Federal Institute
for Drugs
and Medical Devices

Should The RWD for relapse prevention studies in mood disorders be updated: *EU Regulatory Aspects*

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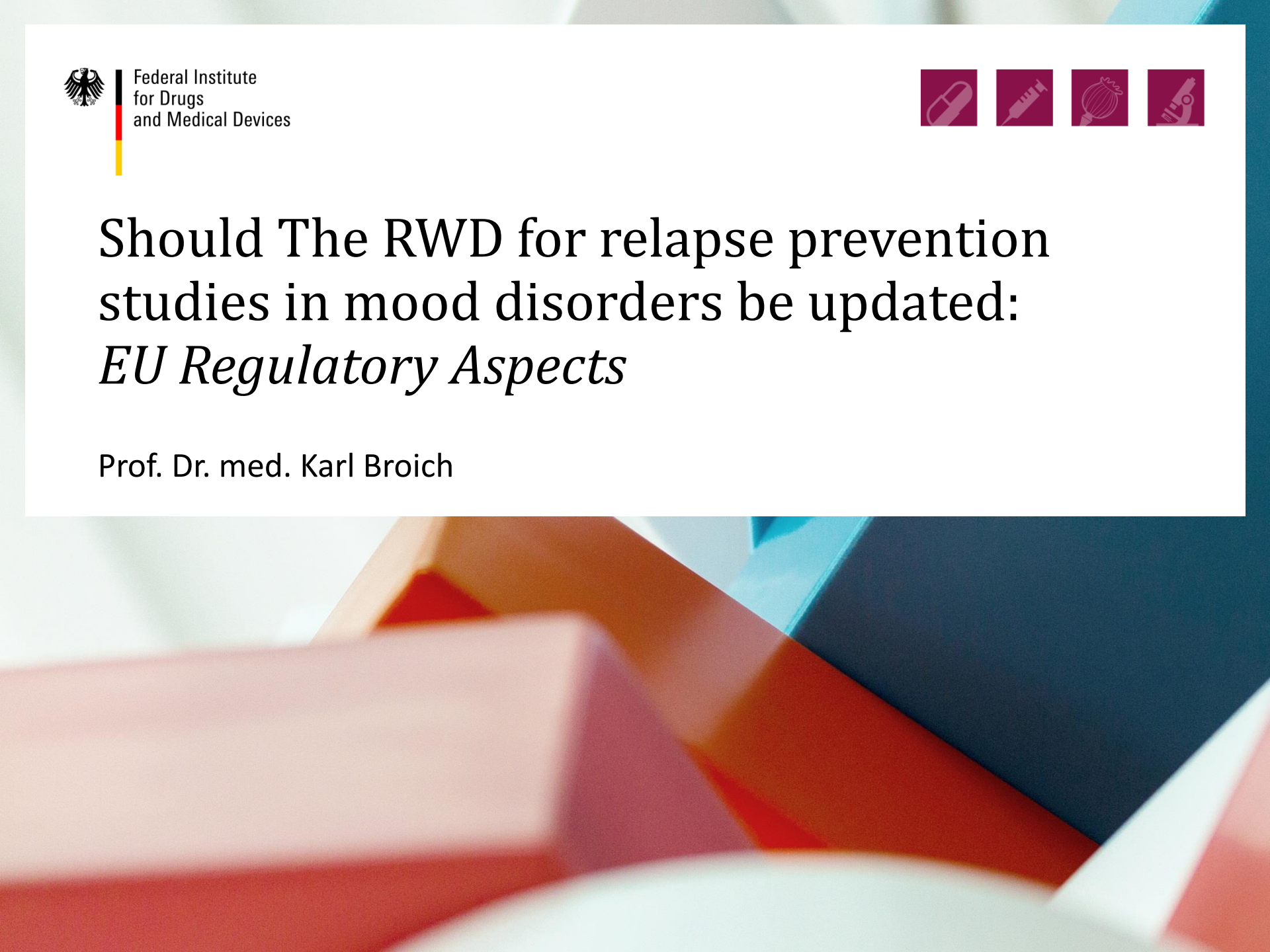

Agenda

- Current status of guidance documents
- Relapse and Recurrence
- Need for longterm maintenance data
  - Schizophrenia
  - MDD
  - Bipolar
  - Anxiety Disorders
- Recent proposals in scientific advice or today in presentations

Affective Disorders: EU Regulatory Practice

- Acute Episodes with possibility of relapse within current episode
- Chronic condition with recurrence of new episodes

- Treatment of MDD
  - At least two positive short-term trials
    - Primary endpoint: Change in established rating scale
    - Responder Rates for clinical relevance
  - At least one long-term study to show maintenance of effect
    - Randomized withdrawal preferred design
  - Safety short- and long-term

Advantages of Randomized Withdrawal Design

- Randomized comparison of long-term treatment in selected patients (responders) to establish maintenance
  - Lower failure rate compared to acute trials

- Usually better to interpret than long-term parallel group studies coming from acute episode (prolonging the acute treatment randomization)

- Key: clear predefined criteria, which are clinically meaningful for
  - Response Responders, Remitters
  - Stabilisation 8 to 12 weeks OK
  - Relapse: Sensitivity,

- Used not only in CNS, but also in gastrointestinal and cardiovascular situations

Discussion Points (1)

- Inclusion: Patients with higher relapse rate
- Sensitive relapse criteria are essential
- Time to relapse vs. %wellbeing / meeting recurrence criteria : probably more statistical power for analysis with time to ...
    - Change of treatment might be acceptable
        - New, some administrative burden
        - More data on internal, external validity needed
    - Avoid clinical judgement / all cause discontinuations
- PRO as secondary outcome welcomed, not as primary

Discussion Points (2)

- Operational criteria for surrogate outcomes short of full episode criteria are required
    - STEP-BD concept of “Roughening” might be a reasonable surrogate for relapse
- Training of raters is key
    - Rater reliability in some trials questionable
    - Clear operationalized relapse criteria needed
    - Computer assisted systems might increase quality/reliability of data
- Alternative design with long term parallel comparisons
    - Have problems as well, e.g. differentiell drop outs as seen in vilazodon trial with in favor of non-active treatment

Contact

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