



CNS PERSPECTIVE TO PROMOTING EFFECTIVE DRUG DEVELOPMENT PROGRAMS

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Where are we today with CNS?

★ High unmet need

More than 700 million people live with psychiatric and neurological disorders globally¹ and expected to double between 2010-2030²

- ★ Brain diseases are the greatest contributor to the global burden of disease, comparable to the impact of cardiovascular disease

★ Highly challenging therapeutic area for drug development

Evolving science, complex diseases, limited understanding of underlying pathologies, difficulty identifying appropriate endpoints (e.g. progression biomarkers), high attrition rates and access hurdles

In our presentation today would like to recognize the Agency's efforts so far, highlight key priority issues for CNS development and propose specific actions

¹WHO: https://www.who.int/mental_health/en/

²Harvard School of Public Health (2011), "The Global Economic Burden of Non-communicable Diseases" (Data on NCD output losses)

Where OND could provide additional guidance or prioritize additional scientific discussion in the near-term to improve clarity and encourage effective drug development?

Need for multistakeholder scientific discussion **specifically for CNS** to address:

- ★ **Outcome** measures for primary and secondary study endpoints with specific focus on:
 - ★ Integrated endpoint approaches in absence of reliable progression biomarkers¹
 - ★ Development of novel ways for data collection and validated outcome measures / scales taking clinical meaningfulness and patient perspective into account
- ★ **Establishing frameworks** for collecting real world evidence from patients in routine care / long term value demonstration and integration of new technologies (e.g. digital tools)
- ★ **Alignment on unmet need** for alternative treatments with better safety and tolerability profiles (e.g. in psychiatry)
- ★ Development of guidances for **combination drug development taking therapeutic area specific** challenges into account

¹Integrated endpoint approaches refer to where combined data on several mutually supportive outcome measures can be interpreted as supporting efficacy as suggested for example in the draft FDA AD guidance (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industry>)

Specific suggestions for guidance or policy development that OND could undertake to facilitate drug development for diseases not currently amenable to targeted therapies

We believe **innovative regulatory approaches** similar to those used in oncology should be **applied to their full potential to medicines developed for dementia and cognitive impairment**, such as real-time review, trans-diagnostic approaches, and optimizing use of BTD coupled with advancement in innovative trial designs

Stakeholders' views regarding the advantages and disadvantages of extending novel trial designs (such as master protocols) to additional therapeutic areas, and what guidance development would be most useful

Novel trial designs broadly applicable across therapeutic areas and an important opportunity for CNS drug development to support:

- ★ Trans-diagnostic drug development using e.g. master protocols based on:
 - ★ Symptoms across diagnostic categories - e.g. psychosis, cognitive impairment
 - ★ Common pathological hallmarks in neurological disorders - e.g. tauopathies
 - Increasing relevance beyond oncology as discussed by Woodcock and Lavange (2017)¹
- ★ Optimizing early development phase to reduce time to decision making on potential failure vs real innovation, e.g. adaptive, Bayesian designs and extrapolation across populations (e.g. pediatrics)

¹Woodcock J., LaVange L.M. Master protocols to study multiple therapies, multiple diseases, or both. *N. Engl. J. Med.* 2017;377(1):62–70

Specific recommendations for topics where further clarity of the Agency's current thinking may be warranted (where OND review divisions are implementing guidances in different ways)

Call for **consistency across review divisions in supporting innovation** through facilitated pathways and how to adjust them to different therapeutic areas

Example: facilitated regulatory pathway designations in CNS

Out of all NDAs approved by FDA between 2012-2017, only **10%** received **Breakthrough Therapy designation** in **psychiatry** and **12%** in **neurology**, compared to **39%** in **oncology**¹

Similarly, only **20%** of **psychiatry** NDAs received **priority review**, compared to **41%** in **neurology** and **73%** in **oncology**¹



Between 2000-2017 the approval phase time for CNS drugs was 38% longer than for non-CNS²

¹Source: Cortellis database, includes NDAs approved until October 2017

²Tufts Center for the Study of Drug Development (2018), "Tufts CSDD IMPACT Report: CNS drugs take 20% longer to develop and to approve vs. non-CNS drugs"

How OND can promote effective drug development programs where applying innovative approaches could otherwise bring additional uncertainty to drug development?

Proposal:

- **Offering more opportunities to interact** and engage early with sponsors on concepts that span across drug development projects (e.g. via scientific meetings allowing discussing of broader challenges)
- **Apply successful FDA initiatives across review divisions such as multi-stakeholder workshops** (e.g. Friends of Cancer Research & FDA workshops), outcome of pilots (RTOR, project Orbis) etc.
- Timely development of Guidances, e.g. on innovative approaches to trial design applied across review divisions

The way forward

- ★ **We call for regulatory focus on 1) key CNS regulatory science discussions and 2) innovative regulatory pathways to be adjusted to CNS and supported by OND**

...in order to address the urgent unmet medical needs of our society

We look forward to working on this with FDA and relevant key stakeholders together!