Industry-Wide Survey of MABEL-Based FIH Starting Dose

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on behalf of IQ MABEL Working Group

ASCPT Webinar

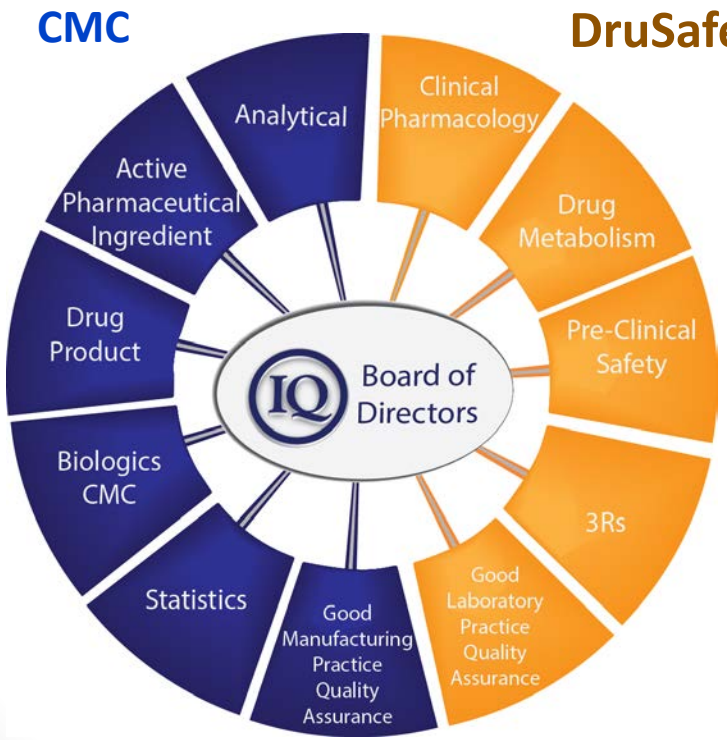
May 22, 2019

Outline

- Introduction to IQ
  - IQ MABEL WG
- Background of survey
- Survey results
- Discussion

International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)

- Composed of over 40 pharmaceutical and biotechnology companies
- Mission is to advance science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community



AbbVie	Incyte Corporation
Agios	Ironwood Pharmaceuticals
Alnylam	Johnson & Johnson
Amgen, Inc	Merck & Co.
Astellas Pharma US LLC	Mitsubishi Tanabe
AstraZeneca Pharmaceuticals	Novartis
Baxter Healthcare Corporation	Otsuka Pharmaceutical Co.
Bayer HealthCare	Pfizer
Biogen	Pierre Fabre Laboratories
Blueprint Medicines	Roche
Boehringer Ingelheim	Sanofi
Bristol-Myers Squibb Company	Sarepta
Celgene Corporation	Seattle Genetics
Daiichi Sankyo	Shire
Eisai, Inc.	Sunovion
Eli Lilly and Company	Takeda
EMD Serono	Teva Pharmaceutical
Genentech	Theravance Biopharma
Gilead Sciences	UCB Pharma
GlaxoSmithKline	Vertex, Inc.

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IQ MABEL Working Group

- Working Group formed in 2016
- Membership on next slide
- Working Group conducted survey in second half of 2017
  - Follow up questions in summer of 2018
- Writing White Paper
  - Include survey results and recommendations
  - Information in this slide deck should be considered preliminary/draft

IQ MABEL Working Group Members and Acknowledgements

Last Name	First Name	Company Name
Bailey	Wendy	Merck
Blanset	Diann	Boehringer Ingelheim
Brennan	Frank	UCB
Chemuturi	Nagendra	Novartis
Chen	Yingxue	AstraZeneca
Clarke	David	Lilly
Dai	David	Agios
Deslandes	Antoine	Sanofi
Dudal	Sherri	Roche
Han	Chao	J&J
Leach	Michael	Pfizer
Li	Chunze	Genentech
Loberg	Lise	Abbvie
Mayawala	Kapil	Merck
Rogge	Mark	Takeda
Shuey	Dana	Incyte
Shyu	Wen Chyi	Takeda
Sun	Lei	Alkermes
Todd	Marque	Pfizer
Wilson	Dan	Incyte
Yang	Zheng	BMS
Yu	Hongbin	Boehringer Ingelheim

MABEL Survey

- **Conducted by MABEL WG on behalf of IQ**
  - Collection of data on current use of MABEL
  - For determining best practices and future improvement
- **Survey questions**
  - 12 questions initially in summer 2017
    - Participant information
    - Development and current practice of MABEL approach
    - Regions where submitted and regulatory agency acceptance
    - Technical approaches to determine MABEL
    - How the MABEL dose performed
  - Three additional questions in summer 2018
    - Target location
    - Cohorts to clinically-relevant dose

Participation in Survey

- Sixteen pharmaceutical companies provided valid data
- Data on 88 molecules were collected
  - Thirteen companies provided cases of <10 molecules
  - Three companies provided 10-20 molecules
  - Submissions during 2009 to 2017 in the US, EU, Japan, etc.
- Most of the molecules that used MABEL were protein-based therapeutics

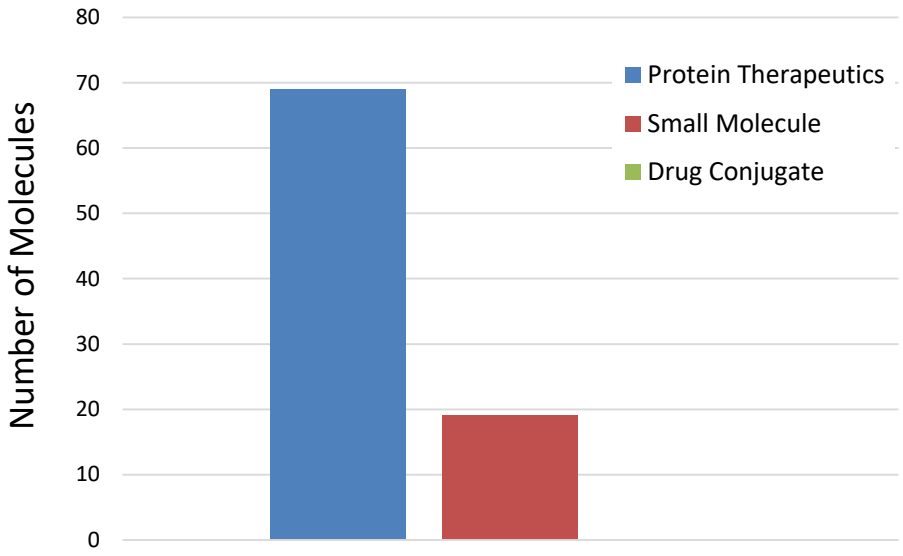


Figure 1. Distribution of modalities in this survey

Therapeutic Areas (TA)

- Molecules using MABEL in >8 therapeutic areas
- Most molecules in oncology and immunology
  - No anti-microbial drugs
  - Others included analgesics, respiratory, ophthalmology and hematology

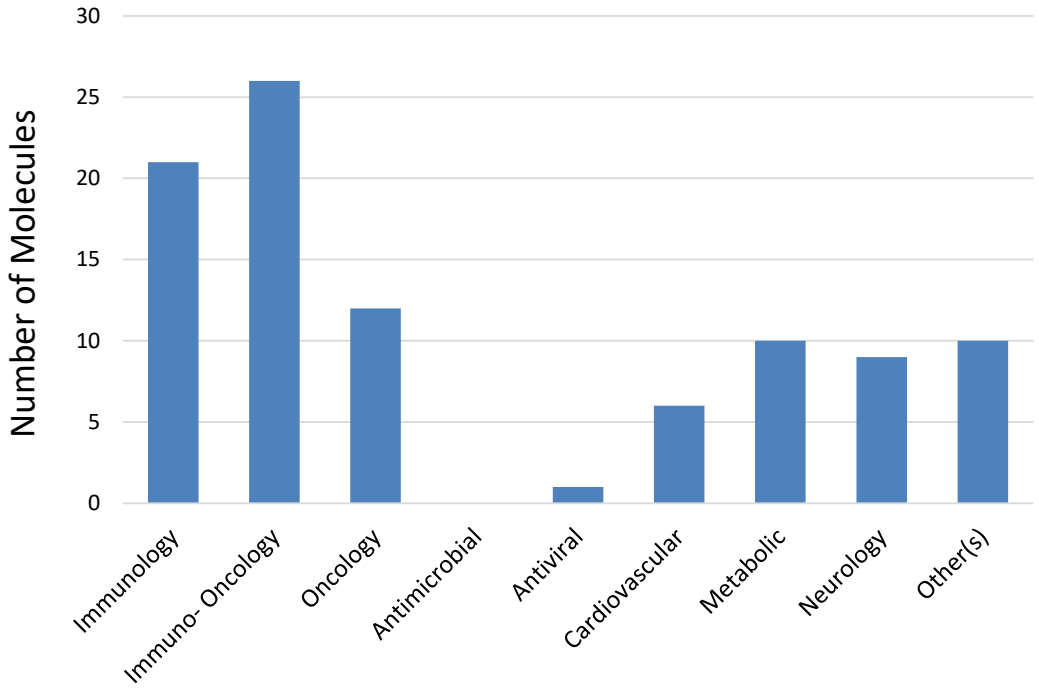


Figure 2. Number of molecules entered under each therapeutic area

Note: a small number of molecules entered more than one TA

Therapeutic Areas by Modality

- Proteins across all therapeutic areas
  - Immuno-Oncology and Antiviral had only proteins
- Small molecules more common in Metabolic, Neurology, and Other(s)

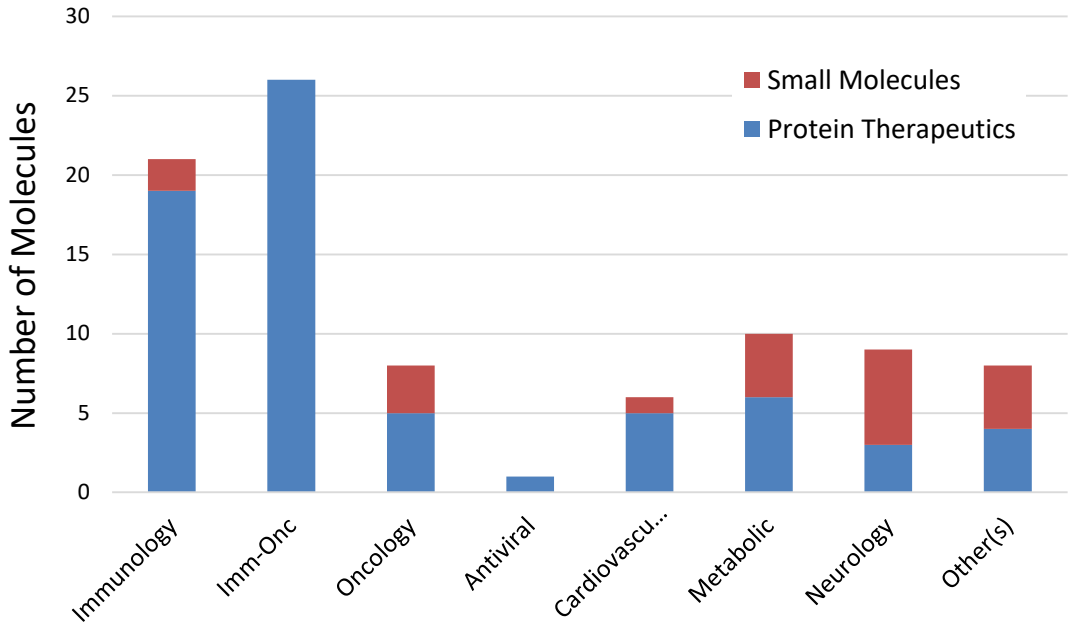


Figure 3. Number of molecules in different therapeutic areas – stratified by modality

Note: when a molecule entered for multiple TAs, only the primary one was counted

Development of MABEL Strategy

- Most (>60%) companies had developed a strategy of using MABEL for FIH starting dose selection
  - Risk-based assessment – consistent with EMA guidelines
  - Governance body at organizational level
  - Attention to specific target/mechanism
- Reasons why MABEL was used:

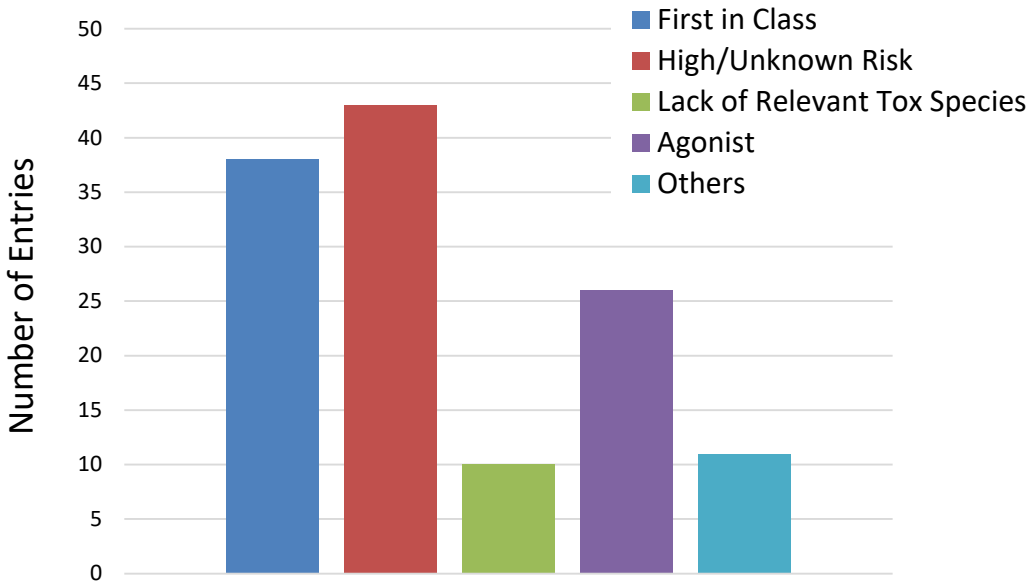


Figure 4. Reasons why a MABEL approach was used to determine the starting dose
Note: some molecules entered more than one reason

Development of MABEL Strategy

- Reasons stratified by molecular platforms and therapeutic areas
  - Protein therapeutics had more concerns about high/unknown biologic risk, lack of relevant toxicity species, and/or agonist
  - High/unknown biologic risk and agonist were leading concerns for oncology (Immuno-Oncology and Oncology)

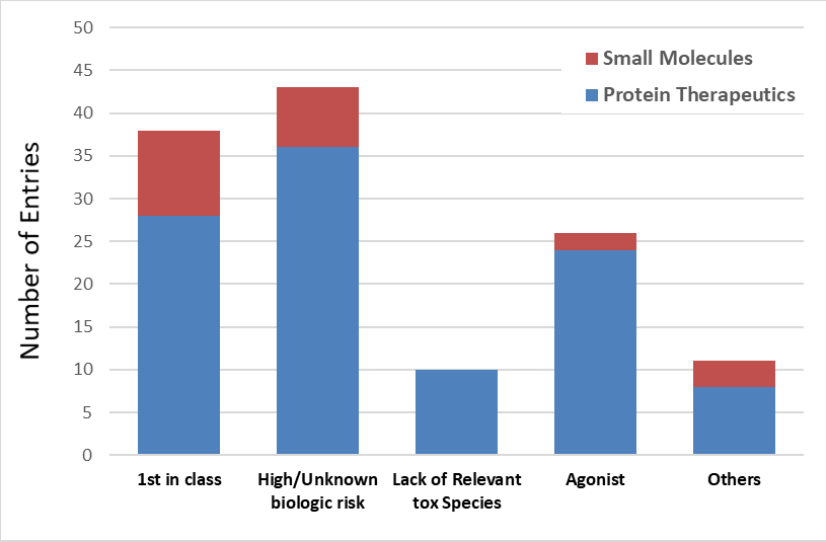


Figure 5a. Reasons – stratified by modality
Note: some molecules entered more than one reason

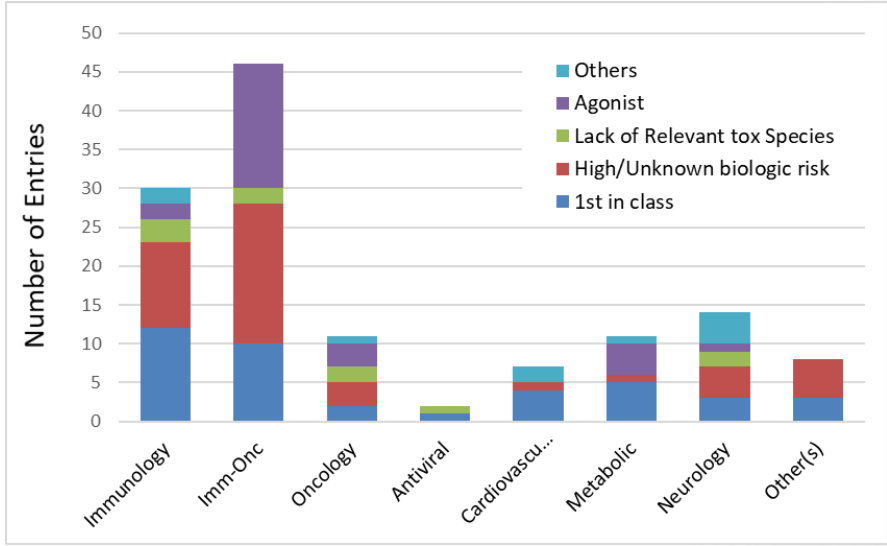


Figure 5b. Therapeutic areas – stratified by reasons

Submissions for IND or CTA

- Majority of molecules (56.8%) filed in US
- About 1/3 (38.6%) filed in EU member country
  - One drug filed in US and EU
- Rest of the World included Canada

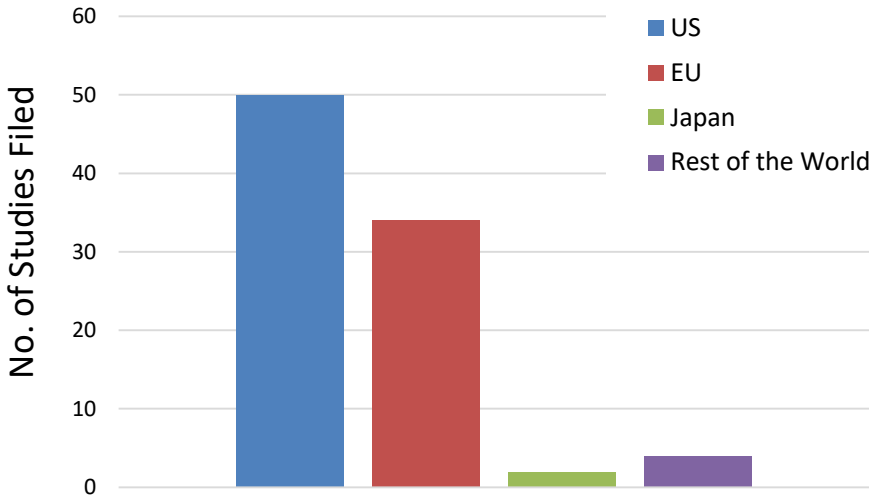


Figure 6. Distribution of country/regions in which IND/CTA was filed

- Overall acceptance rate by regulatory agencies was >95%
  - USFDA: 47 (94%) molecules were accepted, 3 (6%) were not
  - EU: 33 (97.1%) molecules were accepted, only 1 (2.8%) were not
  - All (100%) the submissions in Japan and Rest of the World were accepted

Submissions for IND or CTA

- More submissions using MABEL starting dose were relatively recent
  - 6% were 2009-2011, 27% were 2012-2014, and 48% were 2015 to date of survey
  - 19% of molecules did not provide submission year

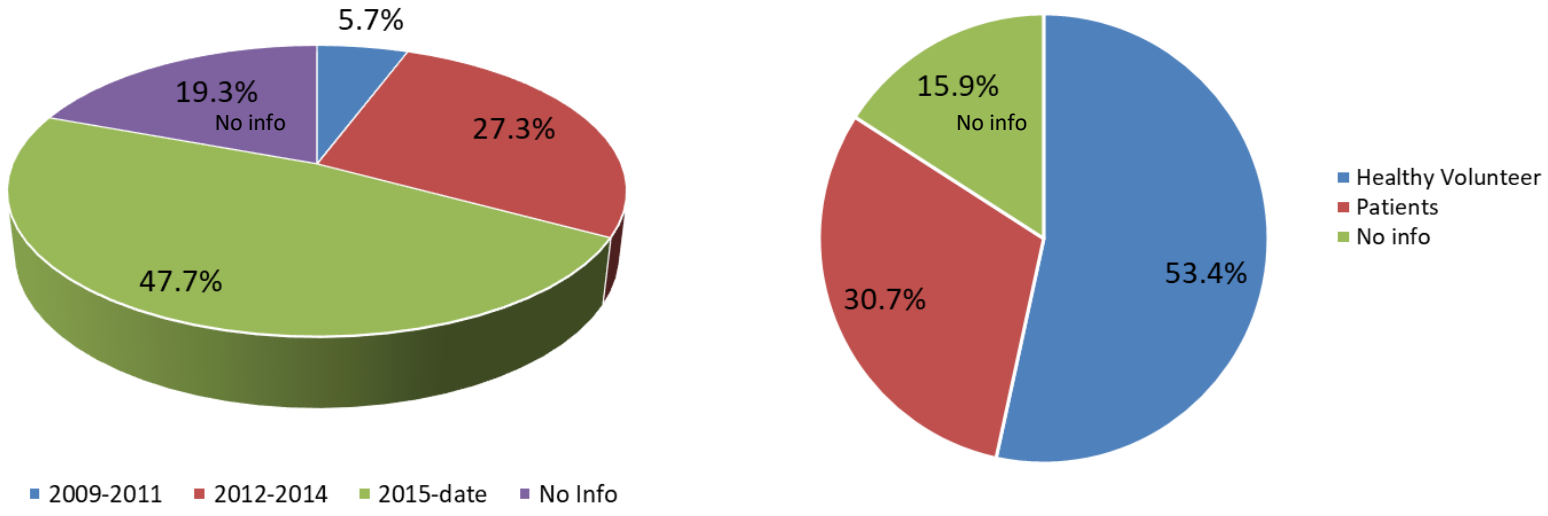


Figure 7. Years of submission and populations in which FIH trial was conducted

- Most (53%) FIH trials in healthy volunteers; 31% in patients
  - 16% of the entries did not provide this information

Submissions for IND or CTA

- Most oncology (Immuno-oncology and Oncology) FIH studies conducted in patients
  - 71% in patients; 6% in healthy volunteers; 24% no info

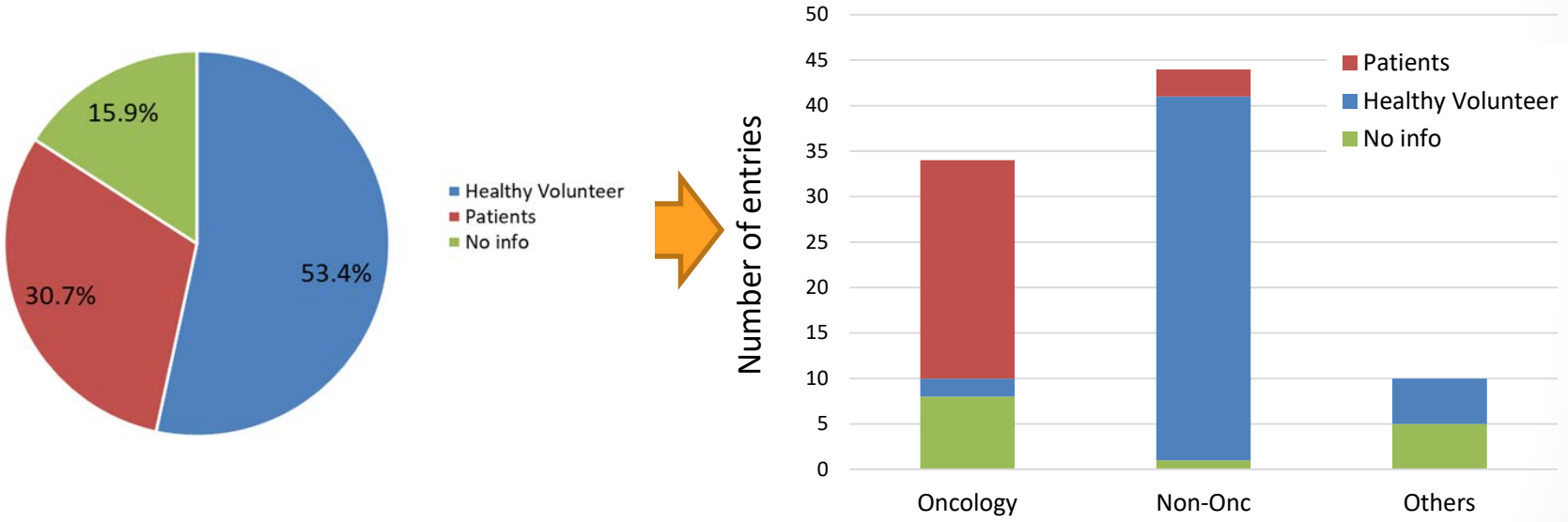


Figure 8. Populations in FIH trial – stratified by oncology and non-oncology therapeutic areas

- Most non-oncology FIH trials in healthy volunteers
  - 91% in healthy volunteers, 7% in patients; 2% no info

Submissions by TA Over Time

- Number and percentage of oncology drugs using MABEL increased over the years
  - Initially (2009-2011), immunology had most (9, 37.5%) FIH trials using MABEL strategy
  - Oncology increased from 17% during 2009-2011, to 33% during 2012-2014, and to 46.5% during 2015 to date

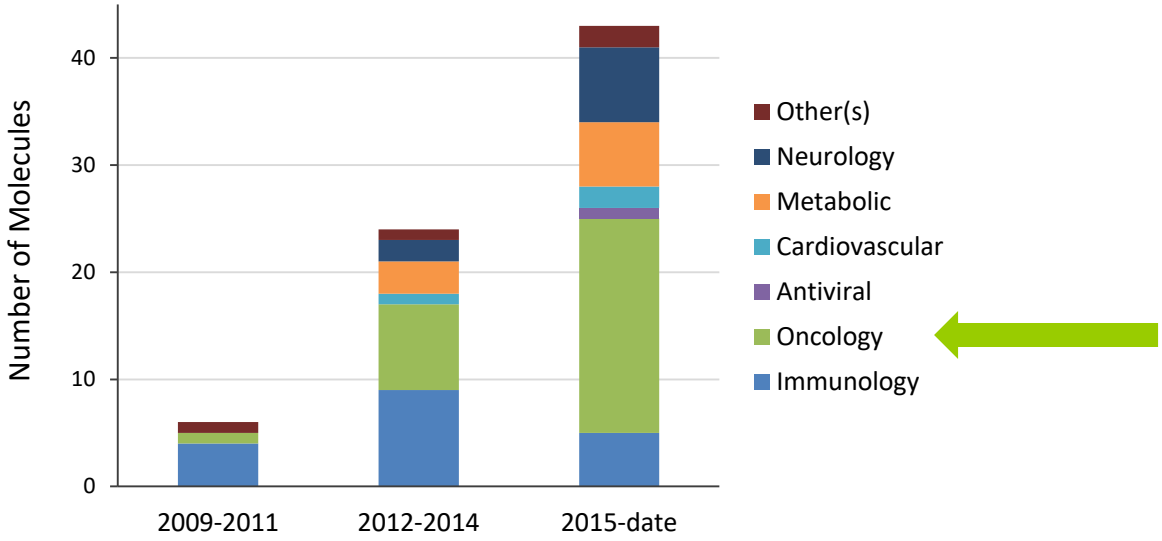


Figure 9. Molecules using MABEL over the years and stratified by TA

Determining MABEL Dose – Overall Approaches

- Data from in vitro and in vivo studies used
- About 8% of cases (of 88 molecules total) used a surrogate molecule, presumably due to lack of pharmacologic activity in animals
- Modeling approaches used based on one or more types of data

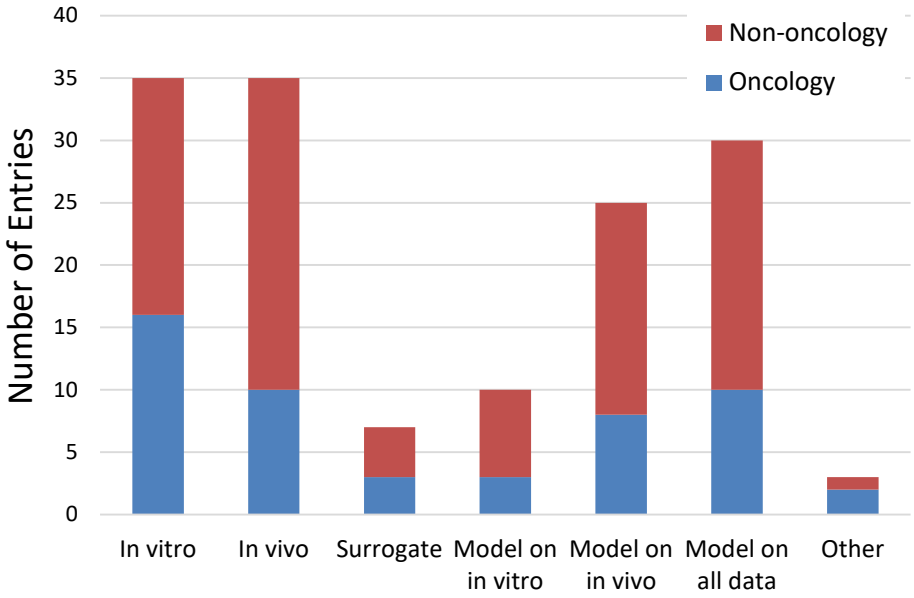


Figure 10. Data sources and methods for determination of MABEL

- When oncology (43% of total) compared with non-oncology
  - More relied on in vitro data and surrogate molecule to determine MABEL

Determining MABEL Dose – In Vitro

- When in vitro data used for MABEL
  - Only 1/3 of cases used what they considered to be most sensitive assay(s)
  - About 1/3 of cases did not use more conservative 0-10% or 11-20% response

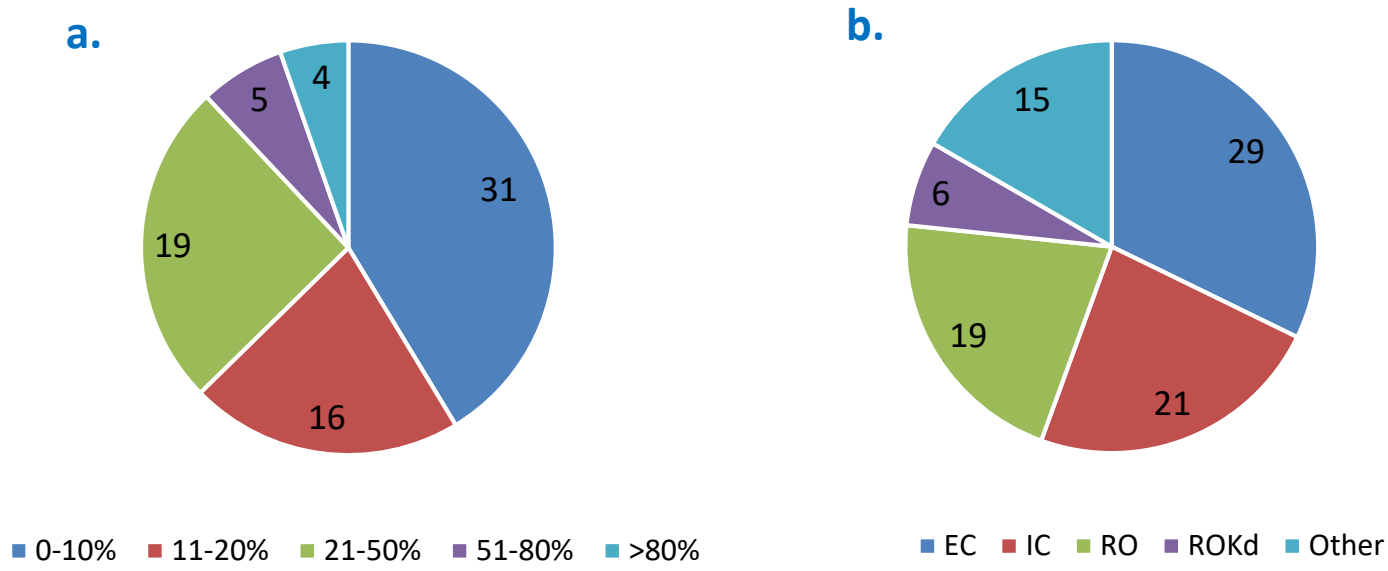


Figure 11. a. Distribution of extent of target engagement or pharmacologic effect b. Type of in vitro assays, EC = effective concentration, IC = inhibitory concentration, RO = receptor occupancy, ROKd = receptor occupancy Kd

Determining MABEL Dose – In Vitro by TA

Table 1. Number of entries (%) using more conservative responses (ie, 0-10%, or combined 0-10% and 11-20%) in different therapeutic areas

	Imm	IO	Onc	Antiv	Cardio	Metab	Neu
Total	29	26	12	1	6	10	9
EC/IC/RO$_{0\text{-}10}$	4 (14%)	3 (12%)	3 (25%)	1 (100%)	5 (83%)	5 (50%)	3 (33%)
EC/IC/RO$_{0\text{-}20}$[1]	9 (31%)	13 (50%)	5 (42%)	1 (100%)	5 (83%)	5 (50%)	6 (67%)
EC/IC/RO$_{21\text{->}80}$	9 (31%)[2]	9 (35%)[3]	4 (33%)	0%	0%	1 (10%)	2 (22%)
No info	11 (38%)	4 (15%)	3 (25%)	0%	1 (17%)	4 (40%)	1 (11%)

Note: 1. Cumulative EC/IC/RO$_{0\text{-}10}$ and EC/IC/RO$_{11\text{-}20}$
2. Two double entries IC$_{10}$ & RO$_{\geq 21}$ were counted as RO$_{\geq 21}$
3. One double entry of EC$_{10}$ & RO$_{>80}$ was counted as RO$_{>80}$

- When stratified by therapeutic area
  - Cardiovascular and Metabolic cases tended to use very conservative EC/IC/RO$_{0\text{-}10}$ (Antiviral only had one case)
  - Immuno-Oncology cases tended to use conservative EC/IC/RO$_{11\text{-}20}$
  - Only a few cases used RO
- Note: not all cases used an in vitro assay or provided information

MABEL Starting Dose vs Clinically-Relevant Dose

- Two < 3-fold cases of total 50 cases – 1 in oncology and 1 in non-oncology
- When desired dose was >100 fold of starting dose
  - Might take longer time to reach clinically-relevant dose
  - Unnecessary exposure to more subjects if trials in healthy volunteers
  - Potential ethical concern if trials in patients with severe/life-threatening diseases

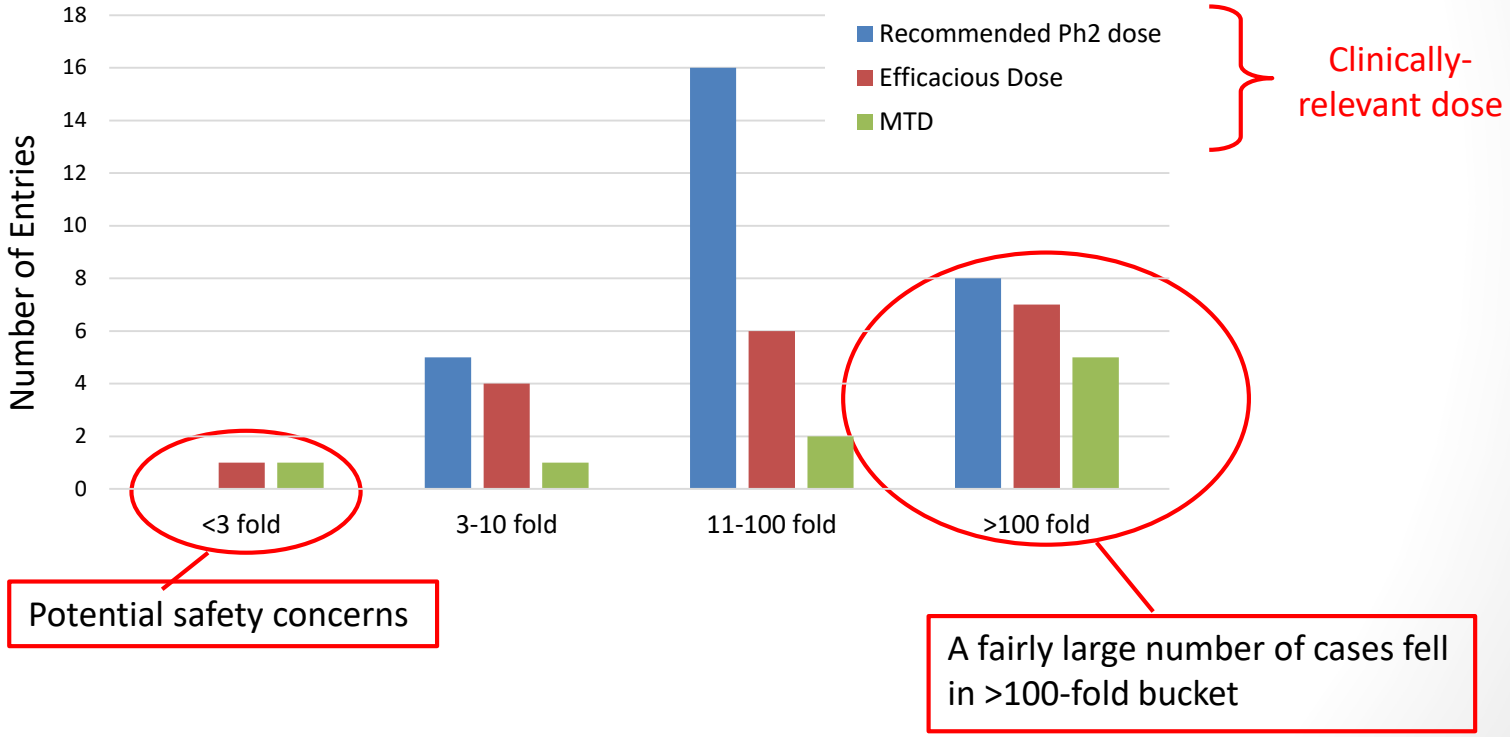


Figure 12. Fold difference between starting dose and clinically-relevant dose

Note: a few molecules entered more than one clinically-relevant dose

MABEL Starting Dose vs Clinically-Relevant Dose – The 100-Fold Bucket

- 17 cases (33%) where clinically-relevant doses were >100 fold of the starting dose
- 8 of these 17 cases (47%) used very conservative 0-10% EC/IC/RO

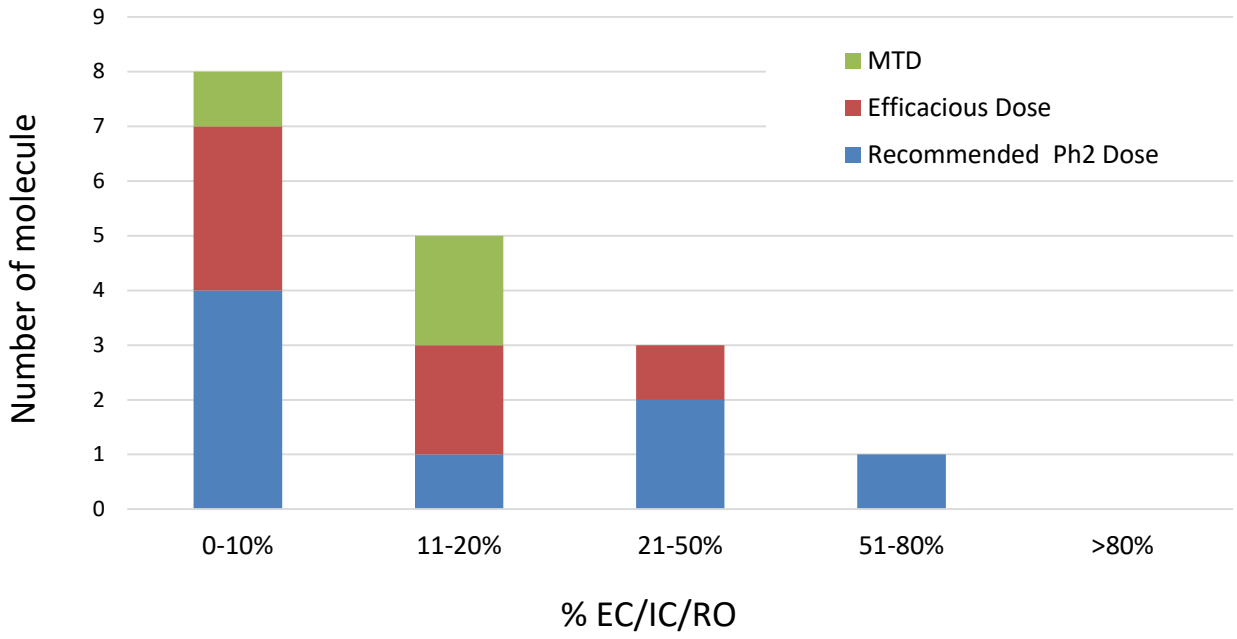


Figure 13. Responses used for MABEL when starting dose was very low (>100 fold)

Number of Cohorts Needed

- Additional survey questions
- Thirteen molecules representing 4 companies provided number of cohorts from starting dose to clinically-relevant dose

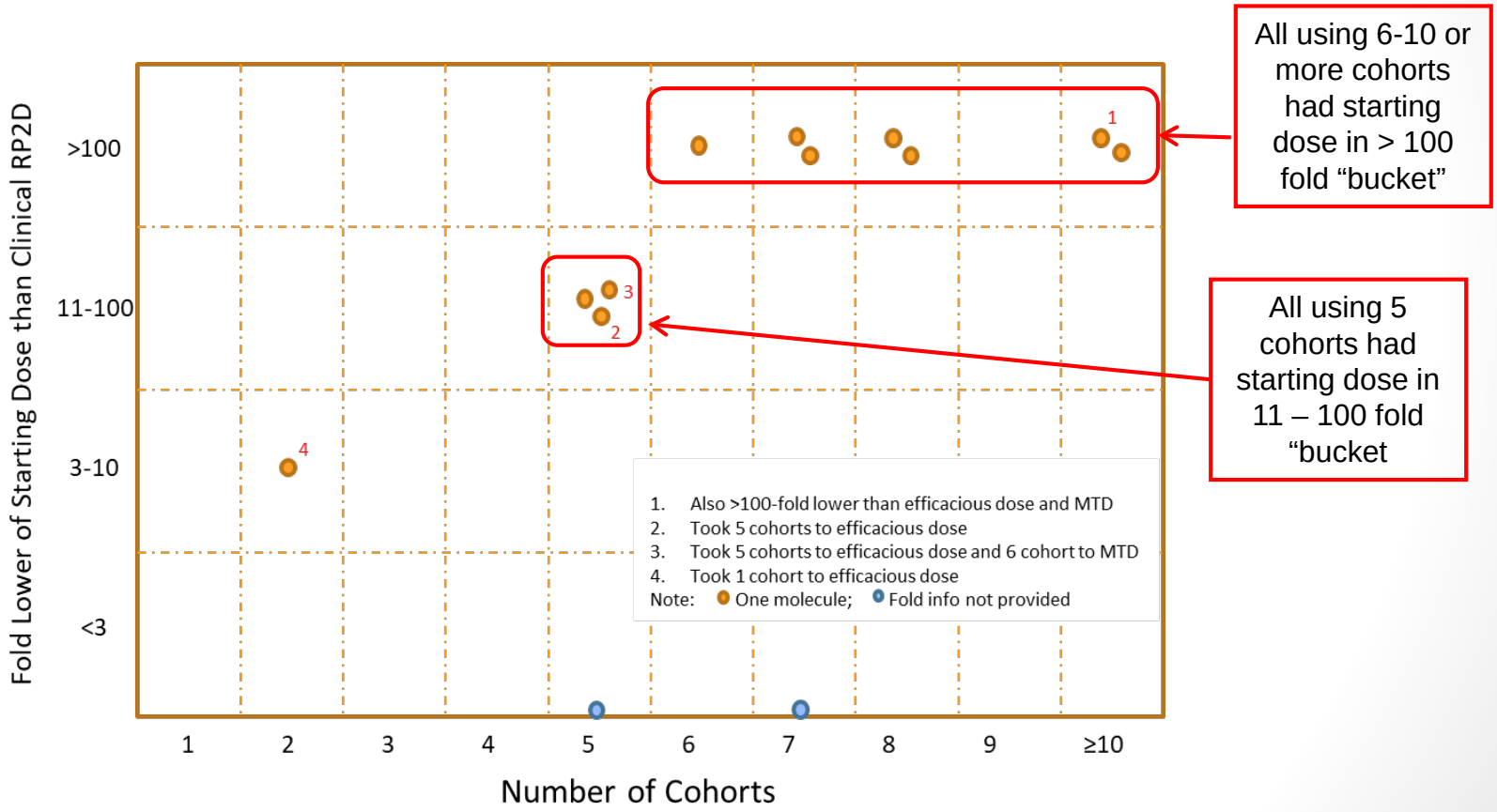


Figure 14. Number of cohorts from starting dose to clinically-relevant dose

Survey Discussion

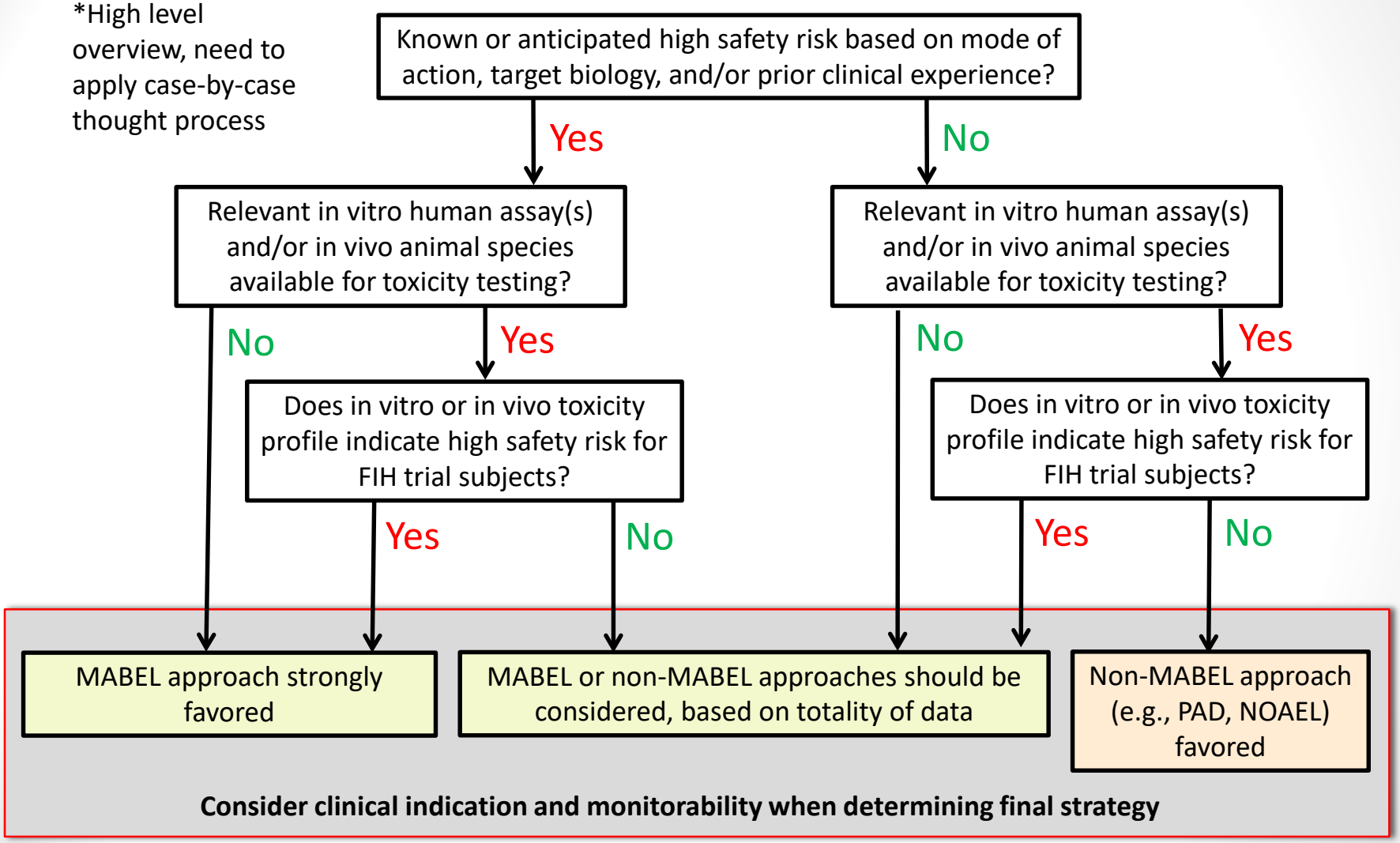
- Strategies for using MABEL developed in many organizations
- Overall acceptance rate by regulatory agencies for FIH program using a MABEL approach has been >95%
- However, MABEL approach may lead to an excessively conservative starting dose
  - Approximately 1/3 of the starting doses were >100-fold lower than clinically-relevant dose (phase 2 dose, efficacious dose, MTD) – raising ethical concerns
  - Limited number of replies suggest many cohorts needed to reach clinically relevant dose
- Two cases had a starting dose <3 fold from MTD or efficacious dose

Considerations for Using MABEL as First-in-Human (FIH) Starting Dose

- **What constitutes MABEL?**
  - Definition of MABEL in WG's view: minimal functional activity that is relevant and meaningful to safety and efficacy of the agent of interest
  - MABEL is not "standardized"
- **MABEL has not incorporated risk:benefit when FIH clinical population is patients**
  - In particular, oncology
- **MABEL-based approaches do NOT address unknown safety risks** (eg, those not directly related to functional activity and/or target biology)
- Based on survey and WG discussions, IQ WG prepared Decision Tree and list of Risk Factors to consider when determining whether to use MABEL approach

Proposed FIH Dose Selection Decision Tree*

*High level overview, need to apply case-by-case thought process



Hope to move decisions away from using MABEL as a default standard

Risk Factors in Selection of FIH Starting Dose – Mode of Action

Risk Factor	Higher Concern	Lower Concern
Mode of Action		
Primary pharmacology	Stimulatory (ie, agonistic action on stimulatory receptor or pathway; antagonistic action on inhibitory receptor or pathway)	Inhibitory (i.e., antagonistic action on stimulatory receptor or pathway; agonistic action on inhibitory receptor or pathway)
Pleiotropic effect	Target is involved in multiple signaling pathways leading to various effects and/or target is ubiquitously expressed	Target is not involved with multiple signaling pathways and/or is narrowly expressed
Amplification effect	Molecule targets a biological amplification cascade and/or bypasses normal control mechanisms (e.g., CD3 or CD28 superagonism)	Does not involve an amplification cascade
Dose Response Curve	Steep	Not steep
Potential for cytokine release syndrome	Mechanism mimics or activates the innate immune system	Mechanism is not associated with innate immune system
Cross-linking	Intended mechanism is to cross-link multiple targets/cells, or the molecule of interest has potential to do cross-linking	Does not cause cross-linking of multiple targets or cells
Fc effector function	ADCC, ADCP, and/or CDC is intended mode of action	Minimal potential for cell killing via ADCC, ADCP, or CDC

Risk Factors in Selection of FIH Starting Dose – Nature of Target

Risk Factor	Higher Concern	Lower Concern
Nature of Target		
Target/mechanism novelty	No prior clinical experience exists for the target of interest, or unknown or partially unknown biology in the case of phenotypic screens	No clinical safety concerns from molecule(s) having same target and mode of action
Target Location	Cellular target, ie, membrane-bound or intracellular	Soluble target in the circulation

Risk Factors in Selection of FIH Starting Dose – Assessment of Nonclinical Toxicity

Risk Factor	Higher Concern	Lower Concern
Assessment of Nonclinical Toxicity		
Availability of animal species for safety assessment of clinical molecule	No relevant animal species identified (leveraging surrogate molecule for hazard identification may be used)	At least one relevant animal species is available (transgenic models may be useful, but need to be well characterized to be considered as possibly supporting lower risk)
Translatability of animal model	Pharmacologic response and sensitivity differs between species and/or has questionable translatability to humans	Pharmacologic response and sensitivity are similar between species and/or considered translatable to humans
Severity of adverse findings	Severely impactful or life-threatening toxicity that occurs with a steep dose-response and/or narrow exposure multiples relative to anticipated clinical exposure	No severely impactful or life-threatening toxicity or such toxicity occurs at exposures that far exceed anticipated clinical exposure
Reversibility of adverse findings	Recovery was not demonstrated or is uncertain or not expected, suggestive of permanent injury	Recovery or trend toward recovery of findings has been demonstrated or, if not investigated, recovery is fully expected
Monitorability of adverse findings	Findings are not monitorable or difficult to monitor comprehensively	Readily able to monitor by clinical signs and/or reliable marker(s)

Risk Factors in Selection of FIH Starting Dose – Clinical Population

Risk Factor	Higher Concern	Lower Concern
Clinical Population		
Disease status	Non-critical, ie, healthy or non-severe disease burden	Critical, ie, terminally or severely ill; no standard of care established

IQ WG Recommendations for MABEL Determination

- **Utilize all relevant in vitro and in vivo information**
  - In vitro data: binding affinity, cellular potency, and RO
  - In vivo data: dose/exposure-response in animal efficacy models
- **Use most relevant assay that reflects in vivo efficacy and safety endpoints as opposed to most sensitive assay**
  - Understand the biology and pharmacology
- **Integrate data, whenever possible, by employing PK/PD modeling-based approaches**
  - Determine dose/exposure-response relationships
  - Evaluate in vitro – in vivo translation
  - Be aware of possible unknown safety factors
- **MABEL approach is only one of many tools that can be used to determine FIH starting dose**
  - Should not be used as default
  - Case by case thought process

Thank you!

Questions and Comments?