MABEL-Based Approach for First-in-Human Starting Dose Selection

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Disclaimer

The opinions expressed in this presentation are those of the presenter and do not necessarily reflect official support or endorsement by the Food and Drug Administration

Abstractions

AE: adverse events

FIH: first-in-human

HED: human equivalent dose

HNSTD: highest non-severely toxic dose

ICH: International Council on Harmonization

MABEL: minimal anticipated biological effect level

MOA: mechanism of action

MRSD: maximum recommended start dose

MTD: maximum tolerated dose

NOAEL: no adverse effect level

OBD: optimal biologic dose

RP2D: recommended Phase 2 dose

STD_{10}: severely toxic dose in 10% of animals

Overview

- Goals of studies intended to support FIH clinical trials

- General approaches for calculating MRSD

- MABEL-based MRSD calculation

- FIH dose selection for immune activating products and CD3 bispecific constructs

- Conclusions

Goals of Nonclinical Studies

- Evaluate pharmacologic properties

- Estimate a safe initial dose level for the first human exposure

- Evaluate the toxicological and toxicokinetic profiles of a pharmaceutical to provide recommendations to clinical protocols

  - identification of target organs, dose-limiting toxicities, exposure (dose)-response relationships and reversibility, monitoring

- Assess potential toxicities that cannot be identified in clinical trials

- Provide recommendations for labeling

Prior to First-in-Human Exposure

- Pharmacodynamics/Pharmacokinetics

- Safety pharmacology core battery

- General toxicology studies (single/repeat dose, rodent and non-rodent, study design dictated by proposed clinical trial)

- Genetic toxicity (*in vitro* studies for mutagenesis and clastogenesis) – for trials in healthy volunteers

- Local tolerance

Relevant ICH Guidances

- ICH M3(R2): "Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals"

- ICH S6(R1): "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals"

- ICH S9: "Nonclinical Development of Anticancer Drugs and Biologicals"

Key Elements Needed for MRSD Selection

- Determine the NOAEL/HNSTD/STD$_{10}$
  - Convert to HED, if needed
- Select the most sensitive species or most relevant for assessing human risk
- Apply appropriate safety factors to increase assurance of safety for the FIH dose
  - Examples: 1/10 NOAEL (healthy volunteers), 1/6 HNSTD or 1/10 STD$_{10}$ (patients with cancer)

Challenges of Toxicology-Based MRSD Calculation

- In certain cases, a pharmacological-based approach for MRSD determination may be more appropriate
  - Lack of relevant species
 - Intended pharmacological effects in humans not observed in test species

- **ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals**
  - *"For biopharmaceuticals with immune agonistic properties, selection of the start dose using a minimally anticipated biologic effect level (MABEL) should be considered."*

- **EMA Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products**
  - *"For investigational medicinal products for which factors influencing risk … have been identified, an additional approach to dose calculation should be taken. Information about pharmacodynamics can give further guidance for dose selection. The 'Minimal Anticipated Biological Effect Level (MABEL) approach is recommended."*

MABEL

- Definition: *"The MABEL is the anticipated dose level leading to a minimal biological effect level in humans"*

- In general, MABEL can be used to determined a starting dose when conventional toxicology testing may not be sufficient to predict serious adverse reactions in clinical trials

Estimation of MRSD Based on MABEL
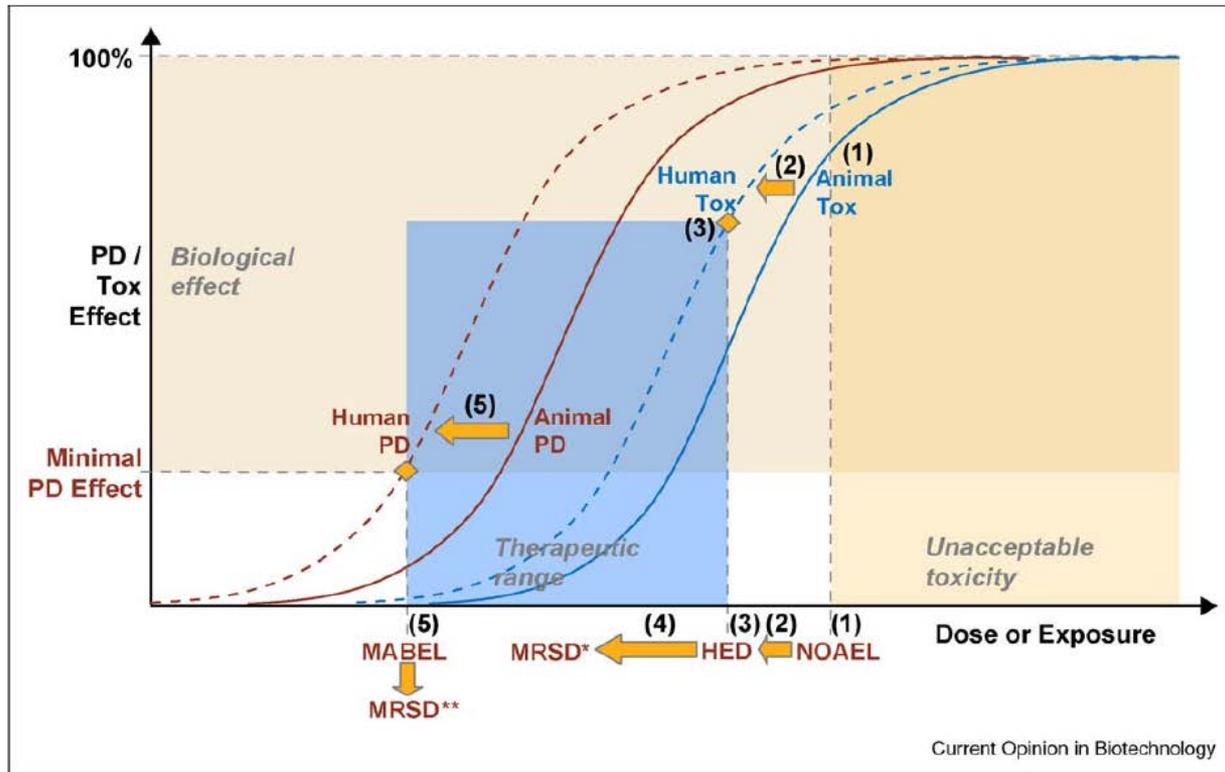
Muller PY et al., Current Opinion in Biotechnology 2009;20:722-729.

Why MABEL?
TGN1412 and Cytokine Release Syndrome

- TGN1412 is an anti-CD28 IgG4 mAb

- In animals, TGN1412 caused expansion of T regulatory cells without toxicity

- In 2006, TGN1412 (0.1 mg) was administered to 6 healthy volunteer subjects by IV infusion (3-6 minutes) 10 minutes apart at 1/500th of the highest dose tested in monkeys

- Near fatal systemic inflammatory response characterized by rapid cytokine release occurred approximately 1 hour post-infusion

MABEL

- Proposed by the Association of the British Pharmaceutical Industry (ABPI)/Bioindustry Association (BIA) Early Stage Clinical Trial Task Force (2006)

- Relatively safe dose with some level of pharmacology activity

- No single method for calculation

- Use all available data
  - Binding endpoints (e.g., binding affinity, receptor occupancy)
  - Functional endpoints (e.g., cytotoxicity, cytokine release, immune cell activation, intracellular signaling)
  - Pharmacokinetic modeling

MABEL – General Factors to Consider

- Mode of action
  - Novelty of pharmaceutical and target
  - Plausibility and extent of knowledge of MOA
  - Concentration/dose-response
- Pharmacology of the target
  - Tissue distribution and pharmacology of the target in normal and pathological states
- Relevance of animal models
  - Compare available data in animals species to humans
  - Degree of species-selectivity for both target binding and FcγR binding
- Patient population
  - Minimize dosing at sub-therapeutic levels in patients

Calculating a MABEL

- There is no universal approach for determining a FIH dose based on a MABEL

- Examples for supporting data:
  - *In vitro* pharmacology data from target cells from human and toxicology species
    - Evaluation of MOA (agonistic vs antagonistic activity), potential for cytokine release, receptor occupancy, concentration response data
  - If using animal data, then provide a comparison of
    - Animal-human differences in exposure/drug distribution, differences in expression level and distribution of target, and affinity of target binding and intrinsic efficacy
    - Duration and reversibility of biologic effect
    - Dose-exposure relationship (PK/PD)

Clinical Protocol Considerations

- Clinical trial population

- Number of subjects per cohort (e.g., single-patient cohorts at potentially sub-therapeutic levels)

- Time interval between dosing subjects within the same cohort (e.g., staggered enrollments within cohort)

- Dose escalation increments (e.g., accelerated titration may be acceptable on a case-by-case basis)

- Criteria and time interval for escalation to next cohort (e.g., extended observation period for dose limiting toxicities)

- Clinical trial site (availability of treatments for medical emergencies and intensive care unit facilities)

FDA Retrospective Analysis of Oncologic Immune Activating Products

- Aim of analysis
  - Feasibility of common FIH dose selection approaches
  - Utility of animal toxicology studies
  - Length of time to complete Phase 1 trials

- 27 products selected
  - CD3 bispecific constructs excluded
    - Low number of products, structural heterogeneity, differences in dosing regimen

Saber H et al. 2016, Regul Toxicol Pharmacol, 81:448-456.

Methods

- Product characteristics
  - Monospecific mAb
    - IgG1 (n = 18), IgG2 (n = 3), IgG4 (n = 5)
  - Trimeric mAb (IgG4, n = 1)
  - Target antigens
    - PD1, PD-L1, CD40, GITR, OC40, OX40L, CD33, CD38, CD19, CD137 (4-1BB), c-fms, B7 family member antigen, CTLA-4

- Data collected
  - In vitro activity (EC_{50}), in vitro binding (K_D), toxicology data, clinical data (MTD, OBD, RP2D, AE)

Summary of analysis

- All MABEL approaches resulted in FIH dose that were considered to be reasonably safe

- Did not identify any one activity assay that was the most sensitive

- FIH doses based on 20-80% receptor occupancy (RO) had acceptable toxicities; doses above saturation also had acceptable toxicities except for Fc-modified antibodies with increased ADCC activity

- FIH doses based on 1/6th the HNSTD or 1/10th the NOAEL in toxicology studies resulted in unsafe doses

- Optimization of FIH dose selection and/or dose-finding trial design is needed to minimize patient exposure to sub-therapeutic doses

- Consider intra-patient dose escalation when FIH doses are ≤50% RO or single patient dose escalation that switches to 3+3 dose escalation at doses anticipated to cause receptor saturation

FDA Analysis of CD3 Bispecific Constructs

- Aim of analysis
  - Feasibility of pharmacology and toxicology-based FIH dose selection approaches
  - Utility of animal toxicology studies

- 17 products selected

Saber H et al. 2017, Regul Toxicol Pharmacol, 90:144-152.

Methods

- Product characteristics
  - MWs≈ 50 kDa- 190 kDa
  - Ab IgG structures
    - Comparable to natural IgGs; monovalent binding for each antigen (~150 kDa)
    - With added fragments (> 150 kDa); e.g., monovalent binding for one antigen and divalent binding for the other antigen
  - Ab fragments
    - Fusion proteins linking scFv regions
  - Second antigens:
    - CD19, CD20, CD123, CD33, CEA, p-cadherin, PSMA, Her2-neu, B7H3, gpA33, EPCAM
- Data Collected
  - In vitro activity (EC_{50}), in vitro binding (K_D), toxicology data, clinical data (MTD, OBD, RP2D, AE)

Product Characteristics

Molecular weight		
50- 105 kDa n = 6	106-150 kDa n = 9	151-190 kDa n = 2
35%	53%	12%

Format			
No Fc n = 5	With Fc n = 12		
	IgG1 n = 8	IgG2 n = 2	IgG4 n = 2
29%	47%	12%	12%

Summary of Analysis

- Core in vitro activity studies
  - T-cell proliferation and activation, CRA, cytotoxicity, and effector function
  - Wide range of EC50s
- FIH doses at 10%-30% PA were acceptable for all products examined.
  - Setting a FIH dose based on 10%-50% PA using the EC_{50} from the most sensitive assay resulted in acceptable doses for all except one construct.
- Drug-related toxicities were observed in studies in pharmacologically-relevant species showed toxicities
- Unsafe to use toxicology data to set the FIH dose
- Unsafe to set FIH dose based on RO
  - Doses corresponding to 10% RO were above the human MTD for several INDs

Ongoing Project

- Collaboration with HESI Immunotoxicology Committee to evaluate FIH dosing of immunomodulators, including evaluation of the MABEL approach for immuno-oncology agents and CD3 bispecific constructs

    – Collection of data from sponsors and literature for current approaches for FIH dosing

    – Determine best practices for FIH starting dose selection

Overall Summary

- FIH start dose selection strategies are highly dependent on drug target and construct, and clinical trial population

- A pharmacology-based approach for MRSD calculation may be more appropriate in cases where toxicology evaluation may under-predict clinical toxicity

- There is no single method for MABEL estimation

- MABEL-based MRSD calculation should be based on the totality of data
  - Mechanism of action, nonclinical data (pharmacology, PK, toxicology), literature assessment, human experience with similar products

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