Reducing Attrition Risk: Evolution of an *in silico* "Compound Safety Evaluator"

Kevin Dack

kevin.dack@pfizer.com

Sandwich Laboratories

Pfizer Worldwide R&D

Designing Safer Medicines in Discovery.

SCI, London

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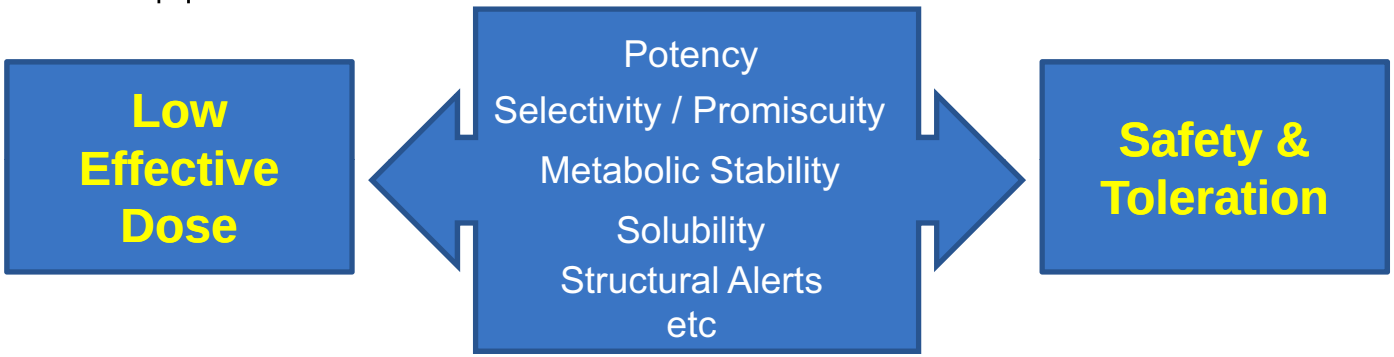
Introduction

- Safety is a major cause of attrition
  - Low therapeutic index (not potent enough, poor PK, high peak:trough, promisicuous.....)
  - High Dose (idiosyncratic tox, active & reactive metabolites & metabolic burden...)
  - Manipulating target/pathway is unsafe (out of scope for today)

- Need to 'flag' earlier those compounds/series at greater risk of safety attrition.
  - Focus resource on leads/series/targets with better chemical equity
  - Save $$ and animals



Outline of Presentation

- Introduction to Compound Safety Prediction Group
- Compound Safety Evaluator v1.0
  - Criteria used & basis for scoring
  - Retrospective analysis of pre-clinical tox studies
  - Retrospective analysis of some Pfizer candidates
- Drugs on the Market
  - Impact of CSE Score and Dose size
- Compound Safety Evaluator v2.0
  - Improving predictions
- CSE vs Dose: getting better dose predictions.

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Compound Safety Prediction Group

- Compound Safety Prediction Group at Pfizer
  - Based in Groton, USA & led by Bill Pennie
- Building a **research program** to characterize underlying mechanisms of toxicity.
- **Building predictive assays** *(in silico* or *in vitro)* for these mechanisms.
- Assembling these assays into a **validated, predictive panel** for compound testing.
- Reporting results to project teams to help define “safer” chemical space and assist teams in series & candidate selection decisions.
- Developed Compound Safety Evaluator (CSEv1.0) to generate a ‘Safety Score’ for compounds

Compound Safety Evaluator: CSEv1.0

- Goal is to help project team **define safer chemical space** by providing an integrated report of the safety ‘profiling’of a compound or series

- Decisions will **always** lie within project teams
  - e.g. an acceptable risk in oncology is different to pain management

Compound Safety Evaluator: CSEv1.0

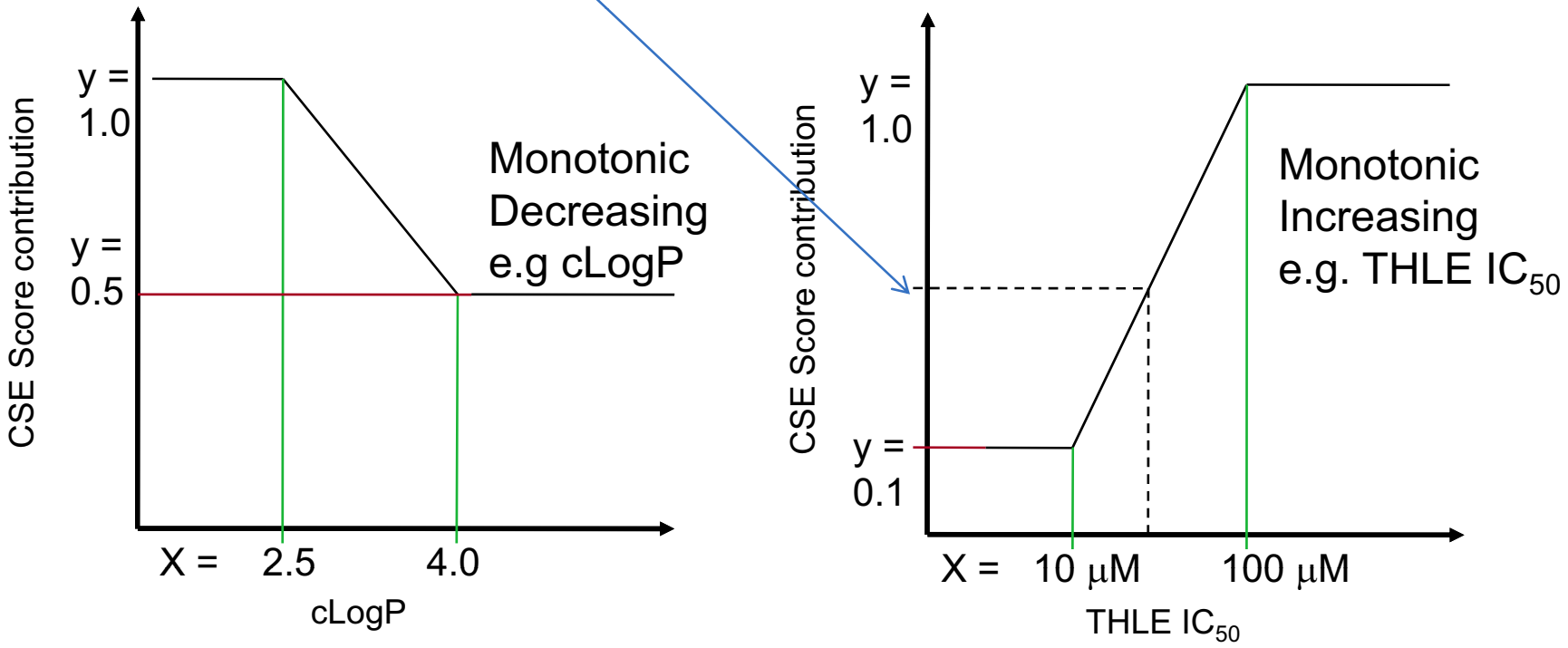
Objective: To derive a single score to allow easy comparison of compounds across a panel of assays and properties.

- Makes use of Multi-Parameter Optimization
  - the Score is on a 0 to 1 scale with 1 = ☺ and 0 = ☹
- Used assays already available to Project teams
  - Cerep binding assays (%inhib @ 10μM)
    - Subset of 15 assays used to assess promiscuity
  - THLE cytotoxicity*
  - Genetic Tox assays (BiolumAmes & IVMN)
  - Dofetilide binding and hERG
- Incorporates knowledge from Beyond Structural Alerts work (Bio. Med. Chem. Lett. (2008), 18, 4872-4875)
  - cLogP and TPSA (3/75 guideline)
  - Basic pKa

* THLE = transformed human liver epithelial

Compound Safety Evaluator: CSEv1.0

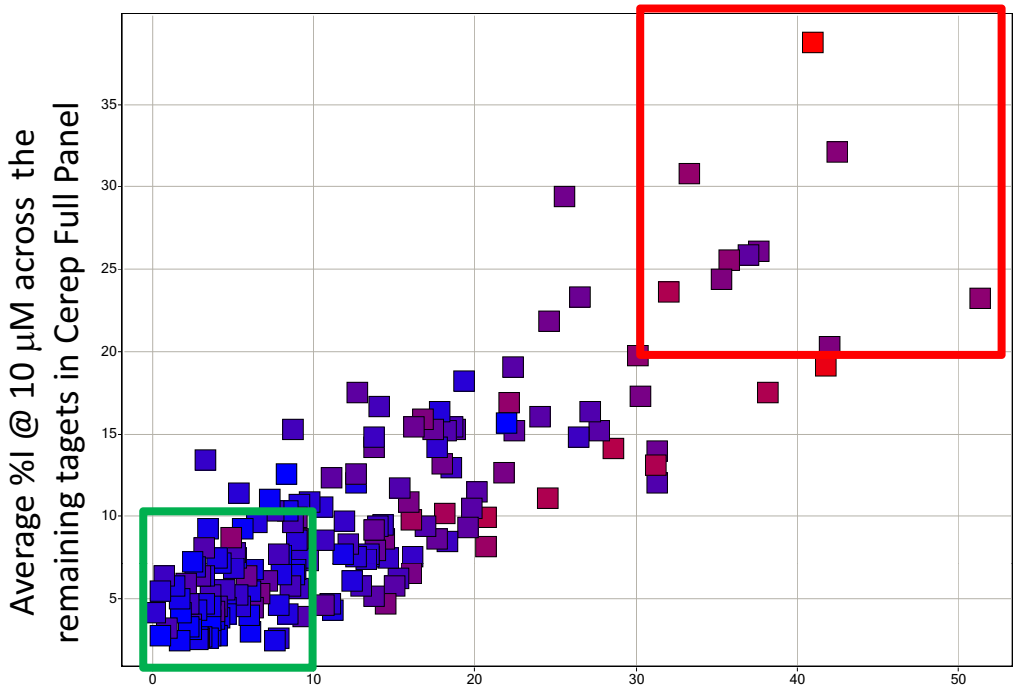
- **MPO Scoring Methodology**:
- CSE Score = $(y_1^{w} * y_2^{w} * y_3^{w} * y_4^{w} * \ldots)^{1/(w1+w2+w3+w4+\ldots)}$
- For each assay: y, X1 and X2 and relative weight (w) were defined e.g.



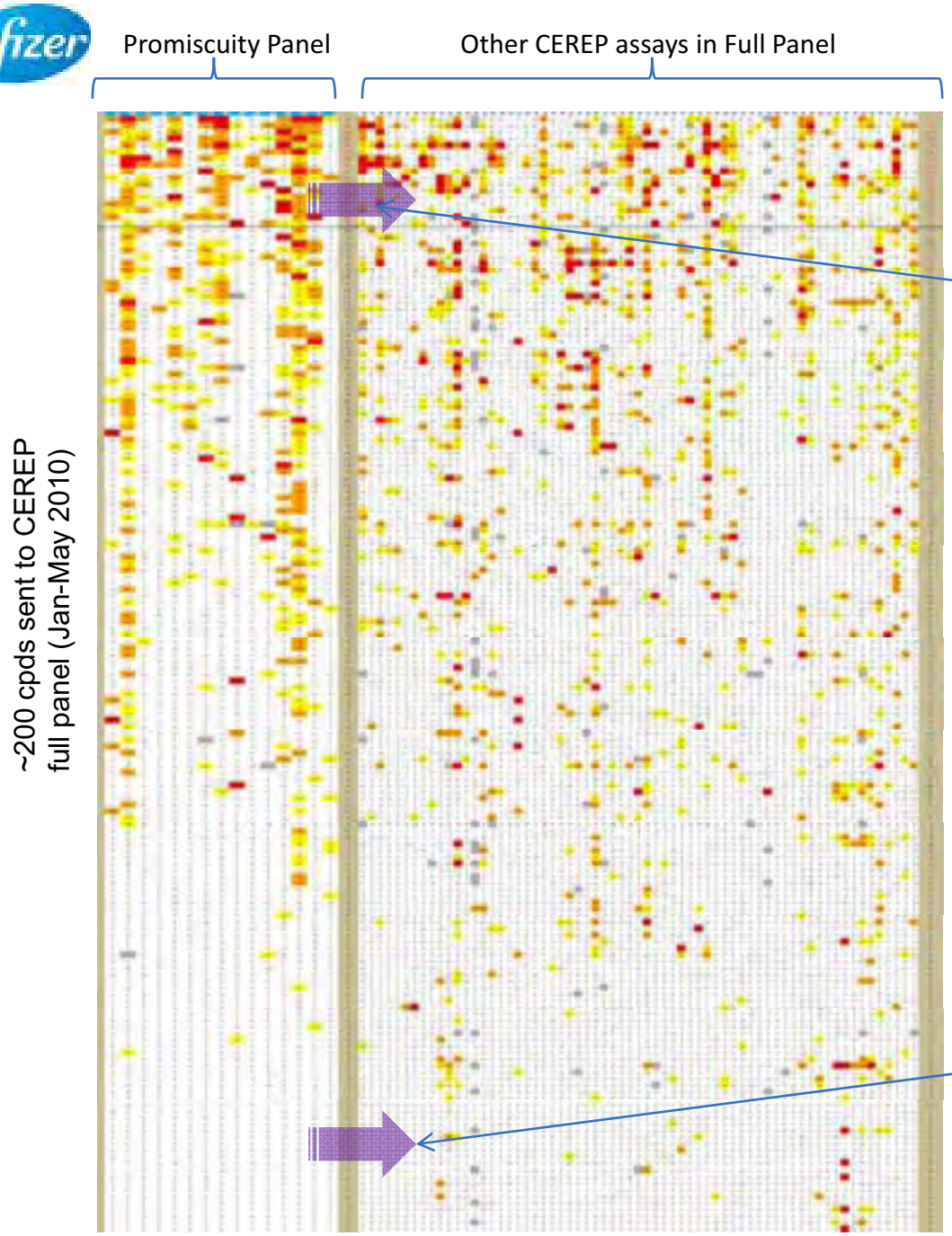
I cannot disclose <u>all</u> the proprietary assay thresholds, weighting and scoring MPO at this time.

Compound Safety Evaluator: CSEv1.0

- Why only 15 CEREP assays?
- 15 targets selected due to known risks/issues - The ‘Promiscuity Panel’
- Covering GPCRs, ion-channels, transporters, PDE
- Provides a lower cost, ‘quick look’ at promiscuity
- High average inhibition of the 15 targets generally correlates with wider promiscuity



Analysis of ~200 cpds sent to CEREP full panel (Jan-May 2010)



Sorted by Average %I across the 15 'Promiscuity Panel' Targets.
Each row is a compound.

The most promiscuous compounds across 15 targets carry on hitting multiple targets in the rest of the Full panel

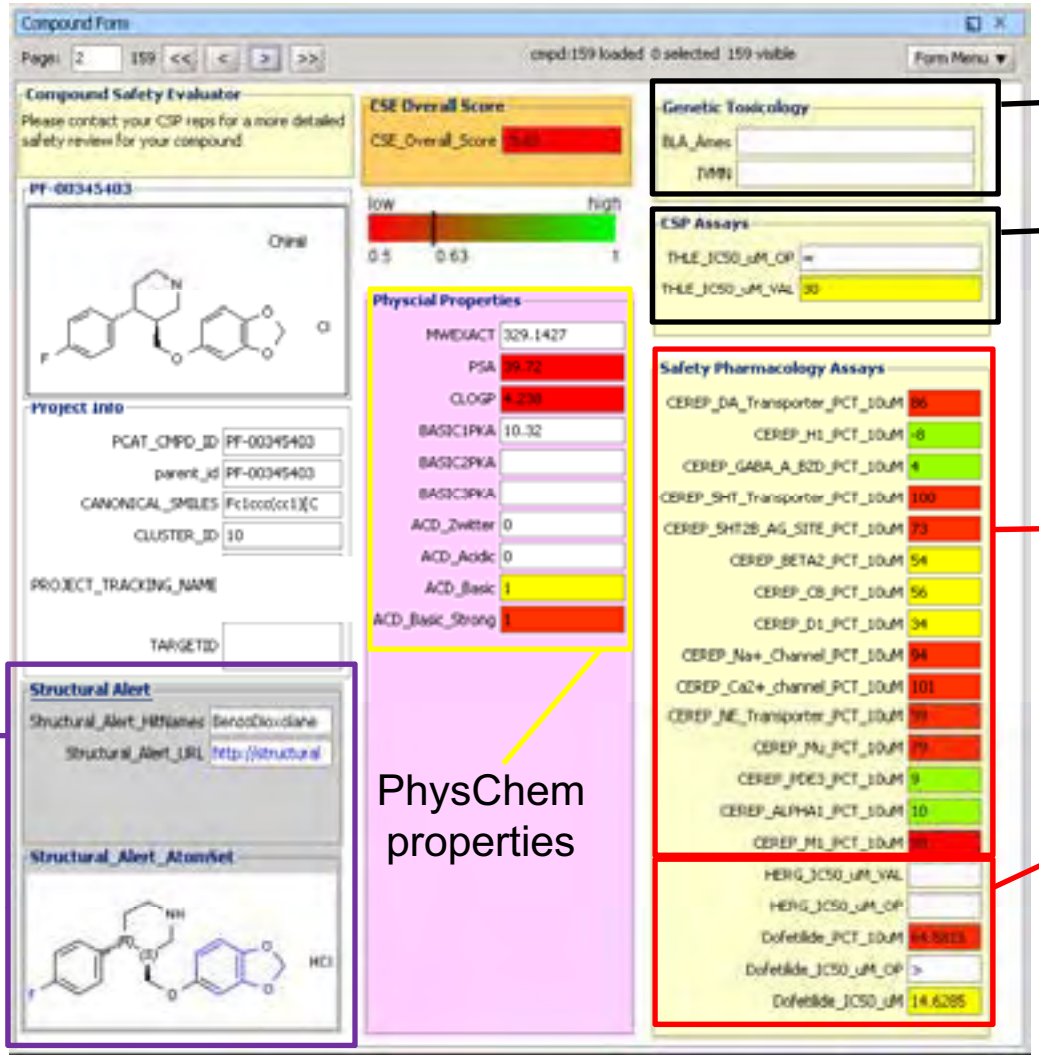
CEREP data: Colour-code
- >85%I
- 50-85%I
- 30-50%I
- <30%I

In contrast, the compounds with low average %I in the P-Panel are generally cleaner across the rest of the CEREP full panel

Compound Safety Evaluator: CSEv1.0

- Representative CSEv1.0 display

e.g. Paroxetine



Genetic tox. risks

THLE: Indicators of cell toxicity

CEREP Promiscuity panel

Potential CV safety

PhysChem properties

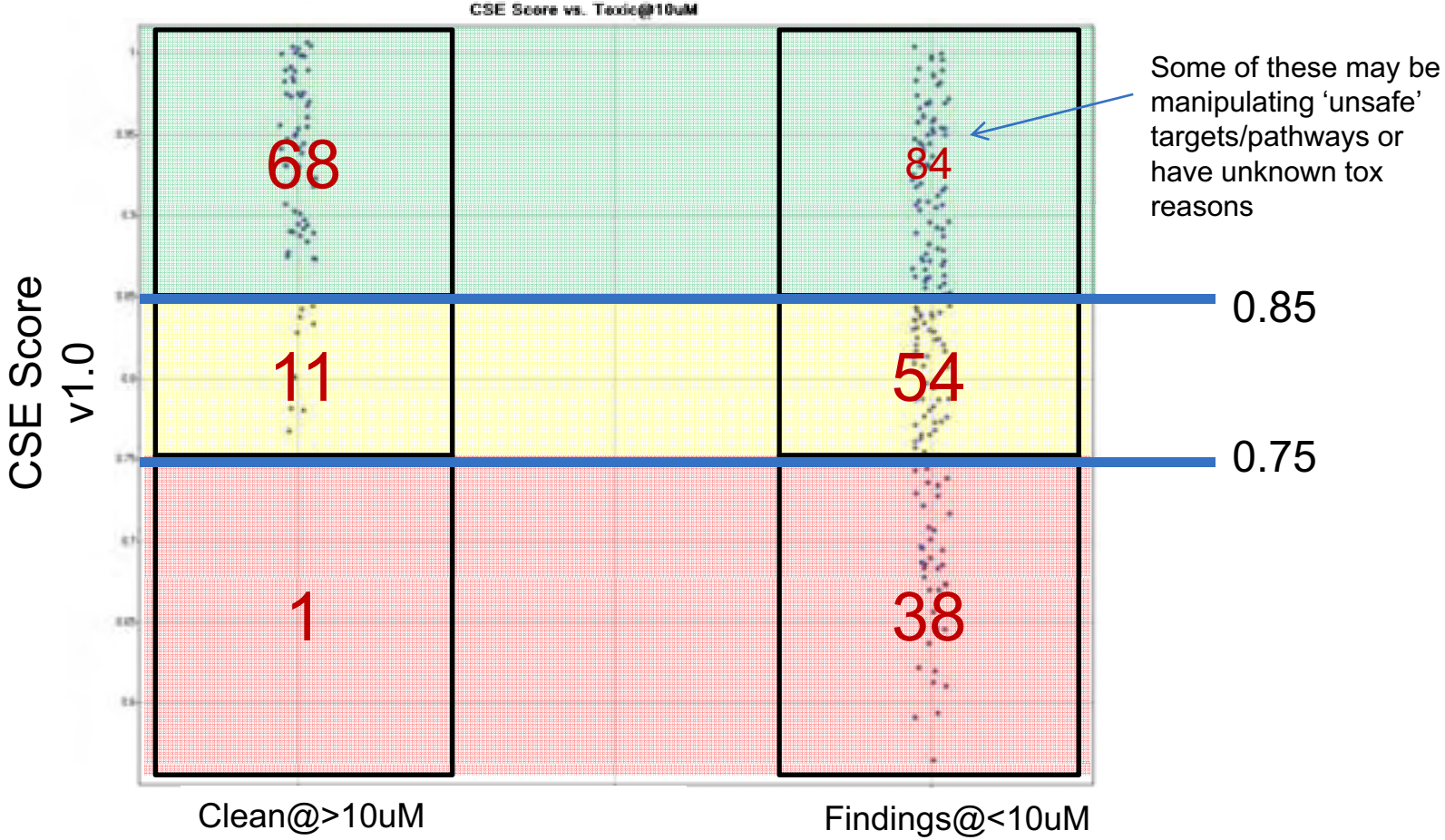
Toxicophore alerts

Compound Safety Evaluator: CSEv1.0

- **Retrospective Scoring of compounds that underwent *in vivo* toxicology assessment**
- Analysis and 'CSE Scoring' of 256 compounds that were profiled in exploratory toxicology studies (primarily in rat).
- Compounds were flagged as either:
  - Clean = No 'adverse toxicity findings' were observed at a Cmax at or above 10μM total drug
  - Toxic = 'Adverse toxicity findings' were observed at a Cmax below 10μM total drug

Compound Safety Evaluator: CSEv1.0

- **Data set**: 256 compounds with *in vivo* toxicology outcomes ('clean' vs 'adverse toxicity findings' at 10μM total drug)



CSE Score <0.75 correlates with greater risk of adverse findings at 10μM

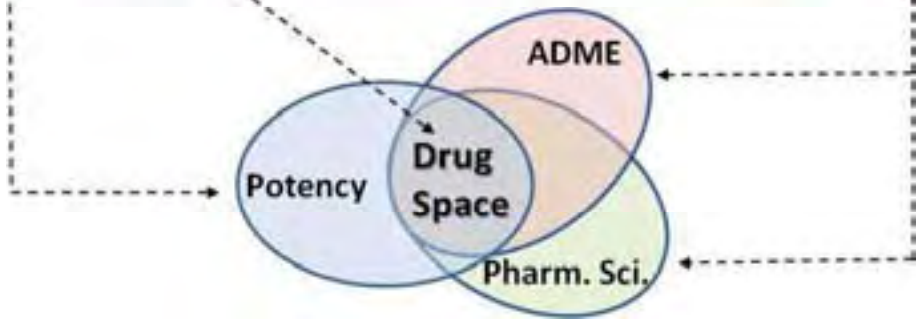
What About the Dose?

- High dose risks:
  - Metabolic burden (esp. liver & kidney)
  - Reactive metabolites ⟶ covalent binding ⟶ idiosyncratic tox?
  - DDIs

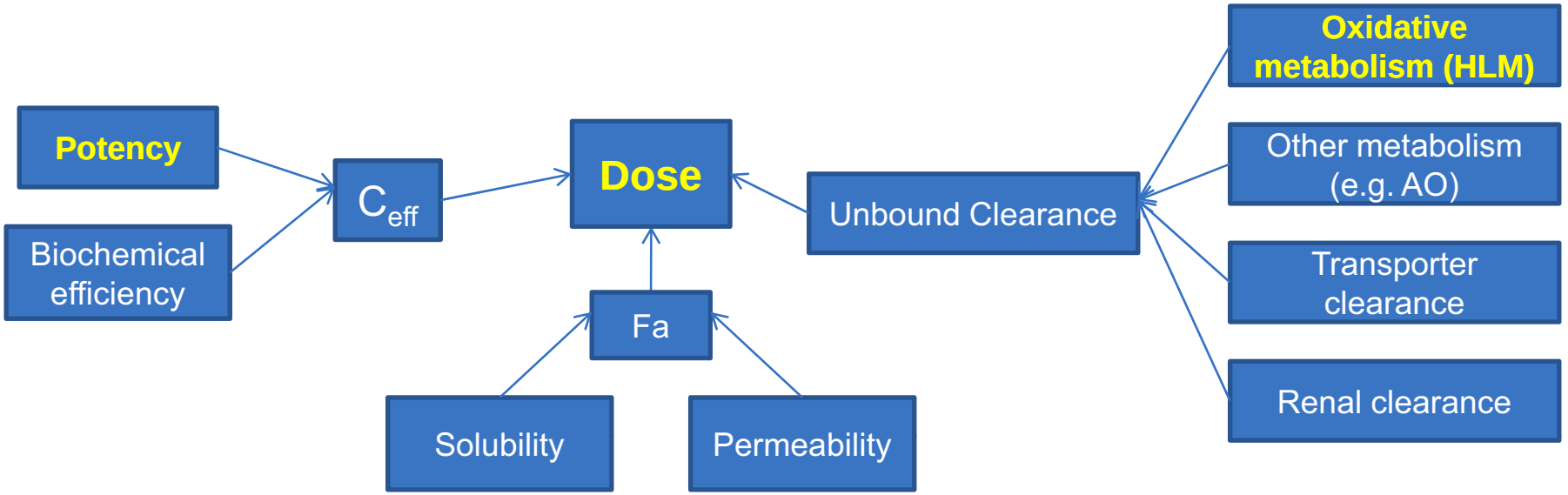
- What defines the Dose?

What Defines the Dose?

$$Dose = \frac{C_{eff,u} \bullet CL_{int,scaled} \bullet \tau \bullet BI}{Fa}$$

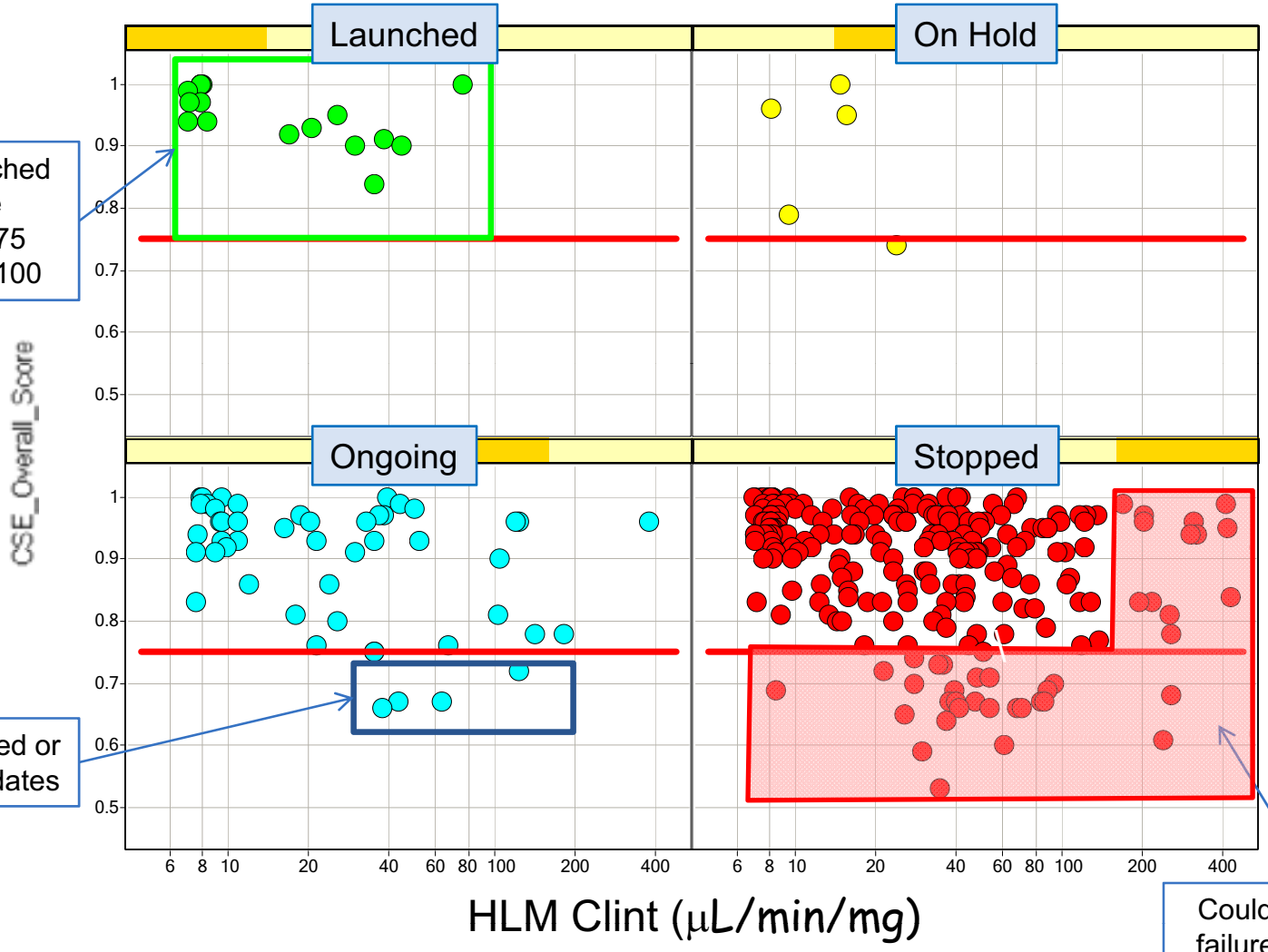


Major advances in predicting and improving HLM over last decade



For a diverse set of compounds/target mechanisms
- it is simpler to track HLM as a component of Dose

307 Pfizer Candidates with CSEv1.0 & HLM



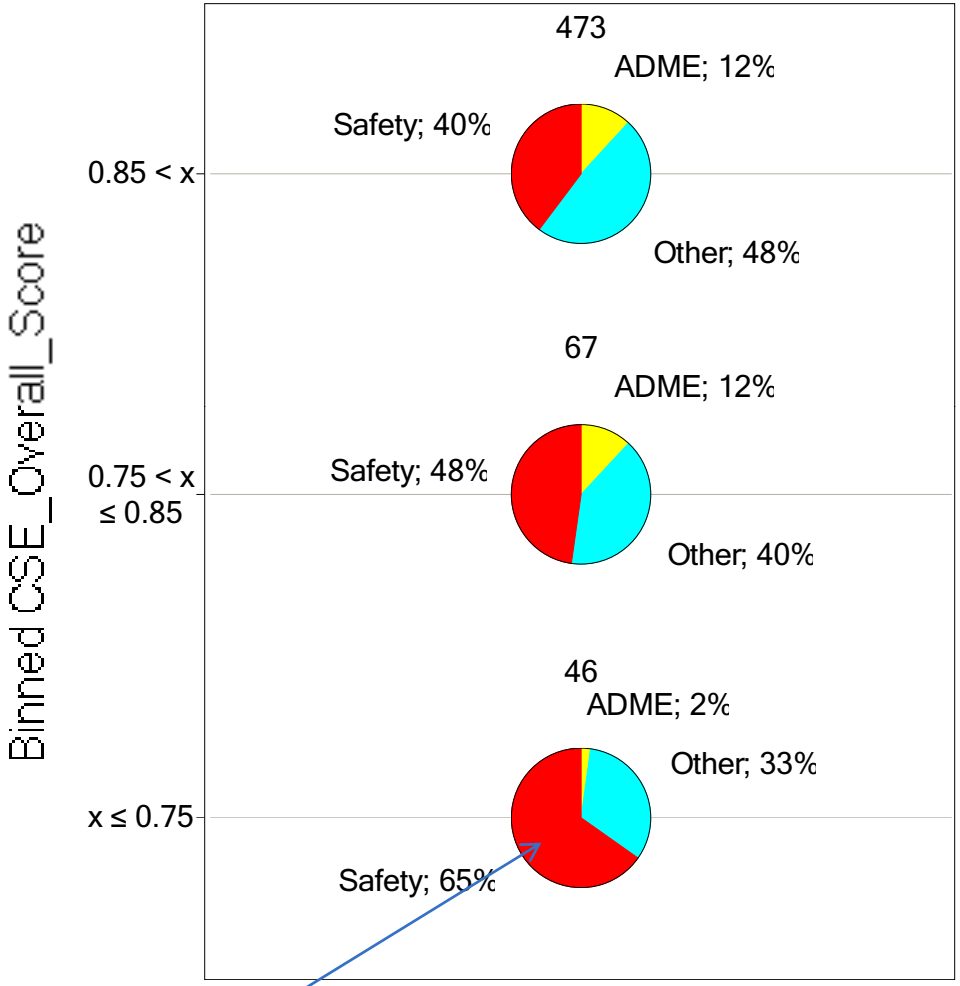
All these Launched Drugs have CSEv1.0 >0.75 & HLM Clint <100

These are inhaled or oncology candidates

Could some these failures have been avoided?

HLM Clint is one component of Dose

586 Stopped Pfizer Candidates



Other reasons includes:

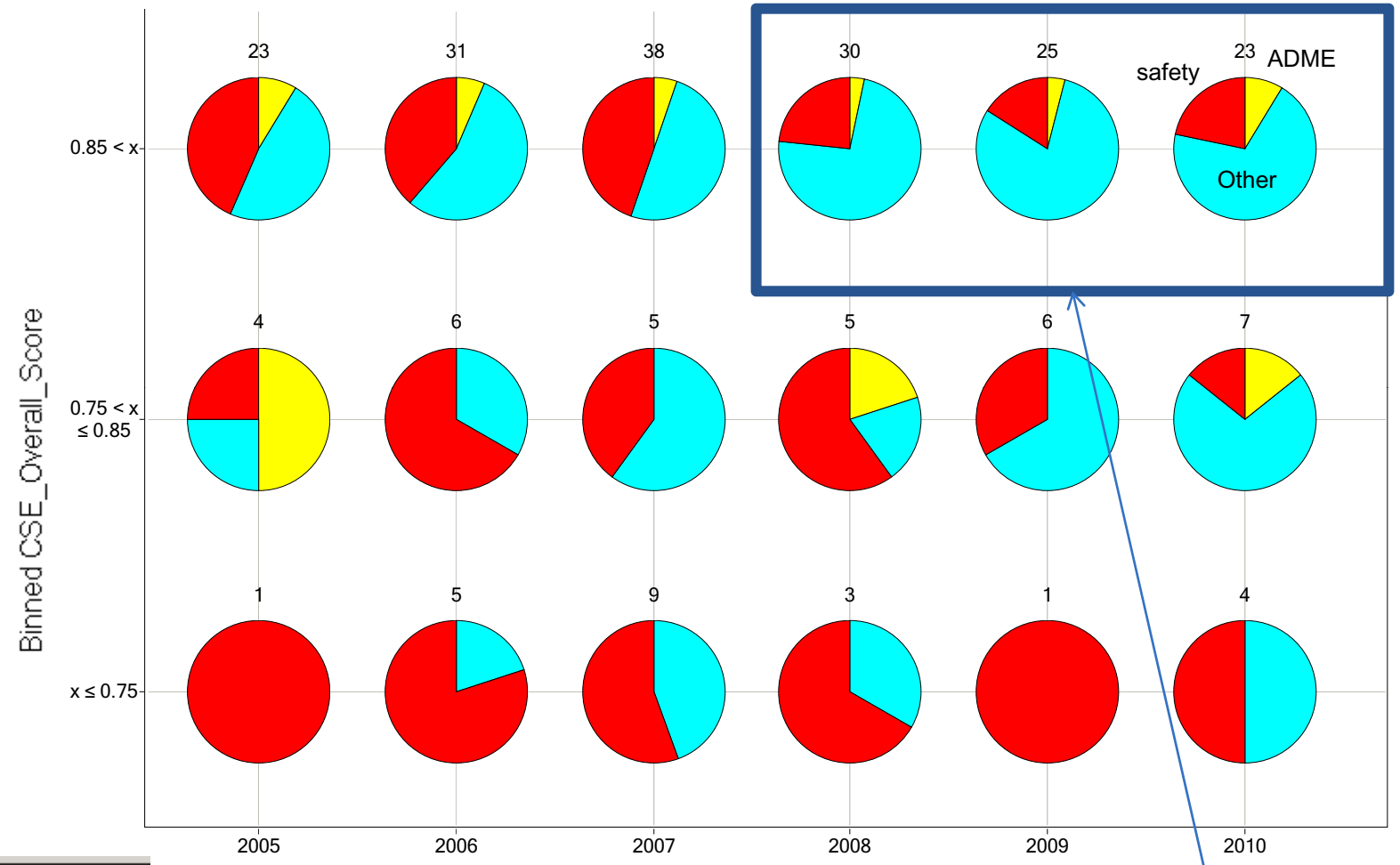
- Pharmacology
- Chemistry
- Biopharmaceutics
- Strategic

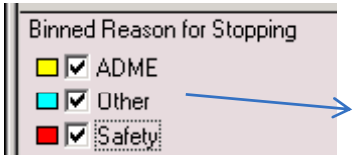
When CSE <0.75: Safety is given as reason for Stopping for 65% of candidates
Total of 244 stopped due to Safety concerns – what type of Safety?

Reasons for Safety Attrition: 244 Pfizer Candidates

When CSE <0.75:
Pre-clinical non-hepatic animal tox is clearly the main reason for attrition

Reasons for Attrition since 2005





Other reasons includes:

- Pharmacology
- Chemistry
- Biopharmaceutics
- Strategic

When CSE >0.85:
Since 2007 fewer cpds are stopping due to safety reasons

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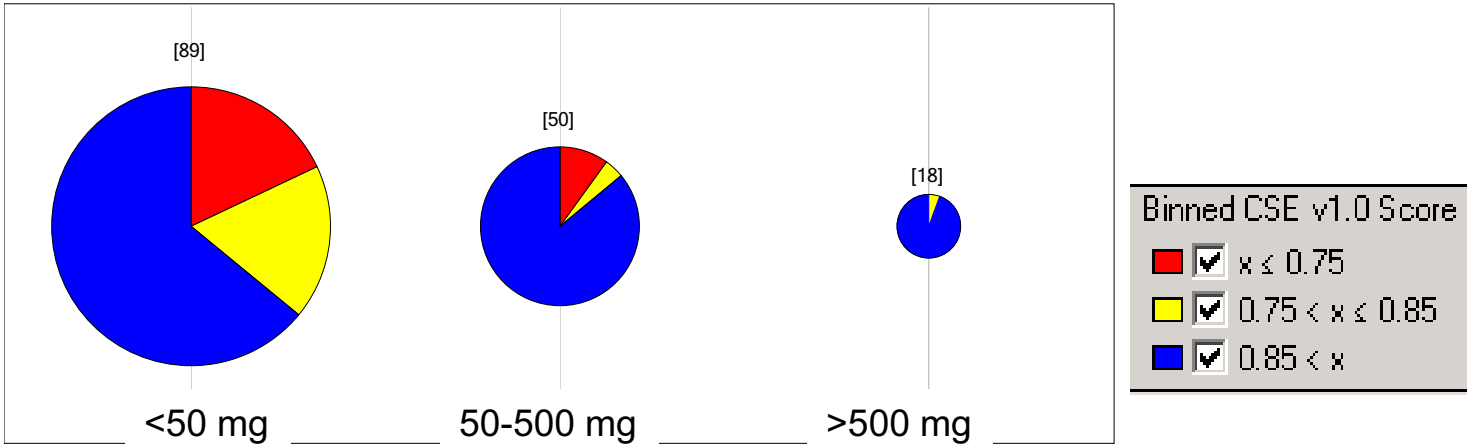
Drugs on the Market

- What would the CSE Score of Launched Drugs look like?
- Safety is more stringent now compared to 1990 or even 2000
- Impact of Dose – we know the dose ranges that are approved

Drugs on the Market

- Data set analysed:
  - Identified all Oral Drugs launched since 1990
  - Filtered to MW <600 to remove large biologics etc.
  - Must be present in the Pfizer File
  - Must already have CEREP data generated in Pfizer database
  - Gave 157 launched Drugs for analysis (a snapshot – not comprehensive)

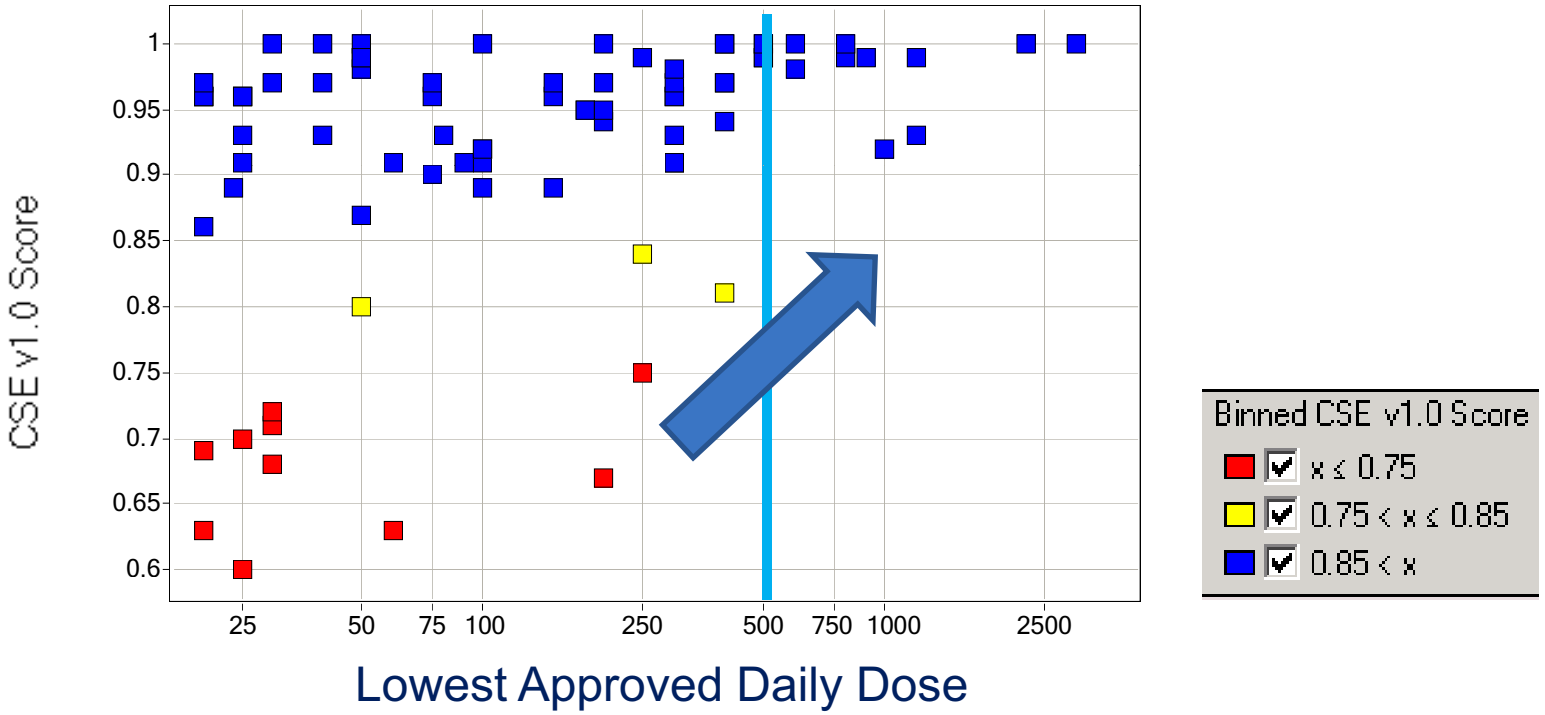


With this data set:
17/18 Drugs with dose >500mgs have CSE Score >0.85
(exception being Gleevec; CSE Score 0.81; Typical oncology dose 400-800mg)

Low dose (<50mg) more forgiving of potential Safety Risks (high potency→ high TI)
Caveat – this is only a subset of all launched drugs

Drugs on the Market

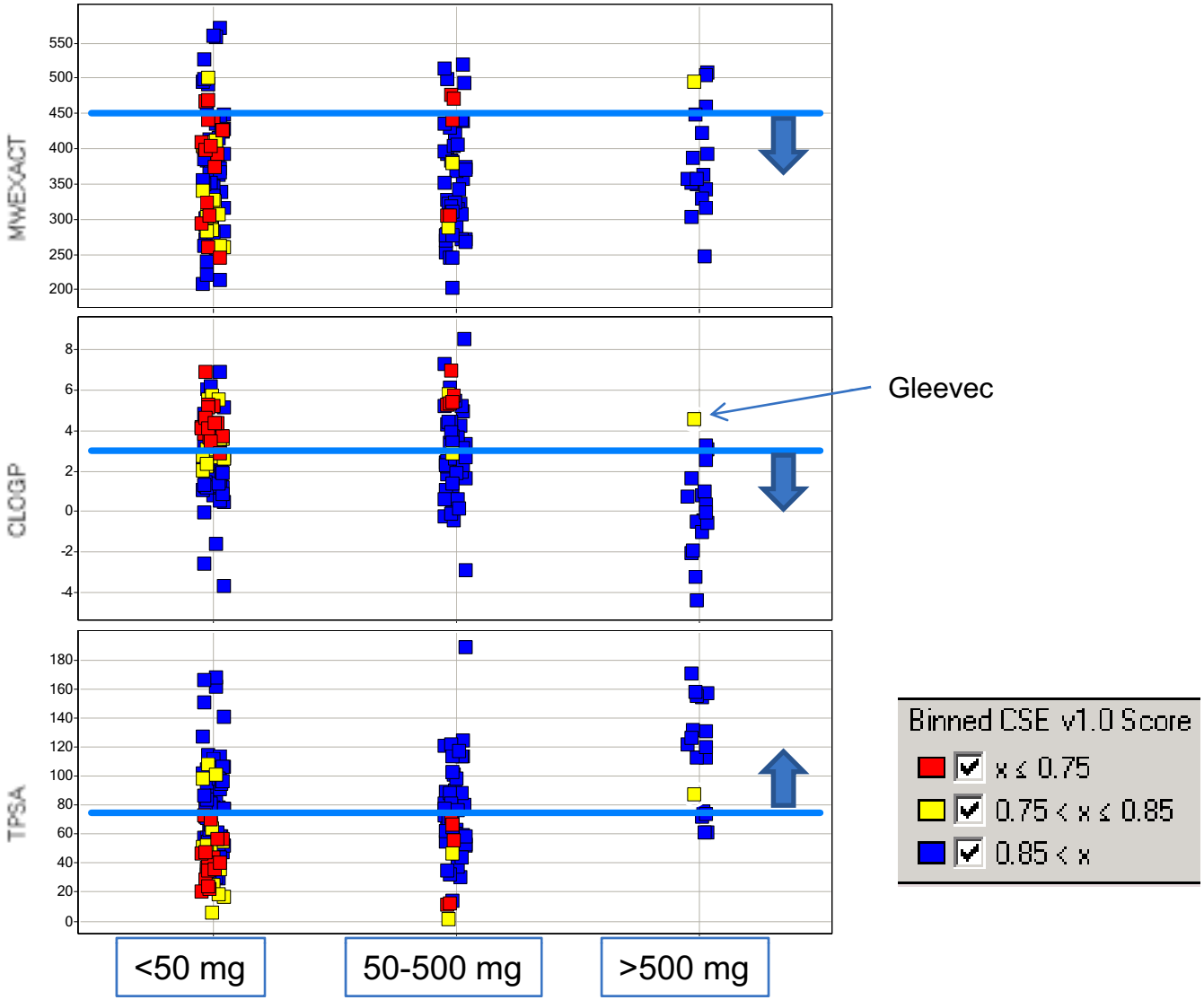
- Focussing on the higher dose Drugs:
  - Plot lowest approved dose vs CSEv1.0 Score



With <u>this</u> data set:

Trend for high CSE Score required if dose has to rise.

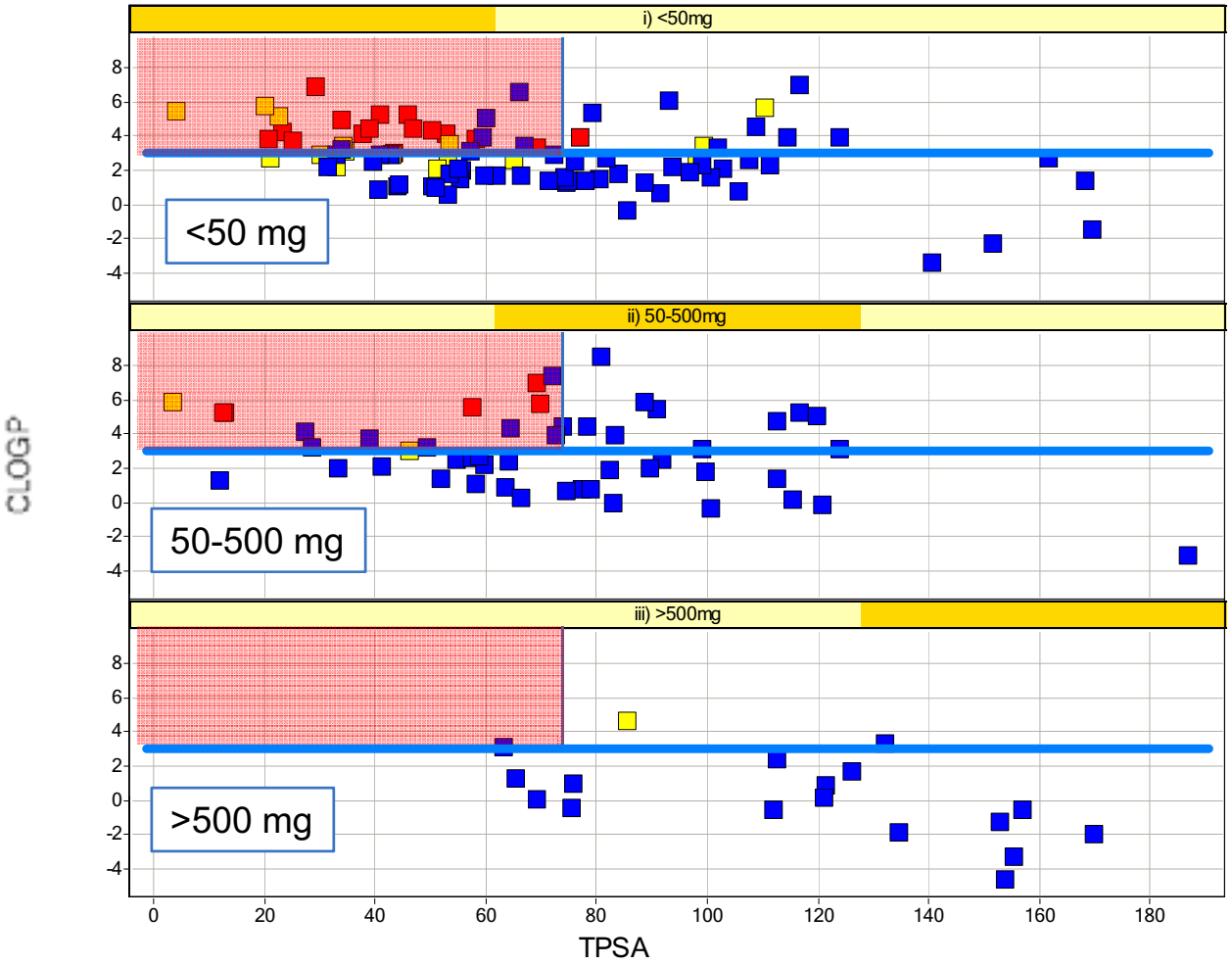
Drugs on the Market



With this data set:

The majority of 'high' dose compounds are MW <450, cLogP <3, TPSA >75

Drugs on the Market



cLogP>3
+
TPSA <75

Binned CSE v1.0 Score
- x ≤ 0.75
- 0.75 < x ≤ 0.85
- 0.85 < x

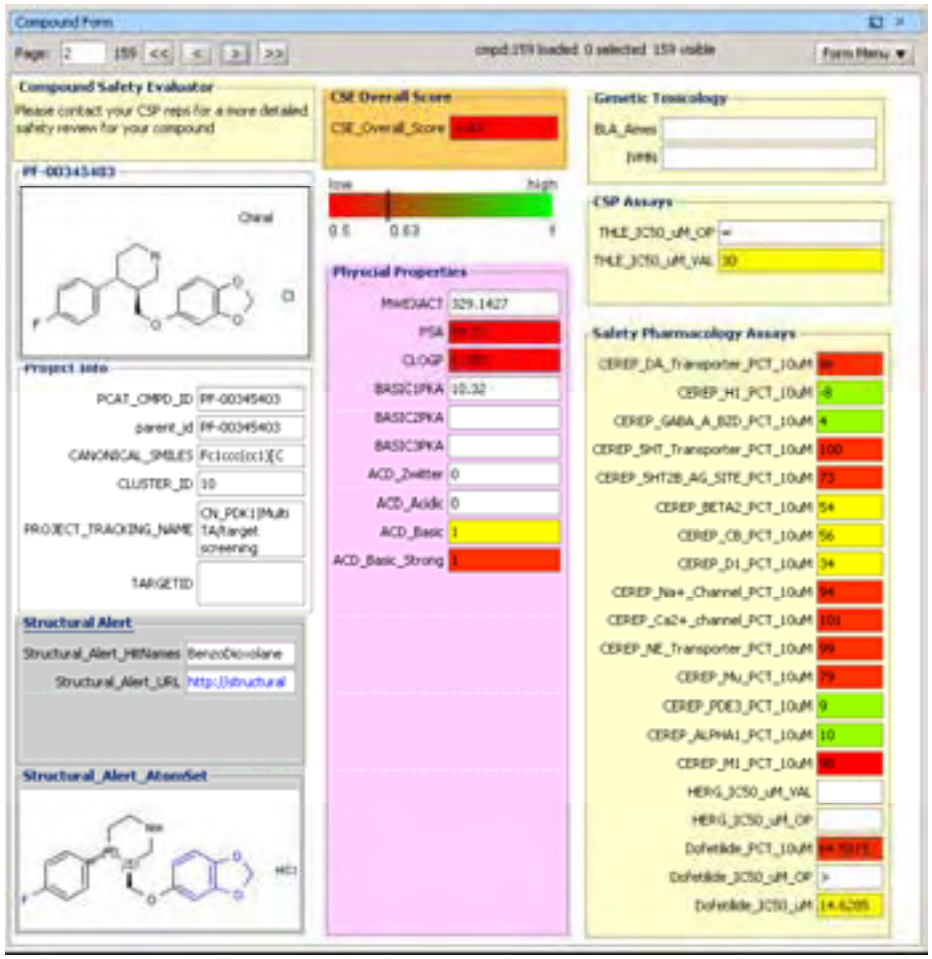
With <u>this</u> data set:

High cLogP and low TPSA can (historically) be successful if the dose is low

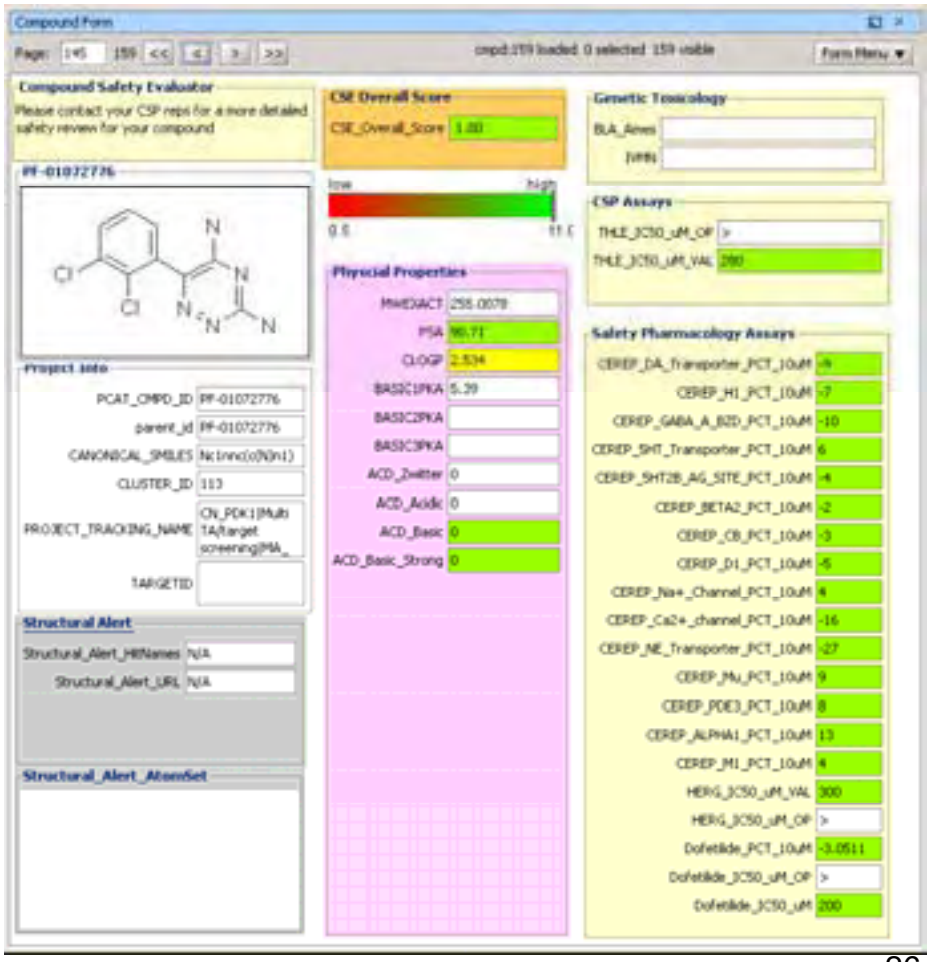
But, many of these drugs carry safety warnings – would they be approved in todays 'climate' ?

Drugs on the Market

Higher risk CSEv1.0 Score:
e.g. Paroxetine
Initially 20mg daily
rising to max of 50mg



Lower Risk CSEv1.0 Score
e.g. Lamotrigine
Daily maintainence dose of 100-500mg



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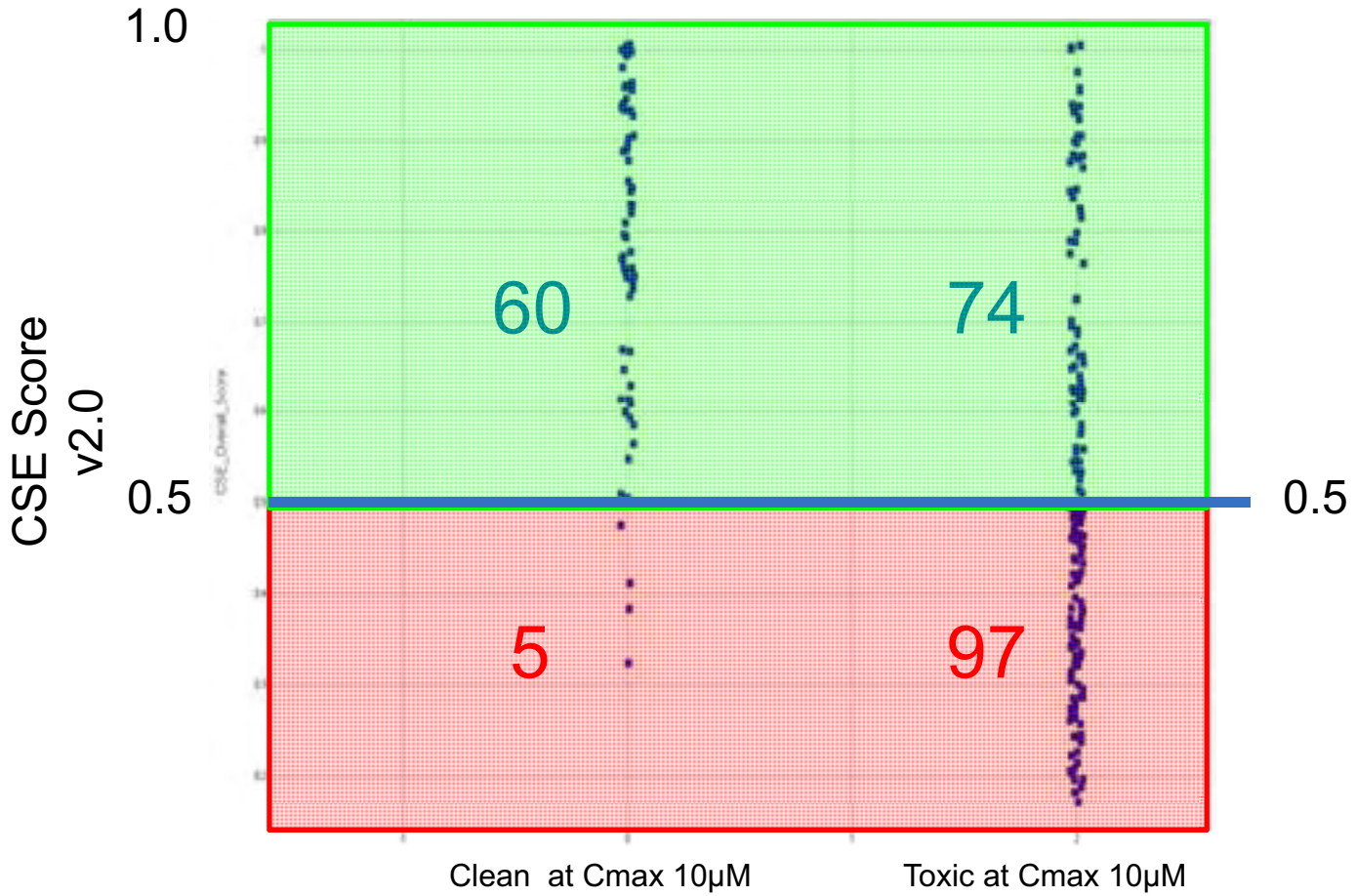
Compound Safety Evaluator: CSEv2.0

- CSEv1.0 was refined….
- The results of the 15 CEREP assays (v1.0) are summarized in a GINI coefficient, which provides a measure of compound promiscuity
- Additional proprietary cell based mechanistic assays have been included in the CSE panel of assays: e.g. mitochondrial function and apoptosis
- A Random Forest method was used to identify the assays that provide the greatest predictive value.
- CSE v2.0 uses 12 chemical and biological endpoints to generate an MPO score

I cannot disclose the assay threshold, weighting and scoring MPO at this time.

Compound Safety Evaluator: CSEv2.0

- **Data set**: Same 236 compounds with *in vivo* toxicology outcomes ('clean' vs 'adverse toxicity findings' at 10μM total drug)



CSEv2.0 Score **<0.5** correlates with greater risk of adverse findings at 10μM

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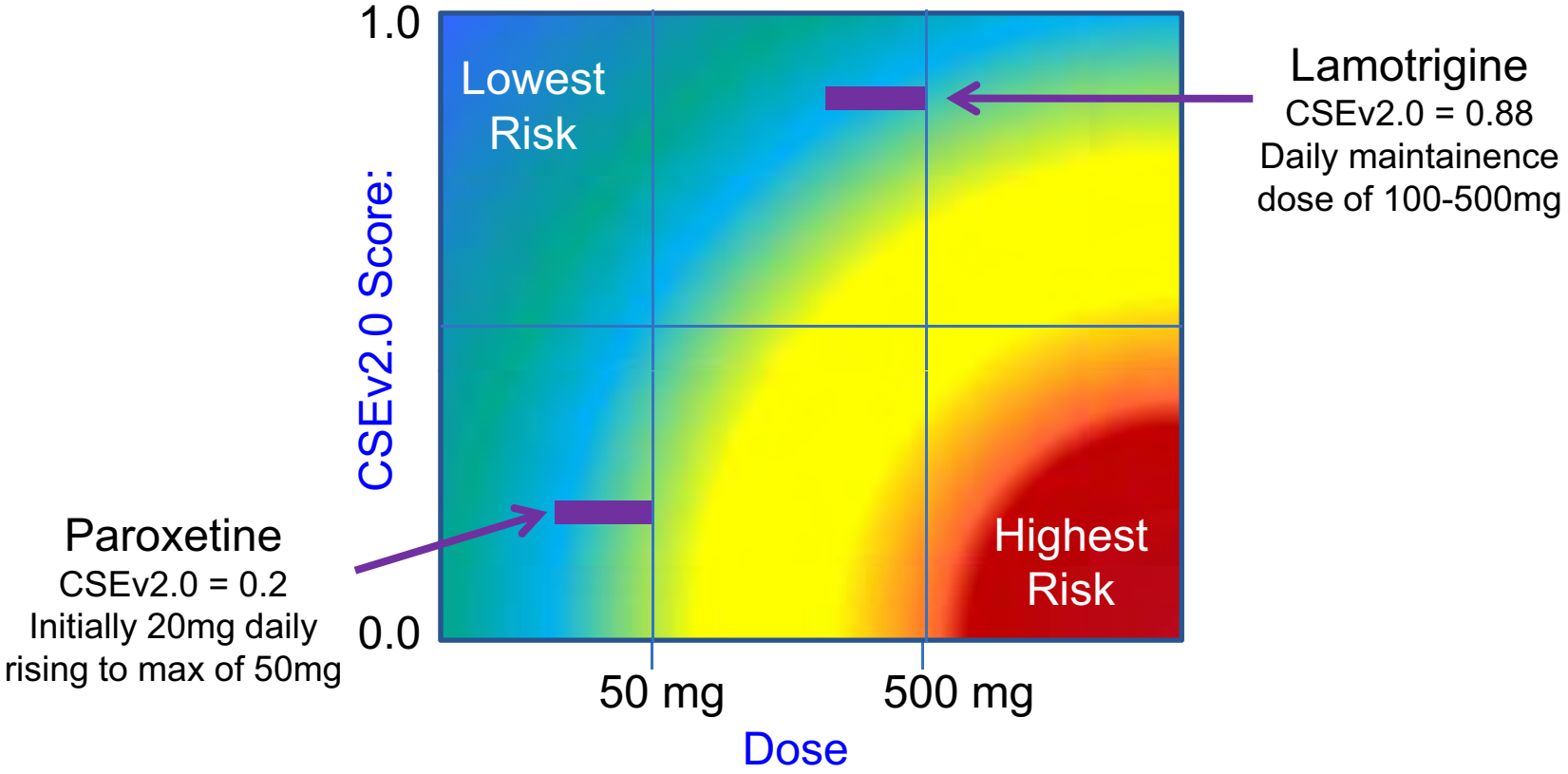
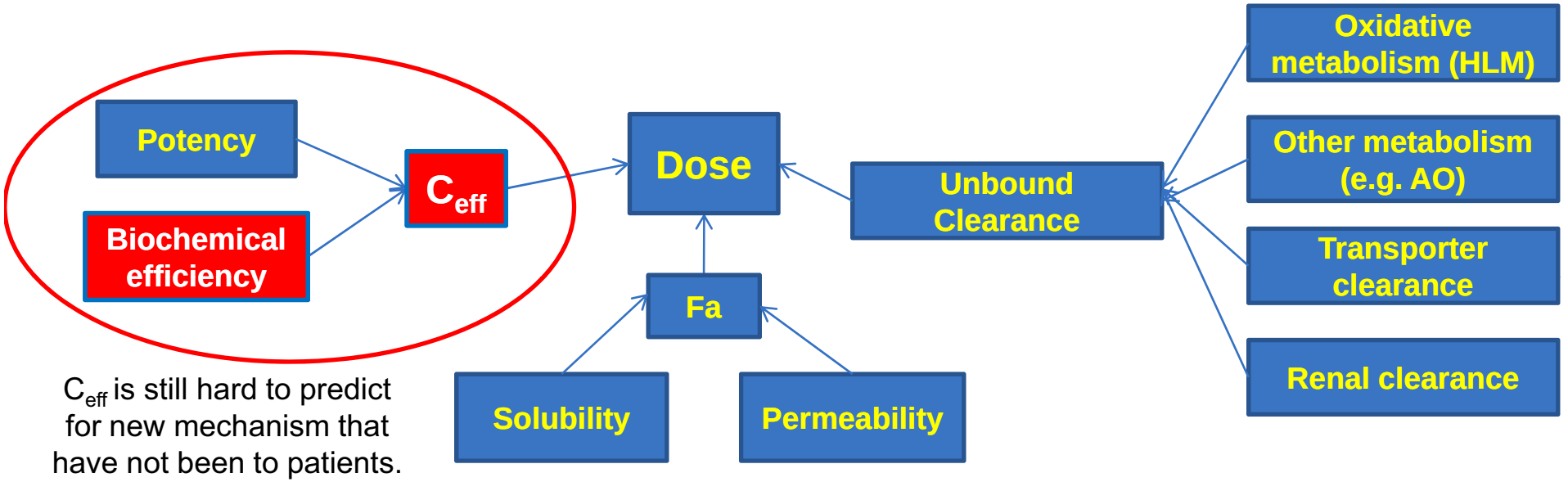
Attrition Risk (CSE vs Dose):

Examples of Drugs on the Market



- Attrition Risk can be mapped as a ‘value-range’ to take into account both these properties.
- Can we improve the dose predition for hits, leads and potential drug candidates?

Improving the Oral Dose Prediction



Bio*Pf*arm-X-treme (BPX) is Pfizer's new in-house program

- ➢BPX-Mini for 1000s cpds to help with series selection etc
- ➢BPX- Maxi for refined Fa and Dose prediction on selected leads

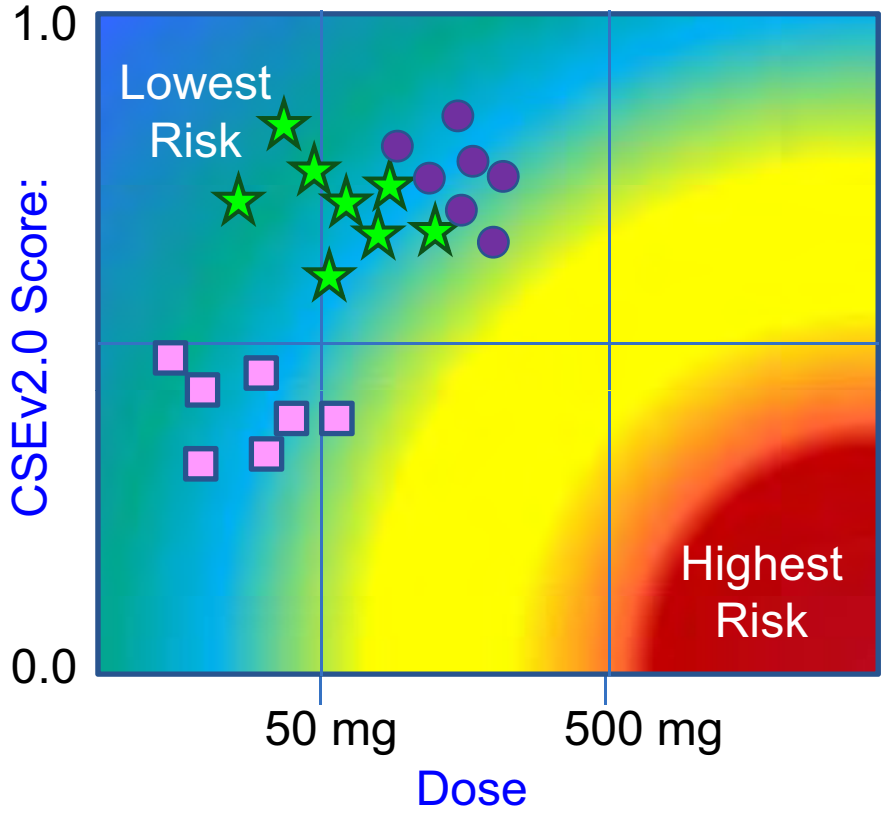
Unbound Clearance prediction is good if mainly HLM mediated, and improving with advancing knowledge of other clearance mechanisms.

Fa module is well validated (Sugano; *Expert Opin. Drug Metab.Toxicol.(2009) 5 (3):259-293*)

C_{eff} can be hard to determine without validated models or clinical data

Attrition Risk (CSE vs Dose):

Examples of Series in a Project



- Attrition Risk Grid can be used to visualise Series risks e.g.

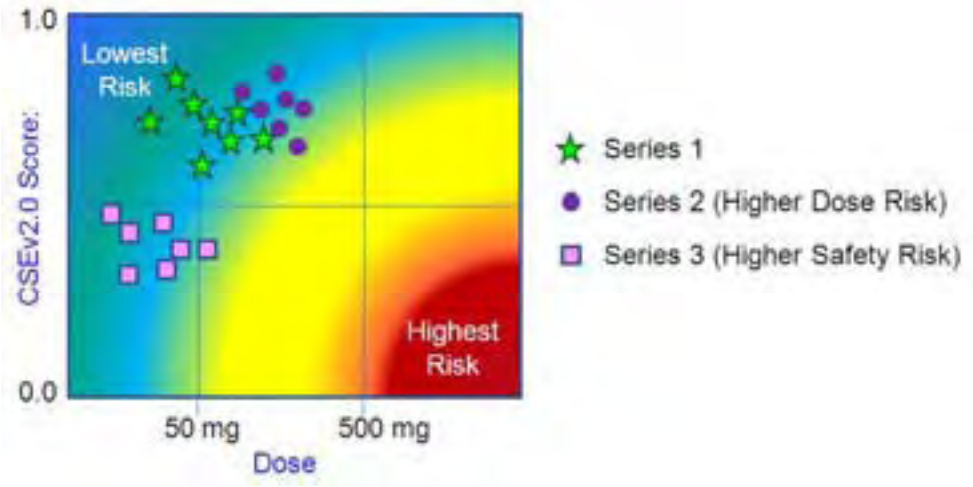
Series 1

Series 2 (Higher Dose Risk)

Series 3 (Higher Safety Risk)

Summary

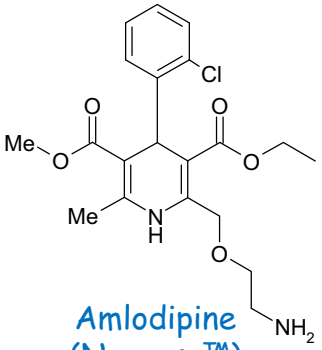
- Compound Safety Evaluator (CSE) is established as a tool to alert Projects to some potential safety risks of their Leads and Series.
- The impact of Dose and TI must be taken into consideration, in view of the acceptable level of risk for the given therapeutic indication.
- A proprietary *in silico* dose prediction method (Bio*Pf*arm-X-treme; BPX-Dose) has been developed, using ADME and Pharmaceutical properties. But C_{eff} is still an issue for many Projects.
- The combination of CSE Score and Dose Prediction for leads & series in a Projects (and Projects within a Portfolio) can be mapped on an Attrition Risk Grid.



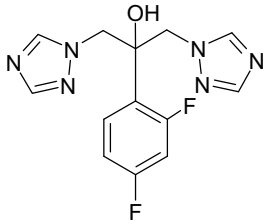
Key Acknowledgements

- Compound Safety Prediction Group
  - Bill Pennie, Nigel Greene, Karen Leach, Sean Wang, Shirely Louise-May
- Non Clinical Statistics & Research Informatics
  - Shibing Deng, Jim Silva
- Computational Sciences & Data and Design Analytics
  - Eric Gifford, Simon Xi, Jackie Klug-McLeod, Daniel Ziemek, Savina Jaeger, Rishi Gupta, Chris Keefer, Bruce Lefker
- Drug Safety Research & Development
  - Krista Dobo, Bob Chapin, Bernard Fermini, Bob Mauthe, Gareth Waldron
- Medicinal Chemistry
  - Tony Wood, Alan Stobie, Andy Bell, Dave Price, Mark Gardner
- BioPfarm-X-treme
  - Stefan Steyn, Kiyohiko Sugano

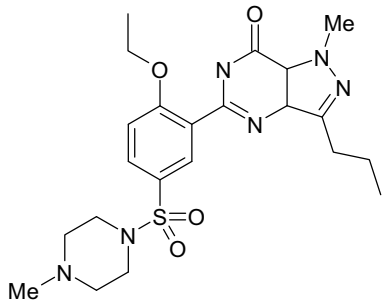
The Legacy of the Pfizer R&D in Sandwich UK



Amlodipine
(Norvasc™)
5-10 mg
Hypertension

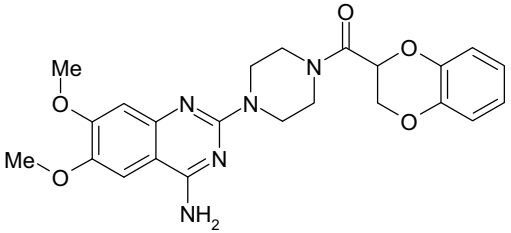


Fluconazole
(Diflucan™)
100-400mg
Antifungal

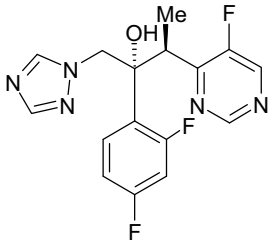


Sildenafil
(Viagra™)
25-100mg prn
Impotence

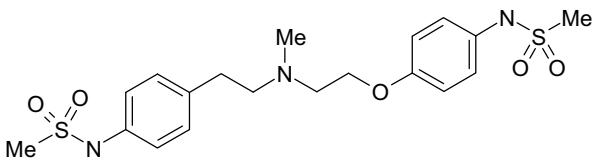
Sildenafil
(Revatio™)
20mg tid
PAH



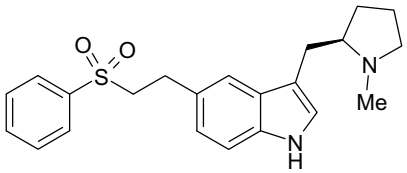
Doxazosin
(Cardura™)
4-8mg
Hypertension & BPH



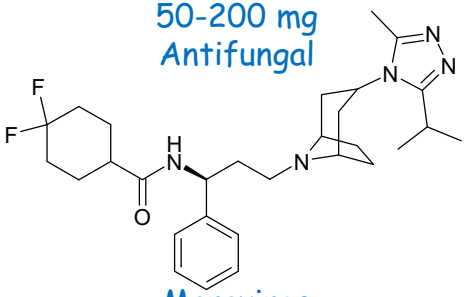
Voriconazole
(Vfend™)
50-200 mg
Antifungal



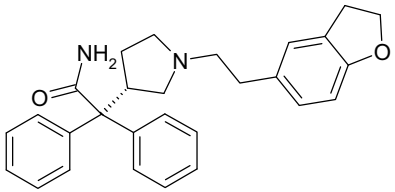
Dofetilide
(Tikosyn™)
<1mg
Antiarrhythmia



Eletriptan
(Relpax™)
20-40mg
Migraine



Maraviroc
(Celsentri™)
150-300mg
HIV



Darifenacin
(Enablex™)
7.5-15 mg
Incontinence