long-term: Randomized Withdrawal still best choice?
  - Monotherapy vs. Add-on
- **Special Populations:**
  - Children and adolescence
  - Elderly
  - **Comorbid conditions**
  - **Partial response/treatment resistance**

Treatment Resistance/Partial Response

- High variability in definition of TRD
- Commonly used in practice:
  - Two products of
    - different pharmacological classes (?)
    - long enough (?)
    - high enough (?)
- Switch Approach not unanimously supported by STAR*D
- Standardized, operational criteria needed:
  - TRD / Response / Remission
- Absence of prospective data for validation of criteria

Proposed/Used Definitions (1)

e.g. Trivedi et al., Int Clin Psychopharmacol 24, 133-138 (2009)

- **Remission:**

  ≥ 50 % reduction in MADRS + Score in MADRS ≤ 10

- **Response without Remission**

  ≥ 50 % reduction in MADRS + Score in MADRS ≥ 10

- **Non-Response:**

  ≤ 50 % reduction in MADRS + Score in MADRS ≥ 10

Staging Methods TRD

- Thase and Rush Staging method
- European Staging method for TRD
- MGH Staging method for TRD
- Maudsley Staging method

Unipolar vs. Bipolar

- How much can we bridge ?
- Bipolar I or Bipolar II ?
- Lessons learned from Quetiapine ?
- Comorbidity / Subtypes ?
  - Stratification
  - Assessment Tools

Note for Guidance on PMDD (severe forms)

- target population (diagnostic criteria, inclusion and exclusion criteria)
- study duration (short-term efficacy, maintenance of effect)
- choice of endpoints (affective symptoms, functional relevance)
- **validity of diagnostic criteria, measurement tools (self-ratings, observer-ratings)**
- long-term safety (including effects on endocrinium)
- special populations (adolescence)
- presence and acceptance of co-morbidity (with regard to mechanism of action, e.g. hormonal products or antidepressants).

Schizophrenia: „*Cognition Claim*“

- **Population:**
  - Distinct „Cognitive Impairment“ in patients in stable phase of disease
  - *Treatment duration < 5 years*
  - Generalizable to community
- **Domain:**
  - *Spectrum of domains of cognitive symptoms as a single target clearly preferred (MATRICS; CANTAB)*
  - Not enough data to focus on specific subtypes/targets
- **Co-Primary Endpoint:**
  - *Functional outcome mandatory or not?*

Reluctance by Regulatory Bodies for a Radical Switch to a „Dimensional Approach“

- **Basic research data are still limited**
- **Increased heterogeneity of study populations**
- **Increased polypharmacy approaches**
- **New assessment tools necessary**
  - Multiaxial dimensions
- **More complex study designs**
  - Large study populations
  - Monotherapy vs. Add-on- vs. Combinations
  - Co-primary endpoints
- **Loss of comparability to earlier approval decisions**

Preferred Option by EU Regulatory Bodies

- **Keep the categorical principle**
- **Improved by addition of dimensional sub-differentiation**
- **Expected Advantages:**
  - Better comparability to earlier approval decisions
  - Refinement of diagnostic entities
  - Better characterization of sub-categories
  - Multiaxial assessments (co-primary endpoints)
  - Improved concordance between DSM and ICD
  - Improved comparability of data from clinical trials from different regions of the world

„Early and Ongoing Dialogue“

- **National/European:**
  - **Contact with Learned Societies**
  - **CNS / Efficacy Working Group**
  - **Scientific Advice Working Group**
  - **Scientific Advisory Groups (SAG‘s)**
  - **Ad Hoc Expert Groups**

- **Dialogue between EMA-FDA**