Regulatory Perspective on RDoC-based Study Inclusion Criteria and Outcome Measures

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Disclaimer

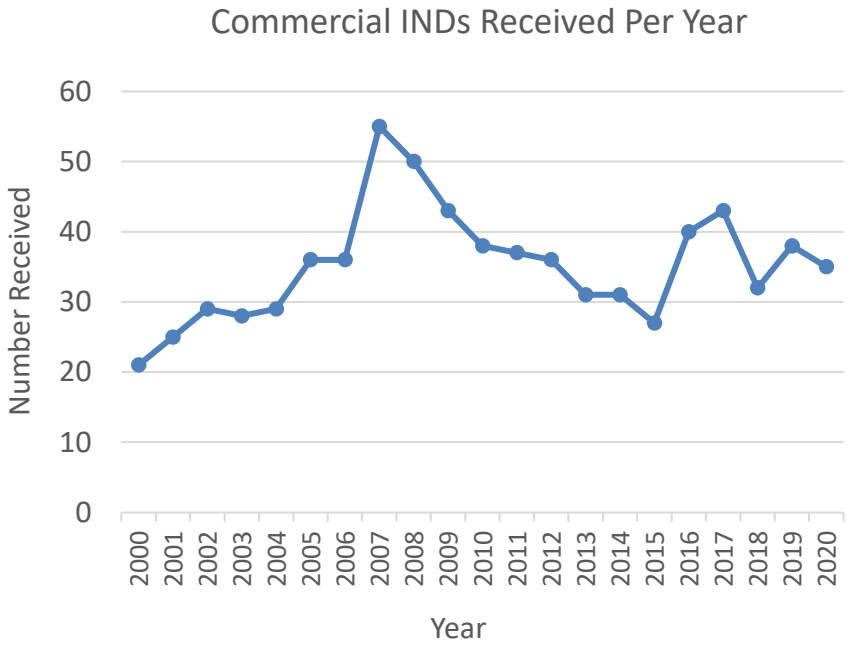
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

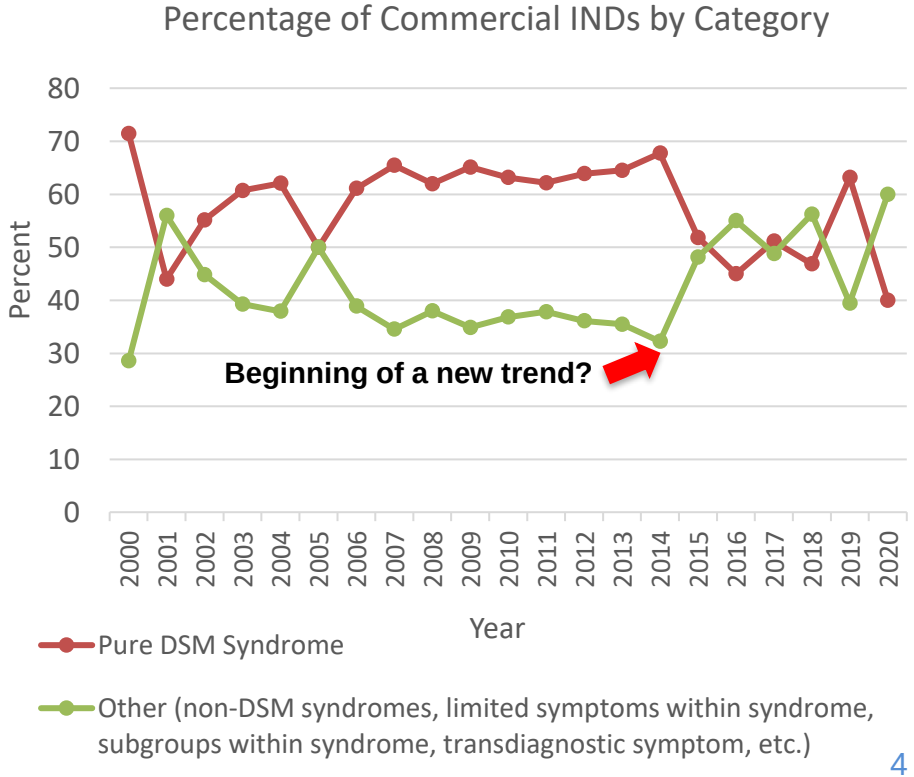
Potential roles for RDoC-based constructs suggested by previous talks

- Early phase tool for proof of concept/mechanism (Krystal)
- Target symptom within a recognized standard diagnostic entity (Salvadore, Kas)
- Enrichment factor in targeting treatment for a recognized standard diagnostic entity (Salvadore, Tamminga)
- Transdiagnostic treatment target (Kas, Tamminga, Sharma)

Current Landscape

Commercial IND submissions to DP: 2000-2020





Unpublished internal analysis

Most drugs approved by the Division of Psychiatry since 2000 use DSM-based indications

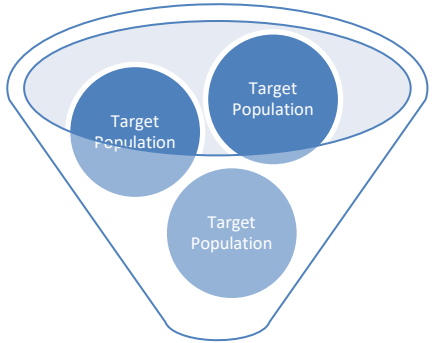
Exceptions: a small number of labeled indications specify either a target symptom/sub-syndrome of a DSM syndrome or a symptom without a specified disorder.

Examples:

Drug	Indication
Ziprasidone (Geodon)	Acute treatment of agitation in schizophrenia
Aripiprazole (Abilify)	Irritability associated with autistic disorder
Olanzapine/Fluoxetine (Symbyax)	Acute depressive episodes in bipolar I disorder
Eszopiclone (Lunesta)	Insomnia

The Big Picture

From Drug Development to Clinical Use



RDoC-based elements

Inclusion + Exclusion Criteria

Phase 3 Study Population

Treatment

Outcome Measure(s): Endpoint(s)

Regulatory review and approval

Product Label

Including:

- Indications and Usage
- Clinical Studies

RDoC framework-based inclusion criteria and endpoints → (most likely) novel indication

Indications

21 CFR 201.57(c)(2) (Labeling Requirements for Prescription Drugs and/or Insulin):

1 Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

Indications should be clearly defined and well-established in the scientific community. A clear understanding of the underlying neurobiology/pathophysiology will be helpful to support validity.

Study Population

Reliable identification of target population using RDoC principles

- Similarity in end clinical presentation does not necessarily mean underlying pathophysiology is the same. Biomarkers may be valuable in identifying population.
- Transdiagnostic populations may manifest target RDoC-based construct differently.
- If drug is approved for a novel transdiagnostic indication, label will need to describe how providers can reliably identify target patient population in the clinic.

Transdiagnostic study population heterogeneity resulting from RDoC-based selection

- Transdiagnostic sub-populations with common RDoC dimension may have different background medications, medical comorbidities, or other neuropathophysiology, potentially interacting with treatment effects.
- Potential for different risk/benefit balance across transdiagnostic sub-populations

Outcome Measures

Defining and measuring the construct

- Will RDoC-based outcome measure behave similarly across transdiagnostic populations?
  - If not, could impact performance of measures across transdiagnostic sample as well as impact assessment time frame

Demonstrating clinical meaningfulness of change

- Does change on RDoC-based outcome measure improve how patients feel, function, or survive?
- Consider COA/biomarker qualification programs

Study Design

- Naturalistic studies may be particularly valuable for validating RDoC construct phenomenology and time course and for collecting preliminary data on outcome measure performance.

- Phase 2 development will be important for validating outcome measure (i.e., sensitivity to change).

- Biomarkers (e.g., diagnostic, predictive, pharmacodynamic/response) may be useful to help characterize the patient population, the target transdiagnostic RDoC construct, and the drug response.

- Although studies would unlikely be powered to demonstrate efficacy in each transdiagnostic subpopulation, it would be important to enroll enough patients with different syndromic diagnoses to support generalizability and characterize benefit/risk for the target US patient population.

Conclusions

- Limited regulatory precedents→ early discussions with the Division
- Novel transdiagnostic indications → symptom(s) clearly defined and well-established; mechanistic understanding helpful
- Generalizability of benefit and risk

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