

*Review***Clinical pharmacology to support monoclonal antibody drug development****Sharon Lu***

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Abstract: Clinical pharmacology is a multidisciplinary function playing a critical role in the monoclonal antibody development. Besides the requirements of understanding pharmacology, pharmacokinetics, model simulation, biostatistics and immunogenicity, wisely implementation of tactics and strategies to fulfill the agencies' requirements per guidance documents are critical. In this review, clinical pharmacology studies categorized as required, target dependent, development strategy dependent, and not usually needed are discussed. The review ends with the outlook of recent initiations in the clinical pharmacology such as the application of QSP with the integration of AI and machine learning technologies.

Keywords: clinical pharmacology and mAb development; first in human dose selection; recommended phase 2 dose selection; drug-drug interaction and organ impairment for mAb; BA/BE and comparability assessment studies for mAb; pediatric study development; clinical pharmacology package for BLA

Abbreviations: QSP: Quantitative systems pharmacology; BLA: Biologics license application; PK: Pharmacokinetics; PD: Pharmacodynamics; DDI: Drug-drug interaction; FIH: First in human; NOAEL: No observed adverse effect level; MABEL: Minimum anticipated biological effect level; HED: Human equivalent dose; STD10: Dose severely toxic to 10% rodent; MTD: Maximum tolerated dose; PA: Pharmacology activity; RO: Receptor occupancy; HNSTD: Highest non-severely toxic dose; TMDD: Target mediated drug disposition; MID3: Model-informed drug discovery and development; iMID3: Integrated model-informed drug discovery and development; TQT study: Thorough QT/QTc study

1. Introduction

Monoclonal antibody (mAb) drugs have recently emerged as one of the cornerstone therapeutic modalities. Four mAbs, including Humira, Keytruda, Opdivo, Stelara and one Fc-fusion protein Eylea are among the top ten selling drugs in 2020 (Fierce Pharma). Especially in the recent advance of immuno-oncology, mAbs and their different variations appear as a major modality [1]. The development of hybridoma technique, a Nobel prize winning technology (1984) from Georges Köhler and César Milstein, has become the foundation for protein engineering including mAb generation and production. In the mid-1970s, immunologist Stuart Schlossman with his collaborators developed the first mAb drug which was approved by Food and Drug Administration (FDA) in 1986. The FDA approved the 50th antibody drug in 2015, 29 years from the first one. Only 6 more years later, the 100th mAb Dostarlimab, GlaxoSmithKline's anti-PD-1 drug, was approved by FDA in April 2021 [1]. The success of the modality in drug development is based on the low failure rate once passing proof of concept, revolution of the technology platform(s) including protein engineering and development knowledge accumulation. The mAb development success rate is about 22% from phase 1 to approval, almost double the rate of small molecule development [1]. The limitation of canonical mAb for the tissue penetration and intracellular target engagement can be overcome by the modification of the mAb, e.g., nanobodies, a camelid-derived single domain format with only a tenth of the size of mAb, and antibody-drug conjugates (ADCs) [1].

Another Nobel prize winning (2018) protein engineering platform, phage display, allows the generation of human antibody libraries, and select clones through high throughput screening tools, such as biopanning and rapid isolation of proteins with increased affinity, specificity, and stability [2]. With the accumulated experience in mAb development, knowledge-based databases can also be applied to the drug development process to avoid known defects in mAb designs. In silico methods have greatly facilitated mAb design in the areas of affinity maturation, allosteric effect, antibody stability, antibody-antigen recognition, epitope prediction, and immunogenicity prediction [3]. Structure- and network-guided design extended mAb pharmacokinetics (PK) half-life through mutation of Fc region residues M252, S254, and T256, resulting in M252Y/S254T/T256E ("YTE") [4].

The success of the mAb drug development depends on the holistic efforts of all functional areas. The effective connection of all the dots during the developmental process is the result of tremendous efforts including: (1) basic research, pathway mining, target identification and validation; (2) proof of concept using tool compound(s) including surrogate antibody; (3) animal model selection and translational thinking with knowledge base of genomics, proteomics, metabolomics, imaging and early evaluation of related clinical databases; (4) lead discovery and lead optimization; (5) candidate selection; (6) phase 1 dose escalation for safety evaluation and recommended phase 2 dose: collection of blood and tissue samples for translational biomarker identification and therapeutic responses, and patient stratification through all phases of trials; (7) phase 2 for efficacy evaluation with the potential requirement for further dose selection for phase 3: PK/PD evaluation; (8) phase 3 proof of efficacy, safety with supporting data package to define PK/PD properties, and dose response to justify the selected dose for long term applications.

Clinical pharmacology, a cross-disciplinary function, is heavily involved in the mAb drug development process from preclinical research to biologic license application (BLA) or marketing authorization application (MAA) and life cycle management. Since the PK characteristics of mAbs are significantly different from those of small molecules, clinical pharmacology support is quite different.

While relatively slim, clinical pharmacology support for mAb development will be drug, target, and development strategy dependent. As shown in Figure 1, PK/PD (e.g., first in human dose selection, single ascending dose (SAD) and multiple ascending dose studies (MAD)) and immunogenicity assessments are required from investigational new drug (IND) to phase 3; population PK and exposure-response analysis can be done as early as the phase 1 trial (in the case with expansion cohorts). Pediatric development plan will need to be ready before phase 3 initiation. Other studies, such as QTc prolongation, relative bioavailability and bioequivalence, comparability assessment and bridging studies due to dosing route and manufacturing related changes, drug-drug interaction (DDI) and organ impairment studies, will be on a case-by-case basis and discussed in the following sections.

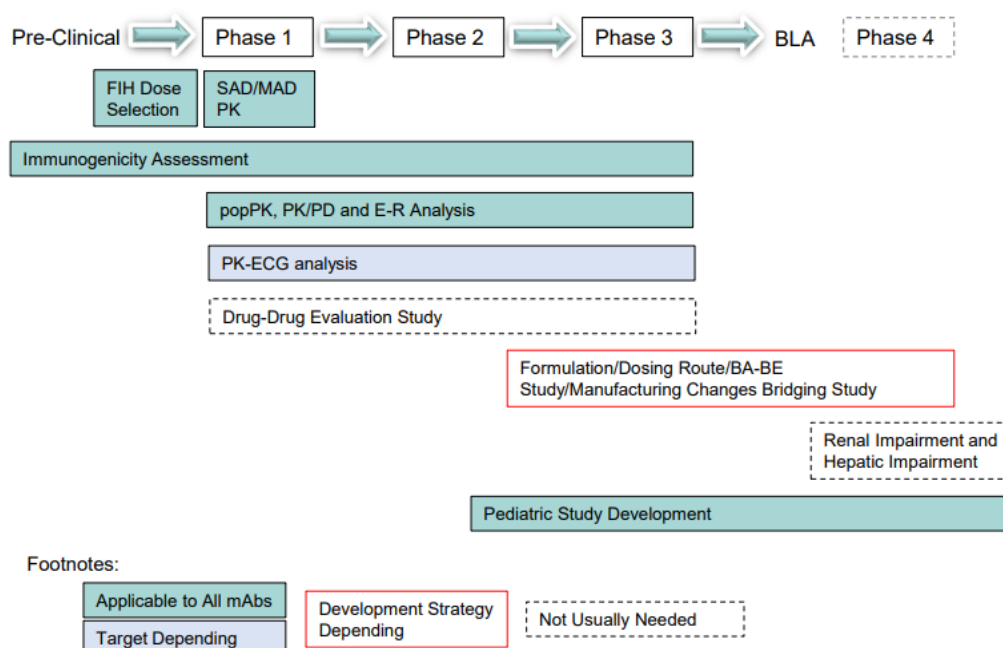


Figure 1. Clinical pharmacology studies for mAb drug development.

2. First in human dosing selection

Clinical pharmacology, depending on organization setting, can be involved in the drug development process as early as preclinical stage, and formulation and method of delivery development. The allometric scaling and model simulation to support the first in human (FIH) dosing selection indicates the start of heavy involvement of clinical pharmacology support through all phases of clinical trials.

Peng Zou et al. (2012) [5] discussed 5 methods for FIH dose selection: no observed adverse effect level (NOAEL)-based approach, minimum anticipated biological effect level (MABEL)-based approach, similar drug comparison approach, pharmacokinetic (PK)-guided approach, and PK/PD model guided approach. To support the application of both PK and PK/PD guided approaches, 17 approaches for human clearance prediction and 3 in silico tools were summarized [5]. Even though PK and PK/PD guided approaches may have the potential to predict more accurate FIH dose and reduce the duration of phase 1 trial, there are assumptions that need to be tested as discussed in the following paragraph.

For the PK guided approach, only parent compound can be active (assumption 1). Equal pharmacological activity, especially safety, are assumed in both non-human primate (NHP) species (selected as benchmark) and human for a given exposure (assumption 2). The assumption 1 applies to small molecule drug only. Thus, the approach may apply to biologics, such as mAb and protein, better since what we normally measure tends to be the total active biologic molecule. For PK/PD guided approach, the assumption is that there is a translational PK/PD model. Thus, the approach applies to “me too” or “me better” classes of molecules for the targets or mechanism of action with established translational PK/PD models. Another simplified approach for “me too” or “me better” modality is the similar drug comparison approach: $\text{Dose} = \text{Dose}_r \times (\text{NOAEL}/\text{NOAEL}_r)$ (r indicates the data from reference modality).

In general, the most applied approaches endorsed by regulatory agencies are NOAEL and MABEL. Before the TGN1412 (a novel CD28 superagonist mAb) trial's catastrophic results [6], NOAEL with safety factor (default: 10, adjust based on data package) was the most common method for FIH dose selection after FDA issued their guidance [7]. One rodent (default: rat) and one non-rodent species (default: dog for small molecule drugs and cynomolgus monkey for biologics) is used for NOAEL determination. The most relevant species, which may or may not be the most sensitive species, with the projected human equivalent dose (HED) should be applied in the FIH phase 1 trial. Justification is needed if NOAEL HED from the most sensitive species is not applied. After the TGN1412 severe adverse event, per EMEA and ICH S9 [8], both NOAEL and MABEL approaches need to be applied in the FIH dose selection. Recently, FDA organized a workshop for the comprehensive safety considerations in phase 1 trial in FDA clinical investigator course 12 November 2019, by Dr Ramya Gopinath, MD. The key messages from this workshop for NOAEL approach align well with FDA 2005 guidance, a 4-step approach (NOAEL in tested animal species, conversion of NOAEL to HED, selection of most appropriate animal species, application of a safety factor), depicted very clearly in Adrian M. Senderowicz's review paper [9]. The default safety factor 10 can be increased or reduced based on the data package as listed in Table 1 [7]. A retrospective review of 150 compounds for all indications including non-oncology, using both rodent and nonrodent toxicology information, reported about 71% of concordance with human safety data [10]. In the case that toxicity may arise from exaggerated pharmacology effects, MABEL may be a more sensitive indicator than NOAEL for lower HED as FIH dose selection. In contrast to NOAEL, MABEL is based on the totality of the pharmacology data and determines the dose in human with a concentration estimated to have minimal biologic effects. The general procedures include [11]: (1) generate in vitro, ex vivo, and in vivo preclinical pharmacology data packages; (2) determine the relevant concentration for minimal anticipated pharmacological effects in human from the preclinical data package including dose response; (3) estimate human PK from preclinical relevant species through allometric scaling; (4) determine dose corresponding to MABEL in humans with concentration response relationship. Whether to use NOAEL or MABEL approach should be based on the mechanism of action and class of the compounds (Figure 2). As shown in Figure 2, agonists tend to have uncontrolled or exaggerated pharmacological effects, thus a MABEL approach with EC_{10} or pharmacologically active dose (PAD) ED_{10} HED is recommended if supported with a data package. For all the antagonists, the conservative NOAEL approach has good safety record and works well, especially for cytotoxic compounds of which 1/10 rodent dose (STD10: dose severely toxic to 10% rodent) or maximum tolerated dose (MTD) can be established. For the molecular target compounds (mAb fall within this category), which tends to be more selective and less toxic to cells and tissues, both NOAEL and MABEL approaches should be

evaluated to balance the desired potential efficacy at FIH dose without safety concerns. Target engagement or in vitro activity data from in vitro or ex vivo functional assay(s) or in vivo efficacy studies can be used for the MABEL approach. Traditionally, EC_{50}/ED_{50} to EC_{90}/ED_{90} of HED can be used for drug development of mAb antagonists in most cases. Depending on the target safety including downstream pathways and target knockout data in mouse model(s), or if it is a novel target or the molecule with increased ADCC activity [12], a safety factor can be added. In an FDA paper [12] for the FIH dose selection of oncology analysis of immune activating products, two approaches through the principle of Hill equation based on either pharmacology activity (PA), ($PA = [C] / (EC_{50} + [C])$) or RO, receptor occupancy, ($RO = [C] / (K_D + [C])$) have been investigated. A FIH dose resulting in 20–80% RO or 20–80% PA had acceptable toxicities for all antibodies examined. The 20% level is currently the most common occupancy and activity level used for FIH dose selection (by sponsors and by FDA/OHOP), and 80% is below the RO that resulted in cytokine storm with TGN1412 (TGN1412 was at 90% RO at the FIH dose) [12]. For about 44% of antibodies examined, the selected FIH dose was at least 100-fold lower than the doses given to patients with manageable toxicities, resulting in long clinical trials to reach the efficacious dose in some of the cases, especially under the shadow right after the TGN1412 severe safety event. However, the selection of the FIH dose for antibodies based on animal toxicology studies using 1/6th the non-rodent HNSTD (highest non-severely toxic dose) or 1/10th the NOAEL resulted in human doses that were unsafe for several antibodies examined [12].

Table 1. Is a safety factor of 10 always appropriate?

Consider Increasing If	Consider Decreasing If
Steep dose-response curve; Severe toxicities; Nonmonitorable toxicity, e.g., histopathologic changes; Variable bioavailability; Irreversible toxicity; Unexplained mortality; Large variability in doses or drug levels that elicit an effect; Nonlinear PK; Novel therapeutic targets; Animal models with limited utility;	Is a member of a well-characterized class and administered by the same route, schedule and duration of administration? Has similar metabolic profile and bioavailability; Has similar toxicity profiles across all species tested including humans; Toxicities are easily monitored, reversible, predictable with a relatively shallow dose-response relationship and toxicities that are consistent across species;

In summary, for mAb agonists, the MABEL approach with EC_{10} or ED_{10} HED will be the FIH dose [12]. For mAb antagonists, both NOAEL and MABEL approaches should be evaluated. The lower HED should be used (Figure 2). For the MABEL HED, it can be based on EC_{20-90} or ED_{20-90} or RO 20–90% HED depending on the target and mouse knockout data, mechanism of action, with or without increased ADCC for the novel target. For “me too” or “me better” mAb development, the highest tested dose or MTD with safety margin or dose multiple can be used for FIH dose selection.

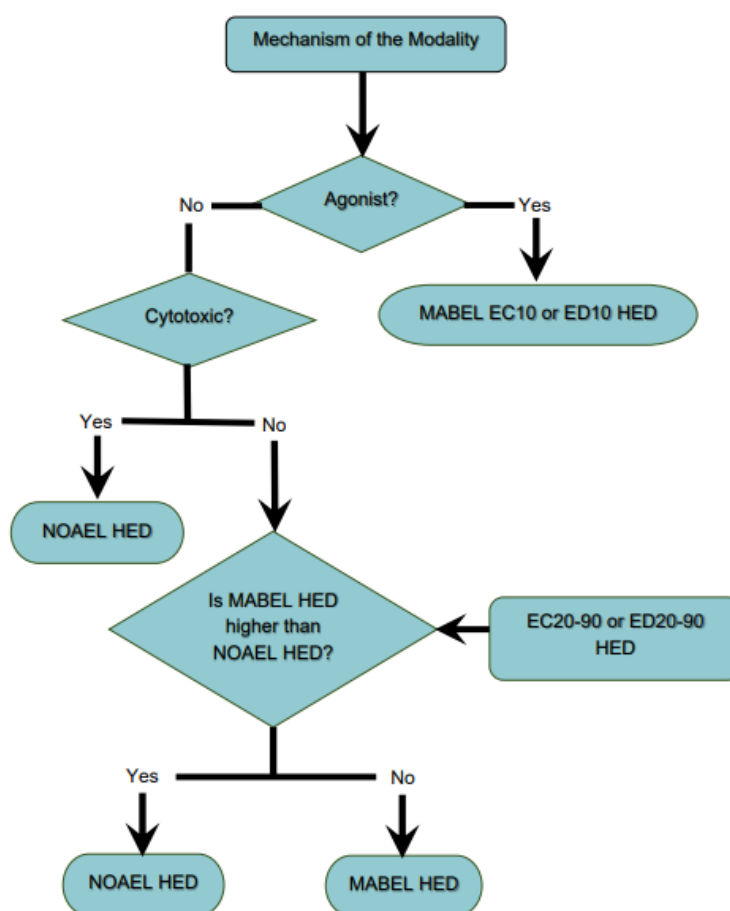


Figure 2. Diagram for mechanism-based first in human dose selection.

3. Recommended phase 2 dose selection

The objectives of phase 1 trial are highly driven by clinical pharmacology approaches. Dose limit toxicity (DLT) defined in the protocol helps to determine the highest dose tested in the trial, thus safety margin after the establishment of the therapeutic dose. Intensive PK sampling will allow to have enough data to evaluate human PK. For novel targets, human PK evaluation is highly recommended done in real time. For example, the PK samples are shipped out once collected for bioanalytical batch analysis. Before dose escalation to the next level, major part of the PK data including at least C_{max} from all the patients of the respective dose level are part of DLT evaluation meeting package. Another aspect for biologics is the immunogenicity evaluation. Although PK in real time can help us to identify whether there is severe impact from anti-drug antibody (ADA), safety and tolerability observations such as infusion reactions and hypersensitivity will trigger the ADA evaluation.

The most important task for clinical pharmacology in phase 1 is to determine recommended phase 2 dose (RP2D). The success of RP2D from phase 1 requires collaboration of multiple functions, especially bioanalytical and translational science with validated bioassays and identification of scientific justified PD marker(s).

Based on 22 biologics approved by FDA for cancer treatment from 2011 to 2020 [13], the dose selection was based on receptor occupancy (~5%), safety (~5%), biomarker/activity/safety response (~13%), early clinical activity (~18%), PK/PD (~28%), and preclinical C_{eff} (~31%). Large percentage (~54%) of dose selection based on preclinical C_{eff} or safety or clinical activity indicates lack of bioassays for target engagement and PD marker(s) identification or determination.

RP2D including the dose and regimen may require at least 2 dose levels evaluated in multiple studies. For example, cemiplimab, an approved anti-PD-1 drug, had RP2D determined in FIH study 1423 at 3 mg/kg Q2W with equivalent fixed dose of 200 mg Q2W evaluated [14]. For the phase 2 study 1540, Q2W, Q3W and Q4W at different dose levels were explored to evaluate clinical benefit in advanced cutaneous squamous cell carcinoma [14]. The therapeutic dose or approved dose through phase 3 trial was selected based on model simulations from data collected in studies 1423 and 1540 where the majority of the patients were dosed at 3 mg/kg. A fixed dose of 350 mg Q3W regimen that generated similar exposure at steady state ($AUC_{0-24h, ss}$, $C_{max, ss}$, $C_{min, ss}$) is the final approved dose regimen for label. This scenario is supported with the availability of target engagement assay(s) established in the early development of anti-PD-1 drugs, nivolumab for the direct binding receptor occupancy assay [15], and pembrolizumab for the IL-2 functional receptor occupancy assay [16]. In oncology space, historically only one dose at a maximum tolerated dose level was moved forward in clinical development to evaluate clinical efficacy. The Project Optimus from FDA is changing the practice in the space. The exploration of more doses, at least two dose levels, at the early clinical development stage are required, which prevents over-dosing patients (Project Optimus) [17].

4. Clinical pharmacology package to support BLA

Dose selection for registration trial, either not well controlled study for accelerated approval or phase 3 including functioning as a confirmatory trial, plays a critical role for achieving safe and efficacious results if the target for the indication(s) is right. Sparse samplings with trough and peak concentration points are sufficient to support PK characterization together with all the available PK data at the time including dose escalation PK data where have with intensive PK samplings. Immunogenicity assessment is mainly based on the trough level samples from the evaluation of 3-tier ADA assay as well as neutralizing antibody assay together with PK concentrations to categorize sample status, positive or negative or inconclusive; if positive, what is the titer and whether it is neutralizing. When the registration trial topline data is positive, sometimes it is a substudy or one cohort of the study, the BLA filing process will be initiated. BLA filing preparation takes 6 months to 1 year depending on the team experience, and more critically the planning and the coordination of each function deliverables. Clinical pharmacology is always the “bottleneck” since the initiation of data domain preparation and analysis is dependent on the final delivery of bioanalytical (BA) data sets and medical domains. Biologics have a relatively slim package (Figure 1). Depending on the targets, mAb may not need cardiac safety evaluation since mAb can not cross plasma membranes and bind with the hERG channel. However, ECG matched PK collection and drug concentration-ECG correlation analysis is recommended to be ready for any potential request. The “must-have” package includes a PK report, an integrated immunogenicity analysis report, and a population PK and exposure response analysis report with data domains associated with each. Integrated immunogenicity analysis takes the effort of multiple disciplines including BA, data management, biostatistics programming, CMC and clinical pharmacology. Both agencies, FDA and EMA, clearly define the scope of the requirements in

their guidance [18–20]. Normally, the evaluation is summarized by dose and schedule, and should be updated periodically with more data available. An example of the integrated immunogenicity analysis has recently been published in *AAPS J* [21]. It covers data analysis as well as assessment of ADA impact to PK, safety and efficacy, method and cut point discussion, patient population factor and product attributes, route of administration, and other driving factors, such as target. The modeling report is the hard core of the package after receiving the final datasets. The datasets, clinical pharmacology summary 2.7.2 together with associated reports form the totality of the BLA package from a clinical pharmacology perspective which will be part of the data structure, module 2 and module 5.

5. Monoclonal antibody has typical PK characteristics

Normally, a two compartmental model fits the data for mAb very well. Typical mAb through IV infusion has CL of 0.15 mL/h/kg with 95% confidence interval of (0.14–0.16) [22]. The volume of distribution of mAb is small, similar to plasma volume, indicating mAb is mainly confined within intra-vascular space with limited access to tissue interstitial space. The inter-compartmental clearance parameter, Q , was estimated to be 0.27 mL/h/kg with 95% of (0.25–0.30) [22]. Body weight (BW) as a patient specific covariate should be evaluated as early as in the dose escalation phase through correlation between CL and BW to evaluate if fixed dose is possible. Even BW is proven as a significant covariate, it has been shown that fixed dosing of mAbs results in less variability in AUC compared to body weight-dosing when an exponent of <0.5 is estimated to normalize the body weight effect on CL during PK modelling [23,24]. A fixed dose is always preferred due to convenience, cost effectiveness, easier compliance, and safer with low/no risk of dosing errors.

Another two important PK characteristics for mAb are target mediated drug disposition (TMDD) and time-varying clearance. TMDD is receptor-mediated endocytosis internalization of mAb through interaction of cell surface receptors with one of the Fab binding domain of the antibody followed by lysosome degradation. Antibodies cleared primarily by TMDD will have nonlinearity especially at low doses or concentrations. TMDD elimination pathway can be saturated at higher doses or concentrations, and PK becomes linear afterwards [25]. Time-varying clearance was observed in oncology mAbs, for example, approved anti-PD-(L)1 drugs (Pembrolizumab [26], Nivolumab [27], Cemiplimab [28], Dostarlimab [29], Atezolizumab [30], Avelumab [31] and Durvalumab [32]) without exception. The clearance change (reduction) was associated with response to treatment. One explanation is that a reduction in cachexia as cancer state improves would result in lowered catabolism thus antibody clearance [33].

Two major factors which may impact mAb PK are charge and glycosylation [25]. The charge will determine how a mAb interacts with negative charged cell surface. Depending on isoelectric point, if a mAb exists as cationic in the physiological condition, it will have higher CL and volume distribution and lower bioavailability with subcutaneous dosing. Significant change of glycosylation pattern may impact both PK and PD profile [34]. In the case that a flat exposure response relationship was observed for a mAb, such as the class of anti-PD-1 mAbs [35–37], the defense of the dose selection will heavily rely on the human target engagement and/or PD marker(s) determined in the phases of clinical development. The lowest efficacious dose is the current drive as represented by mAb drug development efforts in the oncology field (Project Optimus) [17].

6. New insights for mAb drug-drug interaction evaluation

Drug-drug interaction (DDI) evaluation for mAb can usually be waived. Most recently, the FDA published with a draft guidance (August 2020) for therapeutic protein (TP) DDI evaluation [38]. The guidance defines two types of mechanisms for DDI, proinflammatory cytokine-related mechanisms and mechanisms of DDIs unrelated to proinflammatory cytokines. When TPs are proinflammatory cytokines which can down-regulate the expression of cytochrome P450 (CYP) enzymes, thereby decreasing the metabolism of drugs that are CYP substrates and increasing their exposure levels [38,39], a DDI study should be planned. When the TP is a cytokine modulator, two scenarios are discussed. When the TP causes an increase in proinflammatory cytokines levels, the time course and extent of the increase will help to determine a need for a DDI study, study design, and the mitigation strategy. The justification to the FDA is needed when the DDI potential is evaluated as low and thus a DDI study is not required. For TPs that modulate proinflammatory cytokines in conditions associated with elevated cytokine levels, extrapolation of a DDI study from one population to another is challenging as the levels of proinflammatory cytokines may differ by disease type and status thus leading to expression variability of CYP enzymes [38,40]. The agency [38] recommends including a DDI potential in the labeling. Justification is needed if the potential for clinically significant DDI is low and thus no labeling is necessary. The suggested justification includes: (1) effects seen with other agents or the same agent in other disease states with similar or more inflammatory burden; (2) differences in exposure levels of sensitive CYP substrates in healthy subjects versus the indicated population; (3) the magnitude of the drug effect or the extent of cytokine modulation; alternatively, when a drug is developed in multiple indications, the potential of a DDI can be evaluated in the disease with the most severe inflammatory burden.

The mechanism of DDIs unrelated to proinflammatory cytokines includes [38]: (1) TP as a perpetrator which affects the physiological processes and alters the PK profiles of co-administered drugs (e.g., GLP-1 receptor agonists, dulaglutide and albiglutide, delayed gastric emptying); (2) co-administered drugs impact TP target expression level. When there is observed TMDD for this TP, the TP will be evaluated as either the perpetrator or the victim drug [38,41,42]; (3) co-administered drugs compromise the function of FcRn [38,43]. Since metabolism of mAb or TP with Fc is dictated by the interaction with FcRn, the change of FcRn function requires TP to be evaluated as a victim drug; (4) co-administration of immunosuppressors change TP PK profiles due to a change of immunogenicity. TP will be evaluated as a victim drug and descriptive analysis can often be considered adequate.

The guidance [38] is summarized in detail for the scenarios in which the waiver of DDI justifications or DDI study are needed for mAb development.

7. Organ impairment studies

Organ impairment studies include renal impairment and hepatic impairment evaluations. Both are normally planned to be done after the first approval if expansion of labels is needed. A review paper on renal impairment [44] offers the practical insights into the application of the FDA and EMA guidance including (1) examining renal function for drug labeling requirements; (2) types of studies; (3) dose selection and regimen; (4) operational definition of renal impairment; and (5) subject inclusion/exclusion criteria.

For mAb development, renal impairment study is not usually needed but may be required for biologics when molecular weight <50 kDa or 69 kDa per EMA or FDA guidance, respectively [45,46]. However, if the target level changes in the organ impairment patient population [46], which can lead to clinically significant changes in exposures at the therapeutic dose due to TMDD, model simulation including TMDD (with available or assumed target expression levels from both healthy and organ impairment populations) can be used to determine if dose adjustment is necessary.

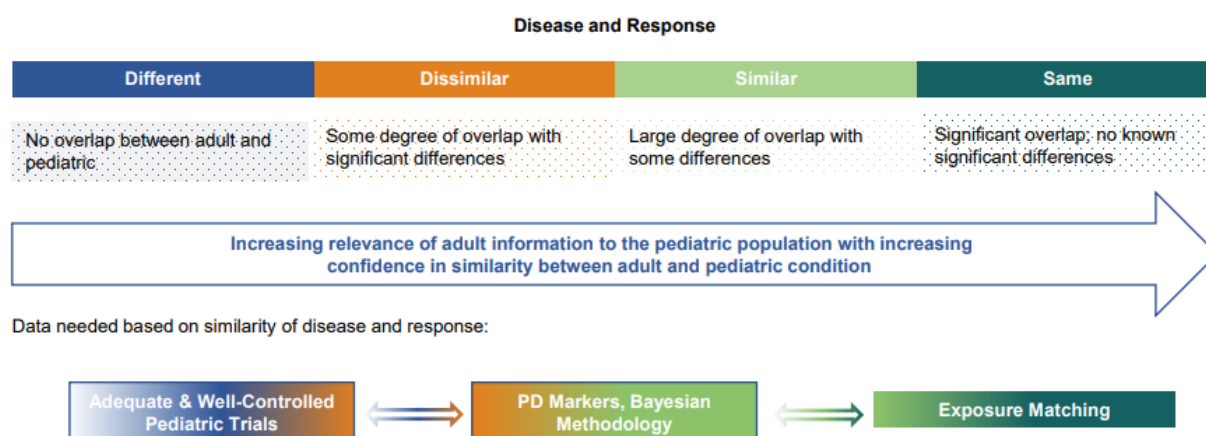
Hepatic impairment (HI) evaluation can normally be waived for mAb development through justification since mAb degradation is non-specific in the lysosomes through endocytosis. If the liver metabolism is <20% and the therapeutic range is wide, there will be no safety and loss of efficacy concern due to the liver impairment [47]. However, mAb metabolism is far more complicated than just non-specific clearance and unsaturable catabolism. Besides known effects such as impact to FcRn and FcγR binding, TMDD, there are unknown factors that can alter mAb PK [48,49]. In the public domain, there is limited information about the HI impact on mAb PK. A recent paper from FDA [49] evaluated HI impact to mAb metabolism based on data between 2013 and 2018 with no data from severe HI, 4 mAb for moderate HI, and about 20 mAbs for mild HI. PopPK approach using HI as fixed effect was validated compared to the dedicated study results. One mAb (evolocumab) had over 30% decrease in AUC. A couple of mAbs including alirocumab, bezlotoxumab, and mogamulizumab had a trend for AUC decrease. There was no mAb with increasing trend in AUC. In addition, a lower albumin level has been found to be associated with lower exposure of several mAbs such as blimumab, bezlotoxumab, infliximab, and trastuzumab [49]. Additional data are needed, especially for moderate and severe HI categories.

8. Pediatric development plan

In 1963, Dr. Harry Shirley first described children as the therapeutic orphan. Pediatric patients should have access to products that have been appropriately evaluated, and product development programs should include pediatric studies when pediatric use is anticipated [50]. Currently, the Pediatric Research Equity Act (PREA) is triggered by an application for new indication, new dosage form, new dosing regimen, new route of administration, and new active ingredient [51]. The assessment in the pediatric population will be used to assess the safety and effectiveness with proper dosing and formulation. The pediatric study plan (PSP) must be submitted within 60 days before the end of phase 2 meeting. When there is no meeting, FDA strongly encourages drug approval applicants to submit the PSP prior to the initiation of a Phase 3 trial. In general, the PSP must be submitted no later than 210 days prior to submission of BLA. When the sponsor believes additional adult data are needed before pediatric studies, the study may be deferred after approval. The sponsor must submit (1) the certification of the grounds for deferring the assessments; (2) a pediatric study plan; (3) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; (4) a timeline for the completion of the study. When the disease does not exist in the pediatric population, the requirement for assessments may be waived or deferred. The final deferral and waiver decisions are made at the time of NDA/BLA approval. Recently, originally exempted orphan indications are required to submit an initial PSP for certain molecularly targeted oncology drugs [52,53].

Another important aspect of consideration is ethics [50]. Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults). In 1994, extrapolation concept was

introduced from FDA Final Regulation Pediatric Labeling Rule. This allows maximizing the use of existing data across the products life cycle to increase efficiency of pediatric drug development [54]. In 2011, FDA published a review of approaches for pediatric drug development with 14% complete extrapolation, 68% partial extrapolation and 18% no extrapolation from adults or subgroup of pediatric population [55]. In 2017, the complete, partial and no extrapolation became 34%, 29% and 37% reflecting a better understanding of pediatric pathophysiology [55]. In the same year, ICH [56] published an addendum for clinical investigation in the pediatric population to further emphasize the extrapolation when there is evidence that the course of the disease and expected responses are similar in pediatric population compared to reference population, such as adults or other pediatric age group(s). In 2018, EMA [57] published with a reflection paper in which the extrapolation concept and categories are clearly defined and aligned with FDA guidance with the emphasis to assess the similarity and fill the knowledge gap(s) through quantitative approach. As shown in Figure 3, disease and response are classified as different, dissimilar, similar and same. Between dissimilar and similar, Bayesian methodology together with PD marker(s) are recommended for partial extrapolation. For the extrapolation study, both PK and safety cannot be fully extrapolated. No extrapolation will require two clinical studies with one adequate and well controlled trial. Both partial and complete extrapolation may require only one well-designed study for the associated indication label to be expanded into the different age of sub-pediatric population(s). Model simulation, either population PK through allometric scaling and organ maturation function [58] or PBPK [59,60] can be leveraged to project dose(s) and regimen in the untested sub-pediatric population(s). Optimal sampling points, especially with the challenge of blood volume limitation for pediatric patients, can be established through model simulations. The success of the extrapolation highly depends on the similarity of the disease pathophysiology, manifestations, progression, diagnostic criteria, endpoints, and PD marker(s) (through PK/PD modeling for partial extrapolation).



The figure is regenerated from Analgesic Trial Design Workshop October 2021, based on EMA Reflection Paper on Use of Extrapolation (2018).

Figure 3. EMA pediatric extrapolation: regulatory rerspectives.

9. Bioavailability/bioequivalence study and comparability assessment

As a part of lifecycle product management, bioavailability (BA) and bioequivalence (BE) studies are required when dosing route, such as subcutaneous (SC) or intramuscular (IM) from original intravenous infusion (IV), needs to be expanded into drug label for patient care convenience and gaining market share. The SC route is the most common mAb delivery method other than IV. It significantly relies on the convective flow to deliver the mAb through interstitial space into the lymphatic system, then draining into the systemic circulation. The absorption process for mAb is slow with T_{max} ranging from 6–8 days (frequent values) [48]. The relative BA ranges from 52–80% [48]. Factors which may impact mAb SC absorption include site of injection, product specific factors (i.e., charge, size, formulation, and dose), subject specific factors (i.e., body weight, gender, age, activity level, disease state, respiratory rate, and blood pressure) [48]. The dose and manufacturing related factors, such as vial, syringe, and formulation, need to be established before a human BA study. A pilot study can be carried out in a small number of subjects before a full-scale study to find out the data variability, determine the sample size to achieve adequate power, and optimize sample collection time [61]. The recommended study population for BA and BE studies are normally 18 years or older of healthy volunteers (HVs) with both sexes when there is no safety concern to preclude HVs. However, the alignment with regulatory agencies is recommended on the population selection. Parallel single dose PK studies will be sufficient for BA/BE study. For most drugs, the guidance recommends that 12 to 18 samples, including a pre-dose sample, be collected per subject per dose. This sampling should continue for at least three or more terminal elimination half-lives of the drug to capture 90 percent of the relevant AUC. Three or more samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of λ_z from linear regression. The exposures used for the BE evaluation are C_{max} , AUC_{0-t} , and AUC_{0-inf} . Log-transformation of exposure measures before statistical analysis is recommended. The geometric mean ratio of exposure(s) for test and reference should be within confidence interval of (0.8–1.25) [62].

Manufacturing related changes may lead to modifications of mAb structure, and have the potential to impact PK, immunogenicity, safety, and efficacy. Risk-based comparability assessment similar to the BE study is necessary with patient safety as the primary consideration [63]. Dr. Zhaoyang Li and Dr. Rachael Easton published a very comprehensive review on the clinical comparability assessment following manufacturing process changes. The following are the major take-aways related to the clinical pharmacology support. The analytical characterization, nonclinical assessment and clinical assessment are the 3 components for this evaluation. Clinical assessment is only required when there are major changes, such as cell line, manufacturing site, formulation, or manufacturing scale. A PK/PD focused comparability study should be performed to support the process change. Depending on the change and associated risks, it can be a small non-BE study in HVs to a large BE study in patients. Most dedicated PK/PD comparability studies are conducted as single dose studies with PK or PD as the primary objective, and safety/tolerability/immunogenicity as secondary objectives. ADA comparability assessment should be done from a repeat dose efficacy and safety trial. The population selection for PK/PD study are normally HVs, except for oncology indications, where patients are more appropriate. If PD is part of comparability assessment, it should be done in the relevant population. Regarding the dose selection, EMA suggest using the target dose for approval and marketing or in the steep part of the dose-response curve [64]. If a final therapeutic dose is not determined at the initiation of the comparability study, multiple doses may need to be evaluated due to no extrapolation in the

scenarios such as nonlinear PK or different formulation at different doses. Though BE criteria are routinely used in many comparability studies, it is not a regulatory requirement. Thus, it is not required to power the study the same as BE study. When there is no dedicated PK/PD study, cross PK comparison or population PK analysis can be used to support the comparability assessment as well.

As part of formulation development, at the early stage for SC or IM development, the primary container is usually vial and syringe (VS) in parallel with the development of a prefilled syringe (PFS) or an auto-injector. When switching, a human factor study is required to assess the adequacy of the device user interface in the target population(s) without the requirement of PK endpoints [65]. The key administration specifications, such as injection force, needle gauge, needle insertion depth, injection time, or accuracy of dose delivery, differ between the original and the new presentations. In the case of switching from VS to PFS or to auto-injector, it is likely to have changes to one or more of these key specifications. A PK/PD clinical bridging study is warranted. When switching from PFS to auto-injector, if we can justify that the mode of administration is unchanged and demonstrate analytical comparability at release and at the end of shelf-life, clinical comparability may be waived.

10. Future directions

The debut of iPhone in 2007, coined by previous Apple CEO Steve Jobs as a magic product, led to a social and cultural revolution. Phones and tablets became part of people's lives, as a "partner", or in some cases, even a "controller" due to power capacity and versatile functions associated with them. The advancement of computing industry, e.g., cloud computing, makes it possible for big data analysis. Based on the data source and type, different algorithms for data processing sprang up. One industry which will definitely benefit from these advancements is the pharmaceutical and biotechnology industry. Just in terms of data quality, scientific data tend to be fact-driven and a lot of knowledge-based databases can be applied to the drug discovery process to avoid known defects in drug designs. Besides the examples of *in silico* application shared in the introduction for mAb development, *in silico* approaches helped to reduce the potential of immunogenicity [66] as well as make the vaccine candidate more immunogenic through immuno-informatics algorithms and computational methods [67]. Even though mAb drug development success rate is almost double compared to small molecule drug development, successful mAb development efforts are focused on limited targets. The explosive knowledge accumulated during years of drug discovery and development, with billions of dollars investments, should be wisely applied in the industry to reduce the cost, attrition rate and improve the success of drug development. According to the National Institutes of Health (NIH), 80 to 90% of research projects fail before they ever get tested in humans, and for every drug that gains FDA approval, more than 1000 were tested but failed [68]. We have accumulated ample knowledge during the drug development process with each dot or function representing big data from a variety of databases. Coming along with the knowledge and data accumulation is the advancement of computing technology and artificial intelligence (AI). With the availability of big data, advancements of machine learning through AI technology, natural language process (NLP) and artificial neural networks, researchers are deploying AI to drug discovery [69]. Highly related to clinical pharmacology field, MID3 initiations [70] are cohesively advancing with the computing and AI technology, e.g., machine learning and deep learning. The associated modeling approaches include empirical, semi-mechanistic, or quantitative systems pharmacology (QSP) techniques integrating current knowledge of the drug, disease, and mechanism of action to allow prediction of new outcomes under new conditions, such as untested

doses, regimens, populations, disease factors, impact of dose sequence in the combination settings. QSP, a predictive pharmacodynamic system, similar to PBPK for pharmacokinetics, together with machine learning has gradually been used for the prediction of treatment efficacy. A great example of QSP application is in the immuno-oncology field [71]. The success of anti-PD-1 drugs triggers a lot of combination therapies—more than 2000 trials started in 2017, which may lack quantitative understanding of complex dynamic factors critical for efficacy, leading to suboptimal combination choices and results. Through the QSP platform, including the models describing tumor-immune system dynamics, tumor vascularization, all cell types in lymph, blood, tissue and tumor microenvironment (including stroma for indications such as pancreatic cancer), cytokines, chemokines, extracellular matrix, paired cell types and receptor ligand interaction, virtual patient population can be generated to be “treated” with the combination therapies through the optimization of dosing sequence and dosing regimen to evaluate the synergistic effects. With the understanding of cascades of pathways and biology involved in the combination therapies, QSP becomes a tool for trial design, combination therapy selection, virtual proof of concept or predictions in different modalities [72–74]. Besides the relevance to QSP, machine learning attempts to predict human mAb bioavailability of the subcutaneous dosing route [75] and is emerging into clinical pharmacology highly related fields such as biometrics and translational science [76]. Another aspect which will be beneficial from the knowledge-based systems for clinical pharmacology is model-based meta-analysis (MBMA) [77]. MBMA was first proposed in 2005 to compare the benefit of eletriptan to sumatriptan for the acute relief of migraine pain-results [78]. The new concept is to support the trial efficacy and safety projection and improve the drug development productivity. The keys for this application are data source and bundling strategy (digitization and database building/big data). The successful development of NLP makes the complicated data forms searchable and usable at data mining. All the new developments move under the regulatory radar [70,79]. FDA clinical pharmacology team, leading the efforts, developed a long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling through machine learning algorithms [80]. With the advancements in every functional area for the application of new technologies related to big data and AI, we may step into the new era of drug development.

11. Conclusions

Clinical pharmacology, as a key function to support therapeutic mAb development, has industry standardized or well accepted practice with the guidance from agencies. As a multi-discipline functional area, cohesive collaboration with medical, translational, biometrics, pharmacovigilance, data management, statistical programming, and preclinical research with the implement of iMID3 and support from data science [81] will lead to optimized processes for mAb drug development.

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Conflict of interest

The author declares no conflict of interest.

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