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First-in-Human (FIH) Trial Design Considerations for Small Molecule and Biological Drug Candidates

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Outlines

1 Overview of Drug Development

2 Considerations of FIH Trial Design

3 FIH Submission Review Process

4 Take Home Messages

Overview of Drug Development

Five critical steps in drug development process:

- **Step 1: Discovery and Development**
- **Step 2: Preclinical Research**
- **Step 3: Clinical Development**
- **Step 4: Regulatory Review**
- **Step 5: Post-market Safety Monitoring**

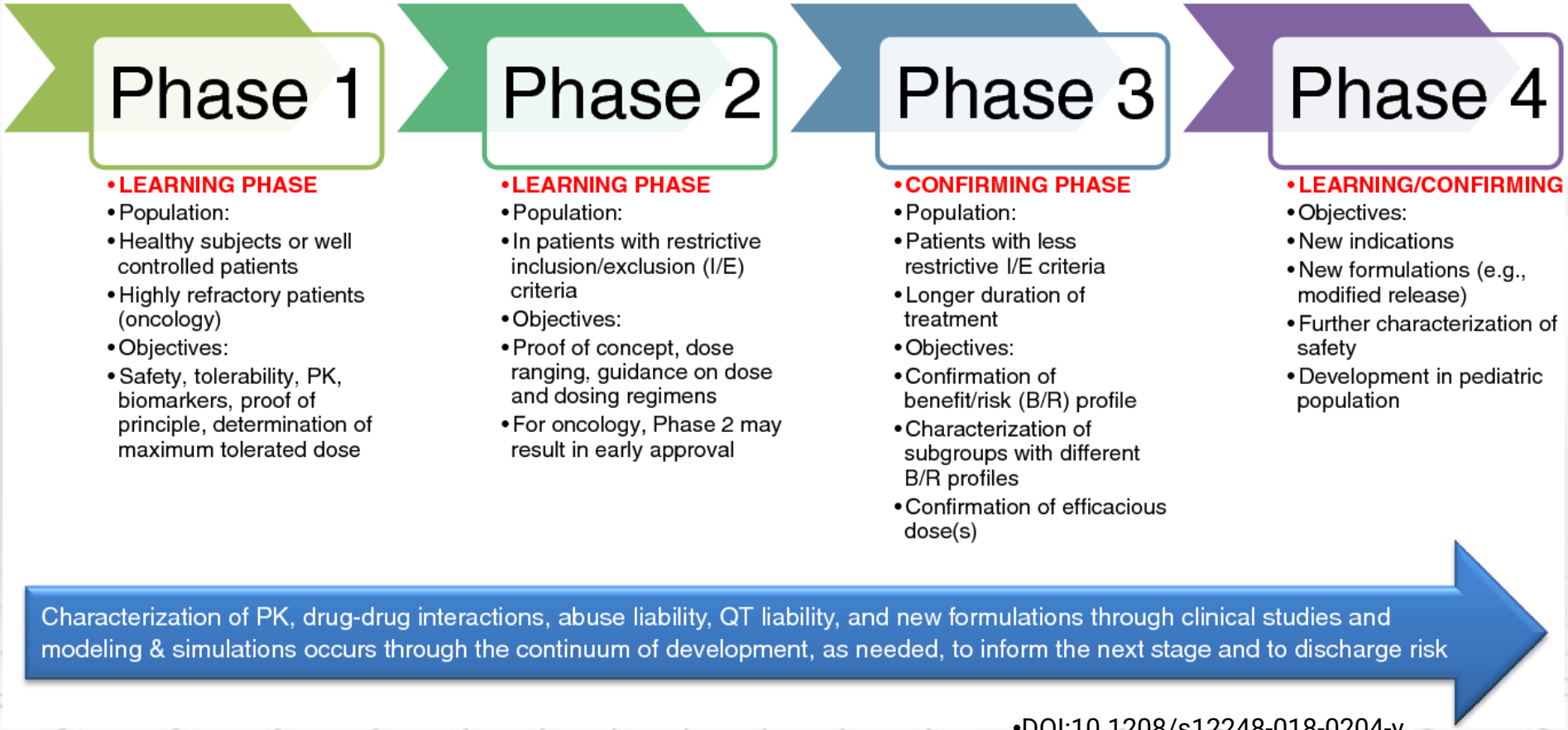
What is (are) the objective(s) of FIH trials?

a) To determine the safety or tolerability margins

b) To characterize a compound's pharmacokinetics (PK)

c) To help determine the potential effective concentration or dose for Phase 2 trial

d) All of the above



•DOI:10.1208/s12248-018-0204-y

First-In-Human (FIH) Trial

• Randomized, placebo-controlled, healthy volunteers, except for life-threatening diseases (not be ethical to use placebo control; not be ethical to recruit healthy volunteers - open label, single arm, dose escalation study designs in patients)

• Starting dose determined by preclinical toxicology studies (rodents and non-rodents)

• Information gained:

– Safety/tolerability, identify maximum tolerated dose (MTD) ; for oncology, to define the recommended phase 2 dose (RP2D)

– PK characteristics, variability, linearity, dose proportionality

– if multiple-dose stage included: PK at steady-state

– PD; potential effective concentration/dose

FIH Trials

- Population selection
- Study design
- Dosing selection
- Safety monitoring
- Risk management

Population Selection

FIH trials can be conducted in both healthy volunteers and patients

- For non life-threatening diseases: Healthy volunteers
  - speed of recruitment
  - ease of scheduling cohorts
  - homogenous → reduce response variation and isolate effects

- For life-threatening diseases and drug with narrow therapeutic windows: Patients – b/c ethical & toxicity issues
  - E.g. Enroll patients with all disease types who have exhausted available anti-cancer therapy; Biomarker-driven trials (rapid, inexpensive genomic testing)

Population Selection

- Do not copy/paste from other trials!
  - Inclusion/exclusion should be study directed
  - Disease type
  - Prior treatment
  - Age, sex, organ function and other variables
  - Measurability and disease status

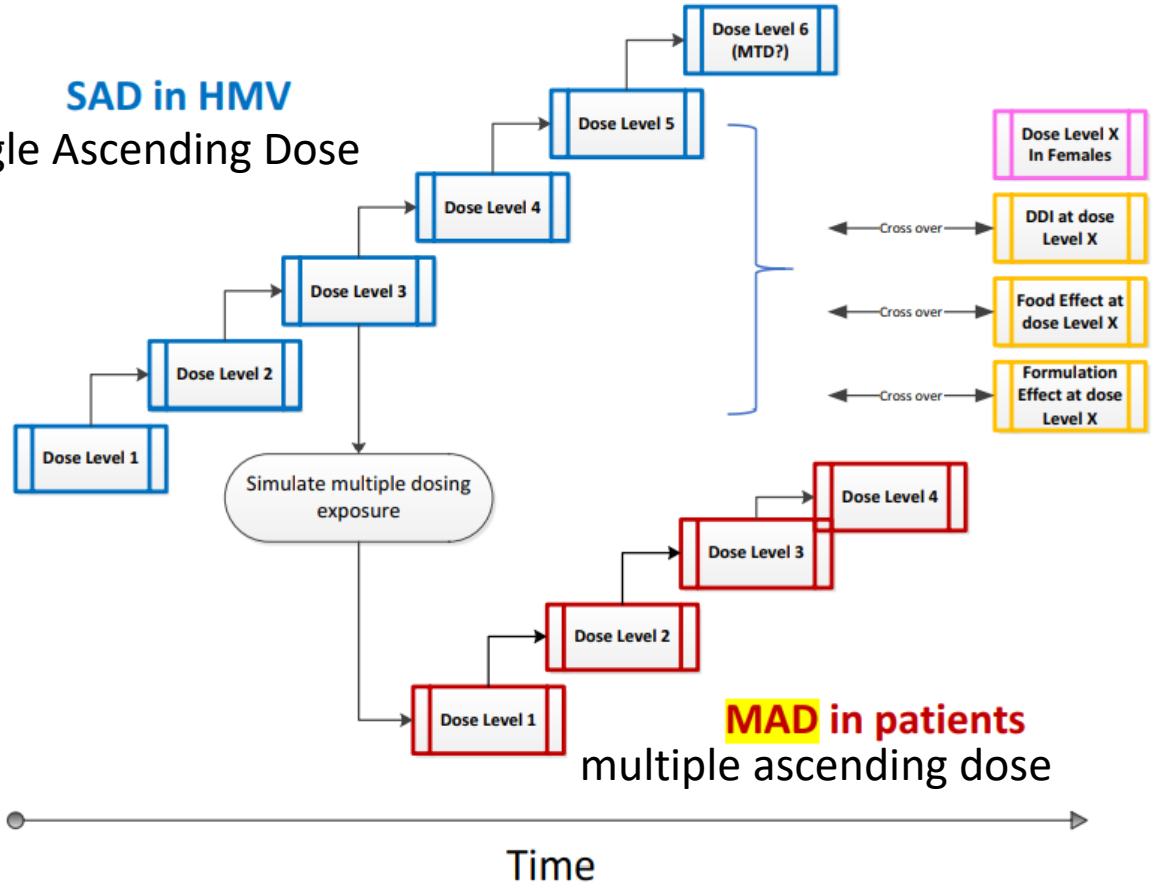
- Each selection criterion should be based on a sound scientific, medical, ethical rationale

Study Design

- SAD only
- SAD/MAD combo --- SAD + a separate staggered MAD) study in parallel but lagging behind

<u>Predefined implementation of restrictive start and stop criteria is needed</u>

- SAD+ Sex/Food/Formulation/DDI



Study Design for Oncology

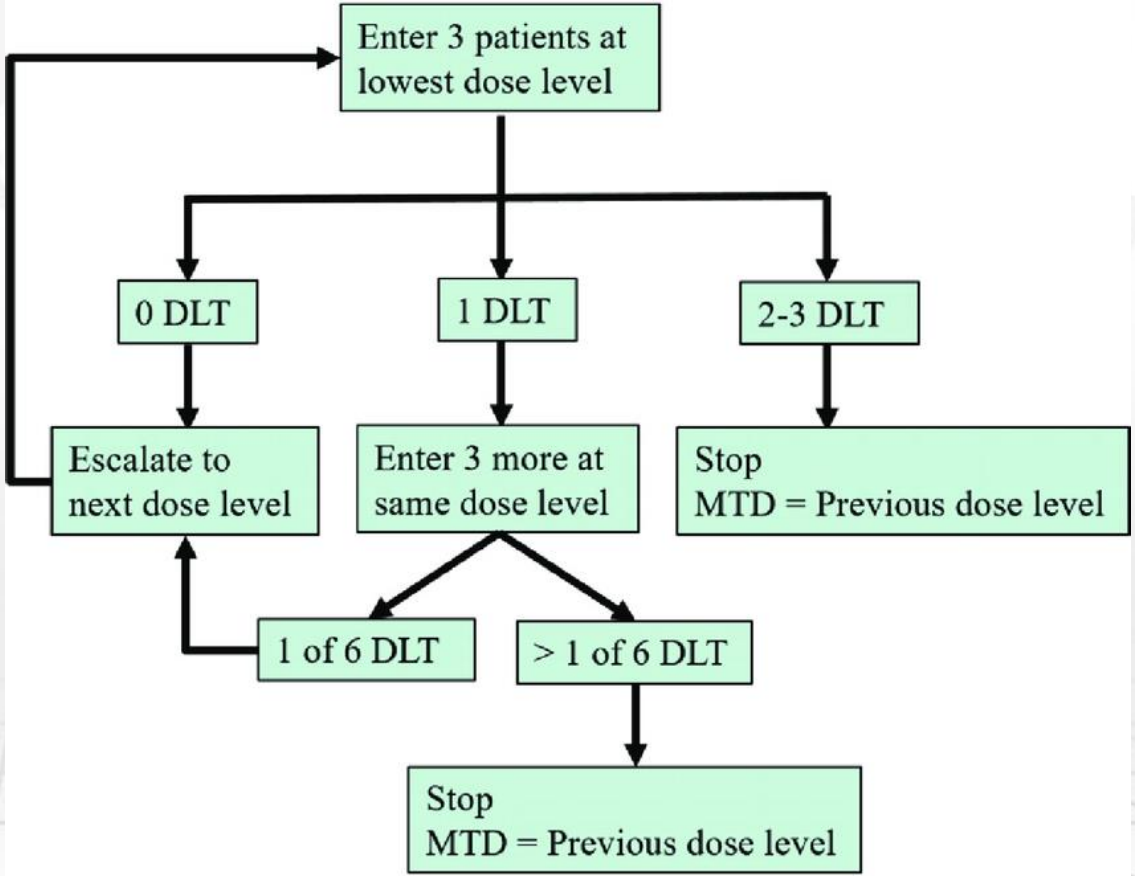
Rule-based:

- **Traditional 3+3 Design**

The estimated MTD is the highest dose level with observed toxicity rate less than 0.33

- Other variations of this design have been implemented, including “2+4,” “3+3+3,” and “3+1+1.”
- Pharmacologically guided dose escalation

Cons: inefficient in establishing the dose - only 35% of patients are treated at optimal dose levels



Design for Oncology

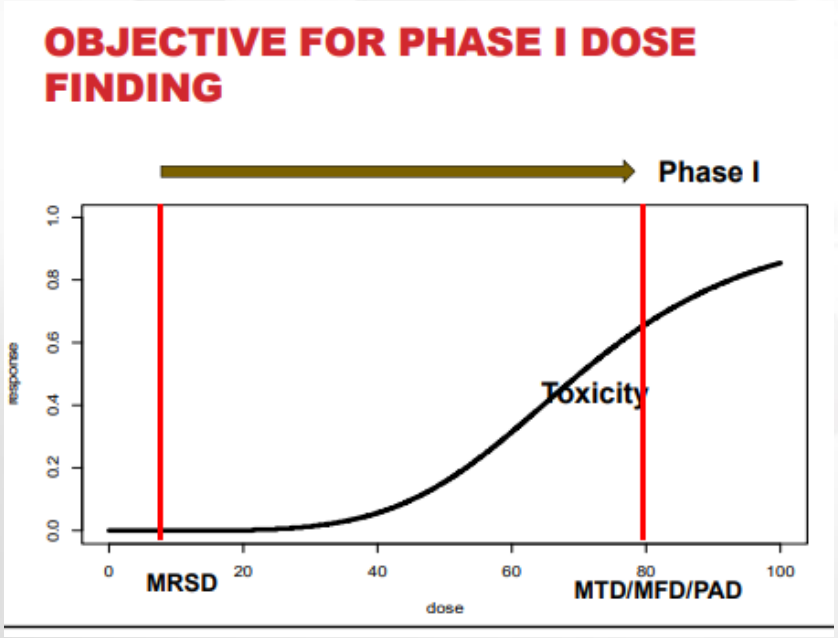
Model-based:

Use statistical models to assign dose levels based on a prespecified probability of DLT by using data from all enrolled patients to compute a more precise dose-toxicity curve.

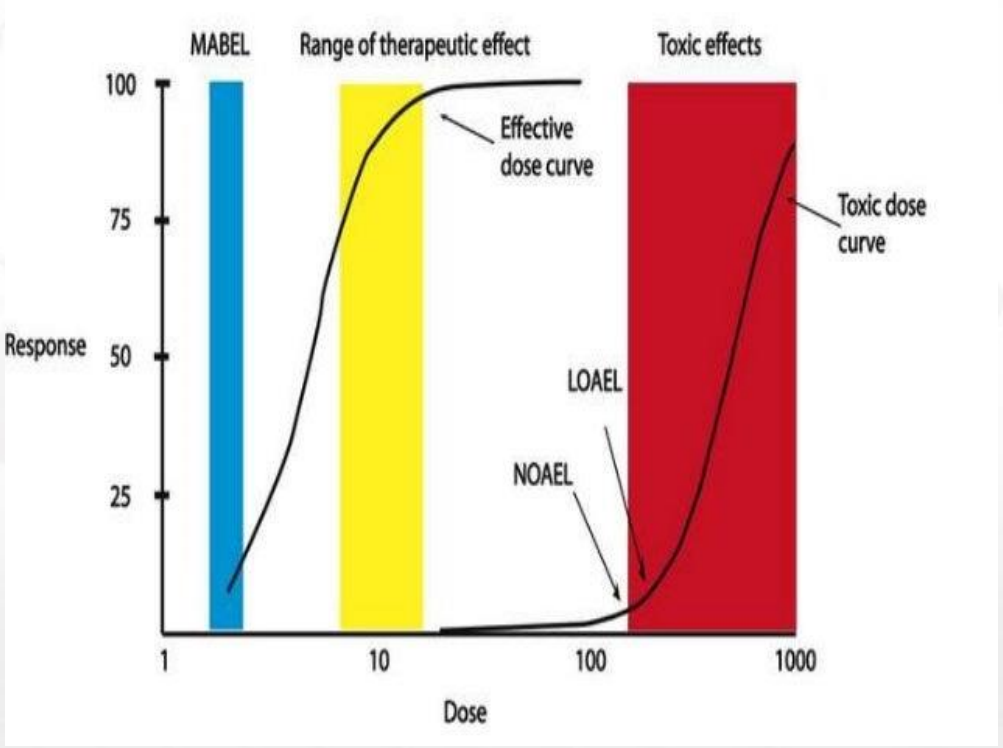
Adaptive Bayesian model-based methods:
Continual reassessment method (CRM)
Escalation with overdose control
Modified CRM that utilizes time-to-event end points for handling late-onset or CRMs.

For high risk compounds: use of sentinel subjects in FIH design is recommended. Dosing a limited number of subjects (often only one with an active compound) before the remainder of the cohort minimizes overall risk and is recommended by EMA and FDA

OBJECTIVE FOR PHASE I DOSE FINDING



MRSD: Max. Recommend Starting Dose
MTD: Max. Tolerated Dose
MFD: Max. Feasible Dose
PAD: Pharmacologically Active Dose



MABEL: minimal anticipated biological effect level
NOAEL (No Observed Adverse effects Level)
LOAEL (Lowest Observed Adverse effects Level)

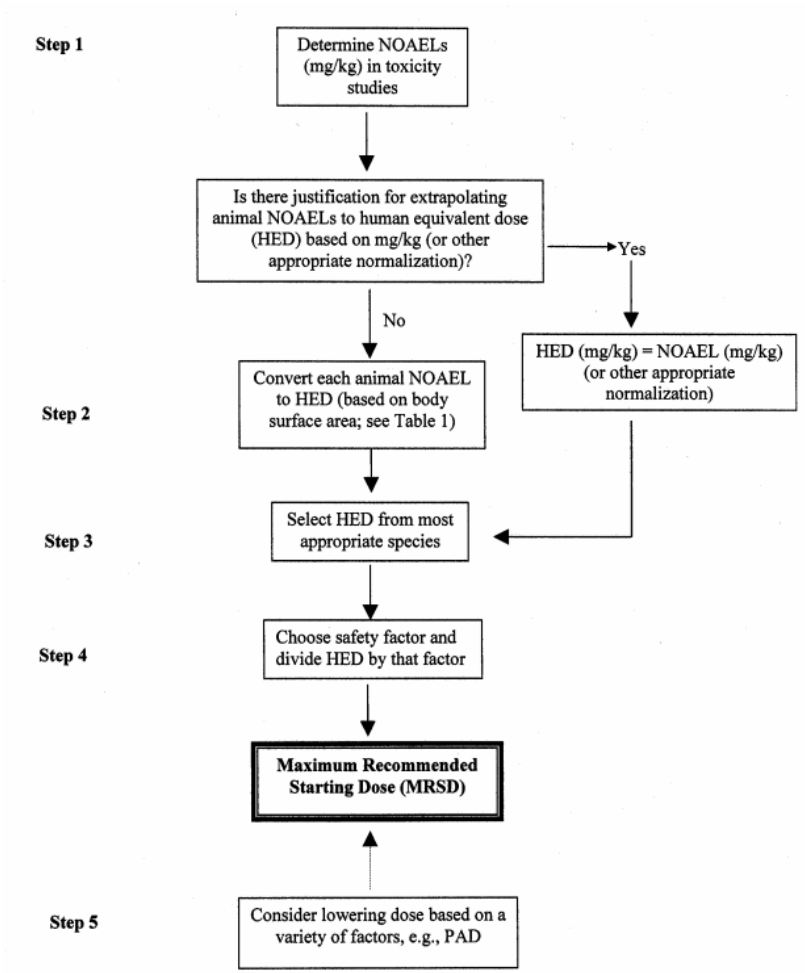
Dose Selection

ESTIMATING THE MRSD-METHODS

1) NOAEL (No Observed Adverse effects Level) Method
2) MABEL (Minimal Anticipated Biological Effect Level) Method
3) Similar Drug Comparison Method
4) Pharmacokinetic (PK) Guided Approach
5) PK/PD Modelling Guided Approach

- For most systemically administered small molecules, interspecies scaling of the animal doses to an equivalent human dose is usually based on normalization to body surface area
- For both small molecules and bio-products, interspecies scaling based on body weight, AUC, or other exposure parameters might be appropriate
- For biopharmaceuticals with immune agonistic properties, selection of the start dose using MABEL should be considered

Selection of Maximum Recommended Starting Dose for Drugs Administered Systemically to Normal Volunteers



Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

- The NOAEL method is based on selecting a dose with **minimal risk of toxicity**, rather than selecting one with minimal pharmacologic activity in humans.

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:

HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, and stumptail.

Guidance for Industry (fda.gov)

Dose Selection for Oncology Drugs

- Should have a pharmacologic effect and be reasonably safe to use
- Starting dose: 1/10th of the lethal dose for mice (LD10), or 1/6th of the highest non-severely toxic dose (HNSTD) in a more sensitive species (e.g. monkey)
- Both rodent and non-rodent models are used for preclinical safety assessments, but it has been demonstrated that non-rodent models may be better at predicting MTD in humans
- Modified Fibonacci is often used: • (x, 2x, 3x, 5x, 7x, 9x, 12x, and 16x) or • Increase of (100, 65, 50, 40, and 30% thereafter
- For drugs having a high risk of adverse events in humans, EMA has recommended using the minimal anticipated biological effect level (MABEL), which incorporates all in vivo and in vitro data to calculate the anticipated dose that will have a biological effect in humans

Other Approaches

Similar drug Comparison Approach

- This may be used when human PK/PD data are available for a drug similar to the one under investigation
- The dose of the investigated drug can be calculated from the dose of the reference drug: Dosei = Doser NOAELi / NOAELr
- The dose obtained is usually corrected by an arbitrary safety factor to accommodate uncertainty.

PK guided approach

- Assume (1) Only the parent compound is active, and (2) The drug shows equal pharmacological activity or toxicity in human and nonhuman animal species at equal plasma concentrations
- The NOAEL and corresponding AUC in several animal species are determined and the species that results the lowest NOAEL is used as the index species for scaling
- The starting oral dose can be calculated using a correction factor - obtained by dividing the clearance of the chosen species by the predicted human clearance.

PK/PD Modelling Guided Approach Calculations based on:

- Animal pharmacokinetic data
- Administered doses
- Observed toxicities
- Algorithmic calculation

Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer Guidance for Industry

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For questions regarding this draft document, contact Brian Booth at 301-796-1508.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)

August 2021
Clinical Pharmacology/Clinical

II. PK-BASED APPROACH

A PK-based approach relying on population-PK (Pop-PK) modeling and simulation can be applied to support the approval of alternative dosing regimens for a PD-1 or PD-L1 blocking antibody that is already approved based on clinical efficacy and safety trials. The Pop-PK model should be established with sufficient PK data from all indicated patient populations over a wide range of dosing regimens (i.e., different from the alternative dosing regimens). The model itself should be well validated and determined to be fit for the purpose. Refer to the FDA Pop-PK draft guidance for recommendations about Pop-PK models.[2] Simulation can be performed to derive the PK profiles and parameters following the alternative dosing regimens.

An application for an alternative dosing regimen of a PD-1 or PD-L1 blocking antibody based on modeling and simulation should have the following features:

- The reference dosing regimen used for the comparison is the one used to establish efficacy in clinical trials.
- Both average AUC and C_{trough} following the alternative dosing regimen at steady state and/or in the first dosing cycle are no more than 20% lower compared to those of the reference dosing regimen.
- Average steady state C_{max} following the alternative dosing regimen does not increase more than 20% compared to that of the reference dosing regimen unless there is adequate clinical evidence that the average steady state C_{max} for the new regimen is unlikely to be associated with an unacceptable safety profile (e.g., safety already demonstrated at higher doses; flat or shallow exposure (dose)-safety relationship).

If the features described above are not present, additional clinical data to support the efficacy and safety with the new regimen may be needed. The nature of such clinical data may depend on the specific product under development, patient population and pre-existing clinical and clinical pharmacology data. The sponsor should discuss alternative pathways of development with the appropriate review division.

Method	Advantages	Disadvantages
MRSD approach (dose-by-factor)	Good safety record, easy to calculate	Empirical approach based only on dose, arbitrary safety factor applied, neglects pharmacological activity, and dose escalation
Similar MOA	Easy to use; minimal data required	Only applicable to a limited number of drugs, does not account for differences in PK or PD between the two drugs
MABEL	Based on pharmacology rather than an empirical scaling factor; safest approach for high-risk drug candidates with a high degree of species-specificity or targeting the immune system	Requires more extensive nonclinical data; unclear which nonclinical model/data is most predictive
PK model	Accounts for species differences in PK parameters rather than empirical scaling of dose; ability to calculate safety margins; demonstrated to work well for compounds that are eliminated renally and monoclonal antibodies with linear elimination	Neglects species differences in pharmacology (assume concentration-effect relationship is the same for animals and humans); dependent on accuracy of nonclinical PK and scaling approach
PKPD model	One step further than the PK-guided approach in that it accounts for species differences in both PK and PD; accounts for pharmacologic activity and can support dose escalation	Requires an experienced modeler and extensive nonclinical data

FIH, first-in-human; MABEL, minimum anticipated biologic effect level; MOA, mechanism of action; MRSD, maximum recommended safe starting dose; PD, pharmacodynamic; PK, pharmacokinetic.

Design and Conduct Considerations for First‐in‐Human Trials (nih.gov)

Highest Dose and Duration

- The highest dose or exposure tested in the nonclinical studies does not limit the dose escalation or highest dose investigated in a clinical trial in patients with cancer. When a steep dose- or exposure-response curve for severe toxicity is observed in nonclinical toxicology studies, or when no preceding marker of severe toxicity is available, smaller than usual dose increments (fractional increments rather than dose doubling) should be considered

- In Phase 1 clinical trials, treatment can continue according to the patient's response, and in this case, a new toxicology study is not called for to support continued treatment beyond the duration of the completed toxicology studies.

Sample Size

- General rule : phase 1 trials require a low number of subjects, **typically 12-20 subjects**
- The exact number of subjects will depend on the dose levels to be tested (determine the MTD)
- Phase 1 trials do NOT need a formal sample size calculation (in contrast with phase 2 and 3 studies)

Safety Monitoring

Why is safety monitoring required in all clinical trials?

To Ensure Subject Safety and Study Integrity

Dose Limiting Toxicities

- **Guide Dose escalation, de-escalation, and MTD determination**

- **Consider:**
  - Healthy volunteers vs. patients
  - Monitoring: outpatient or hospital ICU
  - Continuous dosing, drug with long ½, delayed responses may need extended observation period

- **Criteria:**
  - Healthy Volunteers: grading are included in the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials at https://www.fda.gov/media/73679/download
  - Cancer Patients: National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) scale for grading adverse events (AEs)

  Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP (cancer.gov)

  Pre-defined clinical stopping criteria is needed in FIH protocol!

Severe Adverse Event (SAE)

- SAE is any untoward medical occurrence at any dose:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Is a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
  - A birth defect
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Toxicity Management

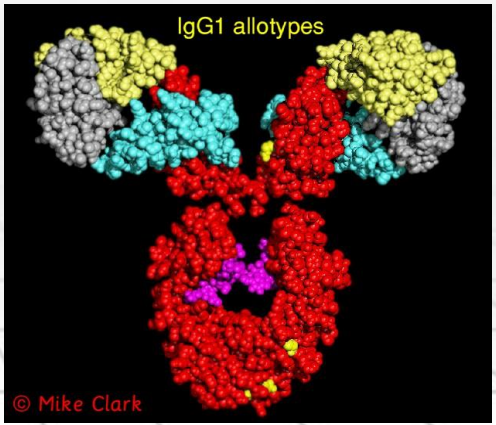
- **What modifications are incorporated to avoid or minimize the risk or severity of toxicity?**
  - Dose reduction
  - Dose delay
  - Dose omission
  - Supportive care (prophylaxis, intervention, secondary prevention)
  - Discontinuation of individual treatment (withdraw)
  - Termination from the study (specify Stopping criteria!)

Key Elements for Biologics

Biologics

- **Biological Product-** “A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypepetide), or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings”

- Therapeutic biological products were transferred from CBER to CDER in 2003



Differences in Pharmacology

Biologics vs. Small Molecules

Biologics

- Highly targeted
- Species specific
- Relevant animal model
- Proteolytic degradation
- Immunogenic
- Exaggerated pharmacology
- Delayed and prolonged PD

Small Molecules

- Less targeted
- Species-independent
- Active in many species
- Specific mechanism
- Metabolism
- Non-immunogenic
- Toxicity from parent drug or metabolites
- Exposure-Response

*Exceptions exist.

PK-PD

- Direct effects or indirect effects
- PD do not correlate with *C*max or Tmax
- AUC and Ctrough are better predictors of PD response
- lag in clinical activity and frequently have a prolonged duration of action
- Certain adverse effects of biologics take time to manifest
  - the time to onset of skin toxicity after panitumumab is administered averages ~12 days.

Exception: rapid adverse reactions, such as infusion reactions and cytokine release phenomena

Specific Considerations for Biologics

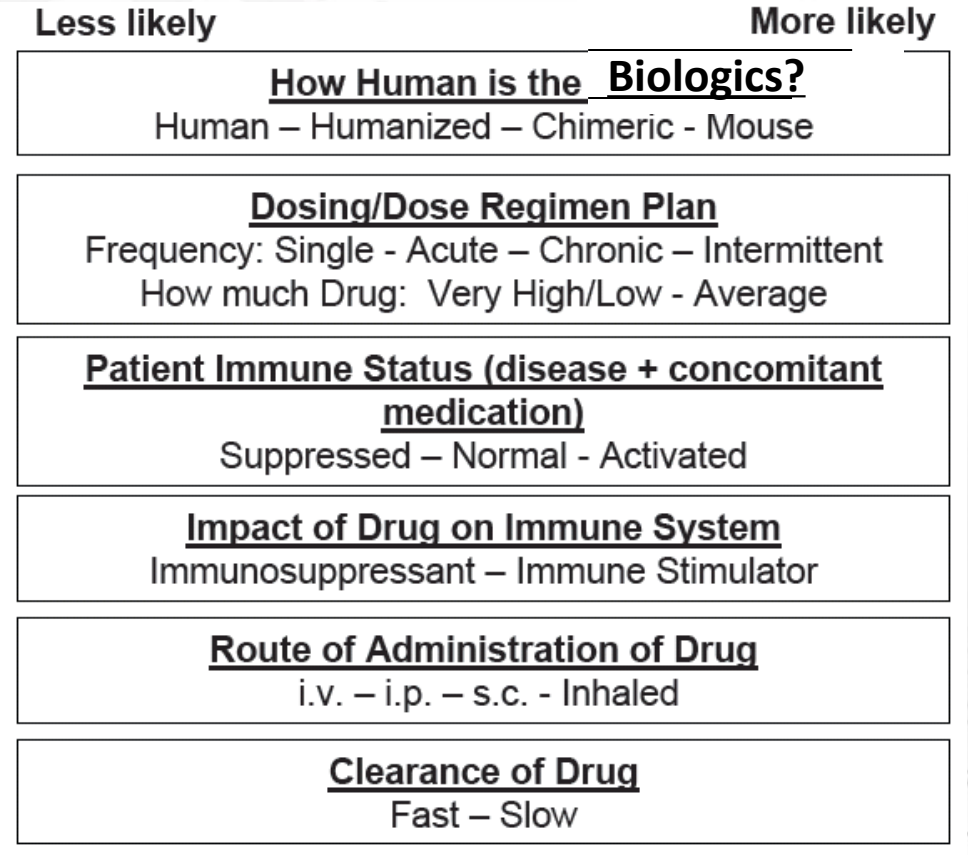
- **Dose Selection:** Several FDA approved agents, such as bevacizumab, imatinib, and, vismodegib, did not have a MTD established in the phase I setting. Instead, endpoints of PK and/or PD were used to determine the RP2D.

- **Comparability:** make sure there is no change triggering high risk (e.g., cell line/formulation etc. changes)

- **Immunogenicity**

- **Drug-Drug Interaction**

Clinical Assessment of Immunogenicity



Immunogenicity

- Immunogenicity testing should be conducted for all TPs
- Timing of ADA samples:
  - For single dose: pre-dose, days 14 post dose, 28 days post dose
  - For long t1/2 TP: longer time is needed (3-6months) when TP levels are not expected to interfere with the assay
  - Serum TP conc. is recommended to be determined at each immunogenicity time point
- Impact of immunogenicity on PK, PD, and safety of TPs should be carefully assessed

Note: The immunogenicity results are highly dependent on the sensitivity and specificity of the assay (binding and neutralizing)

DDI

- Indirect P450 Induction/Inhibition
  - Interferons - causes inhibition of P450 enzymes (1A2, 2C19, 2D6) at transcriptional and post-transcriptional level
  - Proinflammatory cytokines (IL-1, IL-2, IL-6) inhibition of CYP3A4
- Antagonism or synergism of pharmacodynamic effect
  - Effect of IFN-α on HCT in erythropoietin (EPO) treatment
  - Synergistic myelotoxicity in Aldesleukin + chemotherapy
- PK interaction through unclear mechanism
  - Methotrexate ↑ infliximab concentration (Maini *et al*, 1998)
  - Aldesleukin (IL-2) decreased dacabazine AUC by up to 42% (Chabot *et al*)

Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry

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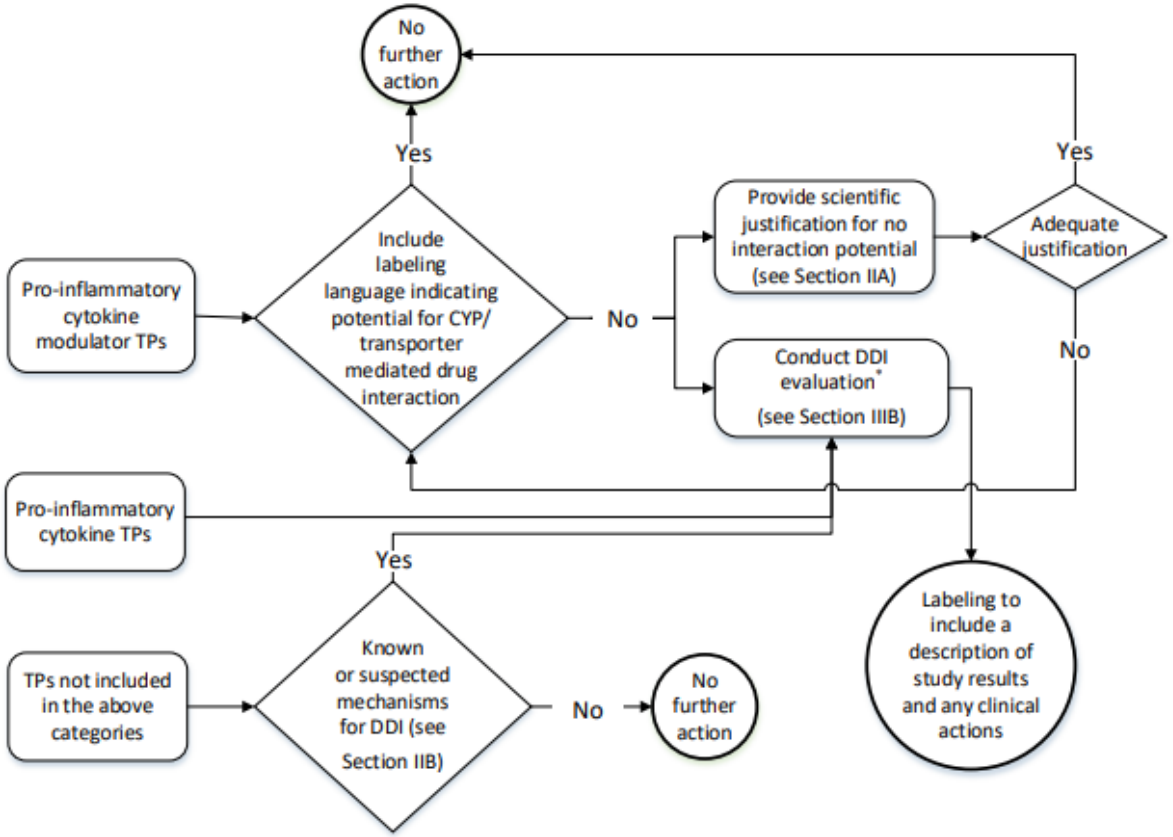
For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov, (CBER) Office of Communications at ocod@fda.hhs.gov, 800-835-4709, or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2020

V. APPENDIX. TP-DDI DECISION TREE



*The Agency recommends that DDI evaluation proposals be discussed with the appropriate review division prior to initiating a study.

The Review Process

21 CFR 312.22

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects and in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety

21 CFR 312.23 (content and format)

Cover Sheet (Form FDA 1571)
Form 3674
A Table of Contents
Introductory Statement and General Investigational Plan
Investigator's Brochure
Protocols – a protocol for each planned study
Chemistry, Manufacturing and Controls Information
Pharmacology and Toxicology Information
Previous Human Experience with the Investigational Drug
Additional Information

Review Team

- Division Director
- Deputy Director
- Team Leaders and reviewers from each discipline
  - Product Quality (CMC)
  - Pharmacology/Toxicology
  - Clinical Pharmacology
  - Clinical
  - Statistics

Study cannot proceed until **30 days** from FDA receipt

Which are the potential hold issues?

- Mechanism of action is not clear
- Aggressive dose escalation (e.g. >3 folds)
- Unqualified investigator
- IB misleading
- No enough PK collection
- Insufficient information to assess risk
- Inadequate safety monitoring
- Metabolism is unknown

Decision

- Safe to proceed
  - may have non-hold comments - advisory

- Partial clinical hold vs. full clinical hold

Phase 1 –

- Human subjects at unreasonable and significant risk
- Unqualified investigator
- IB misleading
- Erroneous or incomplete, or insufficient information to assess risk

Institutional Review Boards (IRBs)

- **IRB** – any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.
- **IRBs ensure that:**
  - Informed consents meet regulatory requirements
    - Obtained for every subject except where there is an exception (emergency, DOD use)
    - Offered in manner to minimize possibility of coercion
    - Presented in understandable language
    - Contains no language that waives subject's rights to release anyone from liability or negligence
  - Risk to subjects are minimized; & reasonable in relation to anticipated benefits
  - Adequate study monitoring for safety
  - Adequate protection of subject privacy
  - Rights and welfare of vulnerable subjects are protected

Case Example

FDA NEWS RELEASE

FDA Approves First COVID-19 Vaccine

Approval Signifies Key Achievement for Public Health

For Immediate Release: August 23, 2021

Español

Today, the U.S. Food and Drug Administration approved the first COVID-19 vaccine. The vaccine has been known as the Pfizer-BioNTech COVID-19 Vaccine, and will now be marketed as Comirnaty (koe-mir'-na-tee), for the prevention of COVID-19 disease in individuals 16 years of age and older. The vaccine also continues to be available under emergency use authorization (EUA), including for individuals 12 through 15 years of age and for the administration of a third dose in certain immunocompromised individuals.

"The FDA's approval of this vaccine is a milestone as we continue to battle the COVID-19 pandemic. While this and other vaccines have met the FDA's rigorous, scientific standards for emergency use authorization, as the first FDA-approved COVID-19 vaccine, the public can be very confident that this vaccine meets the high standards for safety, effectiveness, and manufacturing quality the FDA requires of an approved product," said Acting FDA Commissioner Janet Woodcock, M.D. "While millions of people have already

Content current as of:
08/23/2021

Regulated Product(s)
Biologics

Health Topic(s)
Infectious Disease
Coronavirus

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2 Clinical Studies supporting its approval

Table 6. Overview of Clinical Studies

Study ID	C4591001	BNT162-01
NCT ID	04368728	04380701
Phase	1/2/3	1/2
Countries	Argentina, Brazil, Germany, South Africa, Turkey, U.S.	Germany
Enrollment	Phase 1: 30 participants Phase 2/3: 43,847 participants	24
Age	16 - 85 YOA	18 - 85 YOA
Purpose	Evaluate VE for prevention of COVID-19 (pivotal clinical endpoint study)	Evaluate safety and immunogenicity
Control	Saline Placebo	None
Groups	Phase 2/3: 2 groups, randomized 1:1 to receive COMIRNATY or Placebo IM	1 group, randomized received COMIRNATY IM
Schedule	D0, D21	D0, D21
Total follow-up	6 Months (follow-up ongoing)	6 Months (follow-up ongoing)

YOA: years of age; VE: vaccine efficacy; IM: intramuscular; D: day

*August 23, 2021 Summary Basis for Regulatory Action - Comirnaty (fda.gov)

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Pfizer/BioNTech mRNA Vaccine

Two clinical studies assessed the safety, tolerability, and immunogenicity of ascending dose levels of BNT162 modRNA vaccine candidates

**US Phase 1/2/3 Study*
(C4591001 / NCT04368728)**

- 15 healthy participants (18-55 or 65-85 years of age) per dose level [12 active vaccine recipients and 3 placebo recipients]
  - 10 µg, 20 µg, 30 µg, 100 µg
- Immunized on Day 1 and a boost dose on Day 21 [No boost for 100µg cohort]

Germany Phase 1/2 Study
(BNT162-01 / NCT04380701)**

- 12 healthy participants (18-55 or 56-85 years of age) per dose level
  - 1 µg, 10 µg, 30 µg, 50 µg, 60 µg
- Immunized on Day 1 and a boost dose on Day 22 ± 2 [No boost for 60 µg cohort]

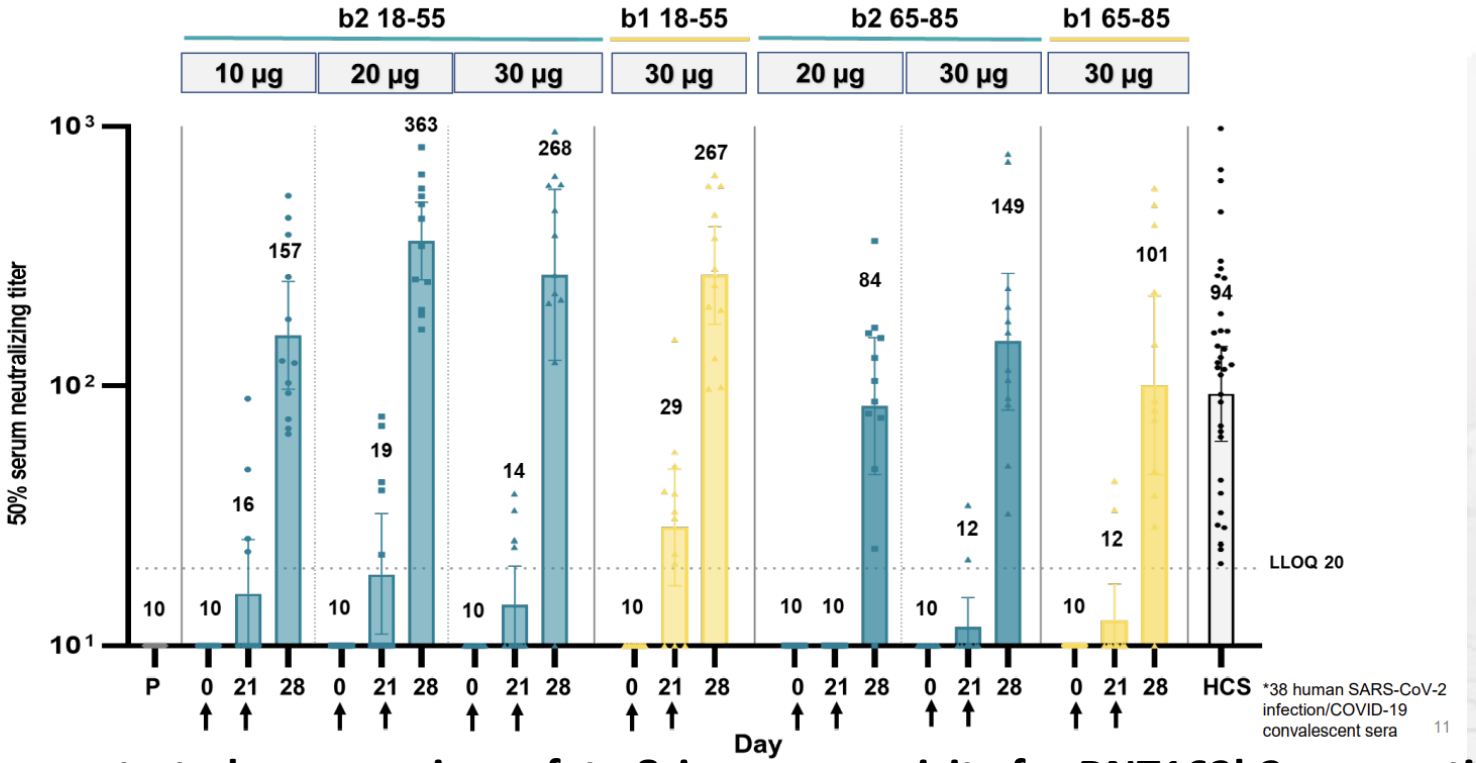
Human COVID-19 convalescent sera (HCS)

- 38 human SARS-CoV-2 infection/COVID-19 convalescent sera from subjects 18-83 years of age
  - N=29, 18-55 years of age
  - N=9, 56-83 years of age
- Collected at least 14 days after PCR-confirmed diagnosis, and at a time when subjects were asymptomatic
- Serum donors predominantly had symptomatic infections (35/38), and one had been hospitalized

* Mulligan, M.J. et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature https://doi.org/10.1038/s41586-020-2639-4 (2020)
* Walsh EW, Frenck R, Falsey AR, et al. medRxiv 2020.08.17.20176651; doi: https://doi.org/10.1101/2020.08.17.20176651 [preprint].
** Sahin U, Muik A, Derhovanessian E, et al. medRxiv 2020.07.17.20140533; doi: https://doi.org/10.1101/2020.07.17.20140533 [preprint].

Pfizer/BioNTech COVID-19 mRNA vaccine-Overview for ACIP Meeting (cdc.gov)

Robust SARS-CoV-2 50% neutralization titers after 2 doses of BNT162b2 in Phase 1 exceed those in a human convalescent panel (HCS*)



P1 demonstrated encouraging safety & immunogenicity for BNT162b2, supporting advancement to P 2/3

Key Messages

FIH Trials:

- Well-defined populations (subject enrollment potential)
- Reasonable Study Design
- Right dose selection
- Collection of biological samples
- Correct endpoints
- Intensive safety monitoring/management

Guidance

- FDA: Search for FDA Guidance Documents | FDA
  - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers | FDA
  - DDI of TP: Guidance for Industry (fda.gov)
- CDE: 指导原则专栏 (cde.org.cn)
- EMA:

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (europa.eu)

Breakthrough Nucleic Acid Therapeutics by QTsomeTM Technology

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