Secondary Pharmacology: Analysis and Perspectives for the Future

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Outline

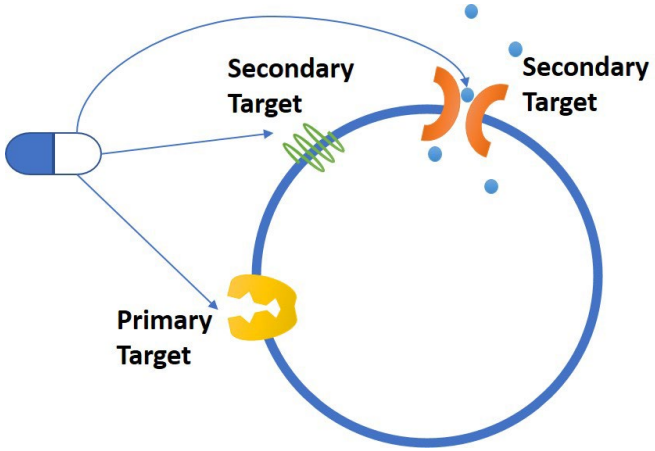
- Background and Introduction to Regulatory Assessment of Secondary Pharmacology
- Secondary Pharmacology Research
- Other Uses of Secondary Pharmacology at FDA

Background

Secondary Pharmacology (Secondary Pharmacodynamics)

Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target

(International Council of Harmonisation Guidance S7A)



Background

- Compounds are screened against many targets, including receptors, enzymes, ion channels, and transporters that are not the primary mode of action
- Screens can consist of binding and/or functional assays
- These screens can help identify potential safety issues early in drug development by defining:
  - The pharmacological profile of a compound
  - A compound's affinity and mode of action at targets of interest

Regulatory Assessment of Secondary Pharmacology

- Assessment is made in conjunction with data about clinically relevant concentrations and drug exposures to determine risk
- Limitations of secondary pharmacology, such as selected targets/extent of testing and format of assays, also taken into account
- Based on this assessment and other submitted data, recommendations are made for nonclinical and clinical studies to evaluate and reduce risk

Papoian et al. Nat Rev Drug Discov, 2015.

Research Methods

- R script identified INDs containing at least one file the Secondary Pharmacodynamics folder in FDA's Electronic Document Room
- All PDFs were manually evaluated to identify in vitro data for off-target activity

Research Methods

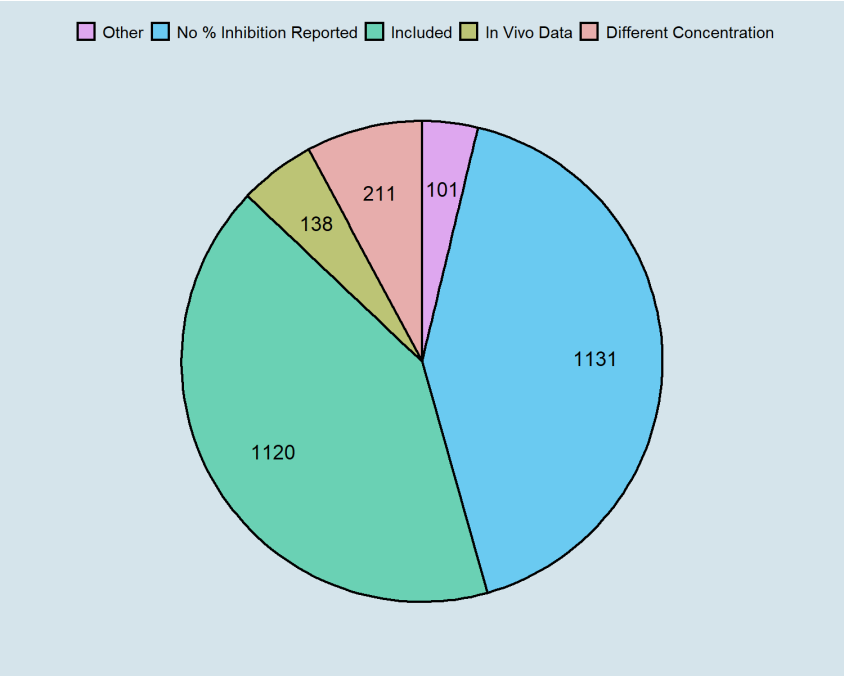
- Inclusion criteria:
  - Small molecule compound identifiable in the Investigational Brochure
  - Report as the percent inhibition of control specific binding
  - Tested at 10 µM

Research Methods

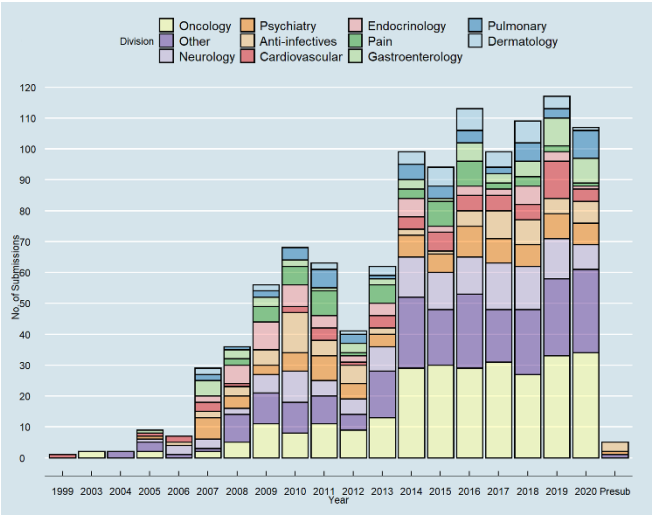
- Additional data was harvested from:
  - Global Substance Registration System (GSRS)
    - Compound name, sponsor, status, submission year, indication
  - DailyMed Drug Labels
    - Safety information for approved drugs

Results

- 2,701 INDs had at least one file in the Secondary Pharmacodynamics folder
- 1,120 INDs contained at least one file of binding assay data that met the inclusion criteria
- Omissions primarily occurred because there was either no binding information or the data was reported in a format other than percent inhibition



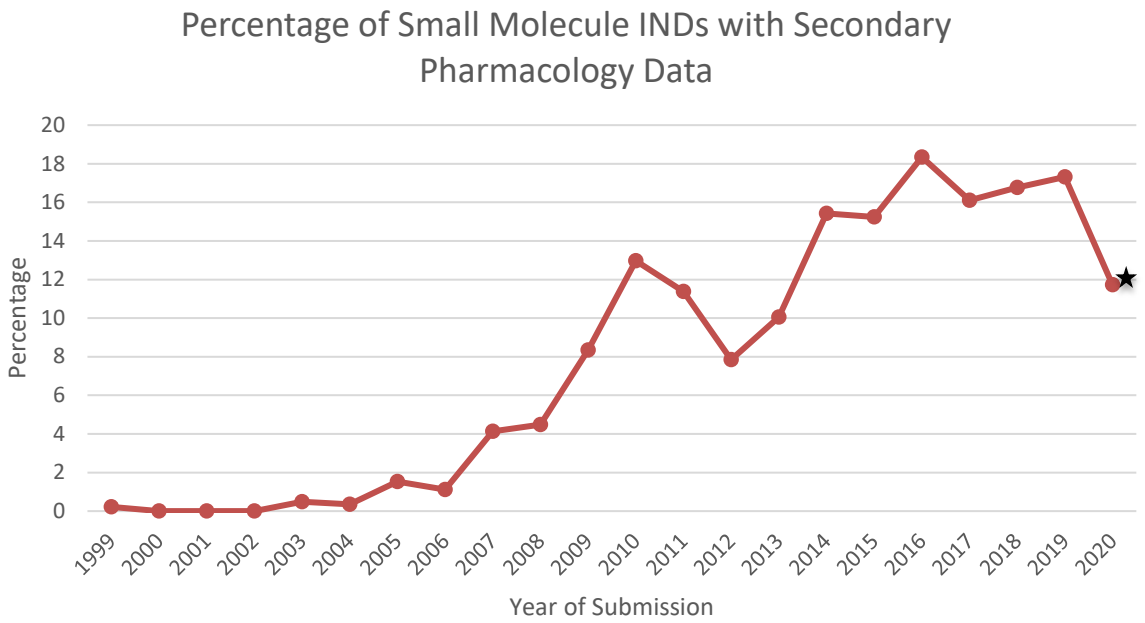
Results



- Submissions from 480 sponsors from 1999 to 2020 were included
- The top three most common therapeutic areas were oncology (276 unique INDs), neurology (130), and psychiatry (92)
- 60.5% of the IND applications were active
- 52 submissions (4.6%) were associated with an approved New Drug Application

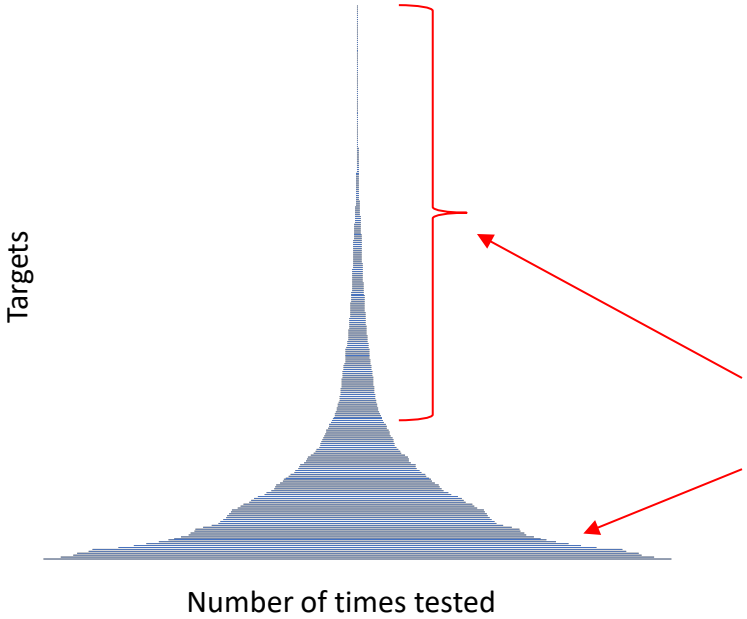
Results

The percentage of INDs containing secondary pharmacology has increased in recent years



★ Artificially low; count of assays through Oct 2020, count of INDs through Dec 2020

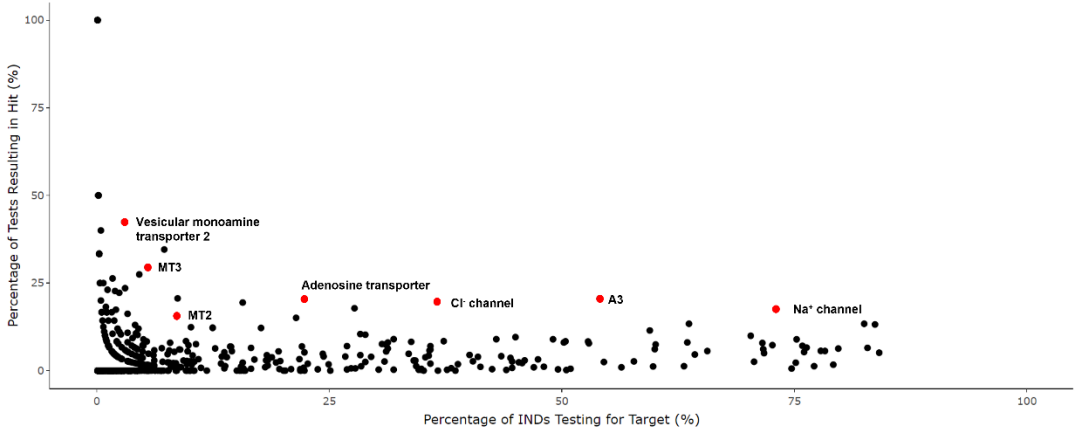
Results



- 747 distinct targets
- 1 to 322 targets per report
  - Mean: 74 (Median: 69)
- 1 to 938 reports per target
  - Mean: 110 (Median: 23)
- Most targets tested only a few times
- A few targets tested very frequently (i.e. serotonin and opioid receptors)

Results

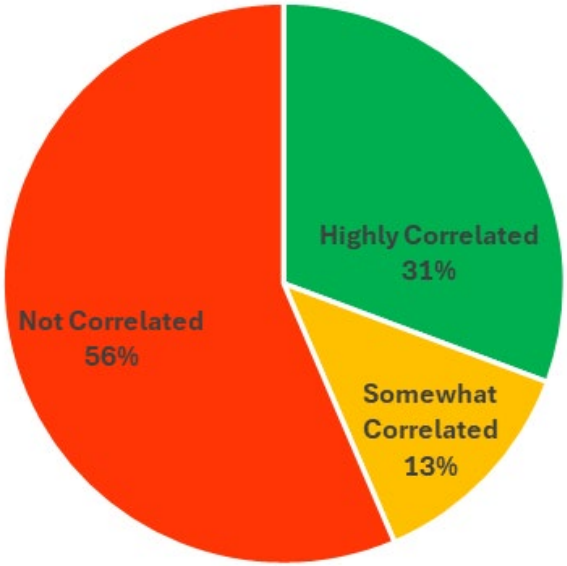
- Targets with low testing rate often had a high hit rate, and vice versa
  - Some notable exceptions include VMAT2, melatonin receptors, Na^+ and Cl^- channels, and adenosine targets
- Enzymes were more associated with low testing rate and high hit rate



Results

- No correlation between testing/hit rates and:
  - Number of labeled safety events
  - Approval of an associated NDA
  - Status (active or inactive)

Additional Research



- Secondary pharmacology has previously been used to hypothesize potential safety concerns
- Our goal: correlate secondary pharmacology with nonclinical study results
  - Evaluated 67 target-nonclinical organ flag pairs to determine if a target hit on secondary pharmacology was associated with positive nonclinical organ toxicity findings
  - Filtered by target-organ pairs that have a known association and pairs that had both positive and negative organ findings
- Findings: secondary pharmacology may be able to predict some nonclinical outcomes

Limitations

- This study only included applications submitted to FDA
- Some data may be outside of the Secondary Pharmacodynamics folder

Future Directions

- Addressing challenges: Lack of harmonization in terminology and file structure
  - Target synonyms and multiple naming conventions
  - Code name in assay results needed to be confirmed in other submission documents
  - Table structure can differ significantly, making automated extraction difficult
- Expanding correlation analysis
  - Incorporate clinically relevant concentrations
  - Evaluate additional nonclinical and clinical datasets
  - Correlation to pediatric developmental safety: more to come!

Other Uses of Secondary Pharmacology at FDA

- Secondary pharmacology results may be re-evaluated during the NDA or postmarketing stages to identify mechanisms for unexplained adverse events

- In silico target predictions and analysis can additionally assist with identifying mechanisms associated with adverse events
  - CLARITY: A predictive analytics platform consisting of six integrated models that make secondary pharmacology activity predictions based on drug structure and publicly-known primary target activity
  - Secondary Intelligence: Software that facilitates informed, evidence-based decisions around secondary pharmacology screening panels

- These methods are frequently used in conjunction with other analyses, such as structural similarity and pathway analysis

Conclusions

- Secondary pharmacology has multiple uses at FDA, including utility in both regulatory review and research
- Analysis of in vitro, in vivo, and predicted secondary pharmacology can generate mechanistic hypotheses and inform regulatory decision making
- Further research is needed to determine the value of secondary pharmacology in predicting nonclinical and clinical outcomes

Acknowledgements

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