Preclinical and Toxicological Aspects in Early Phase Development of Pharmaceutical Products

Liat Hershkovitz, Ph.D
Director Scientific & Regulatory Affairs
ADRES-Advanced Regulatory Services LTD

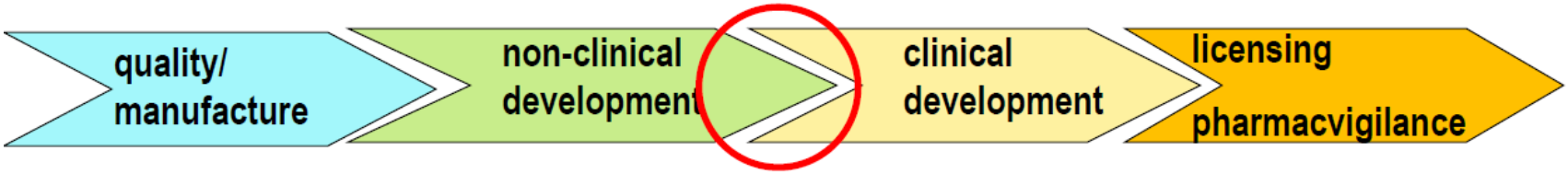
PDA Israel
Key areas for strategic drug development planning
Ramat Gan, 24th Oct 2018

Definition

- Preclinical studies are conducted to define pharmacological and toxicological effects not only prior to initiation of human studies but throughout clinical development.

- Both in vitro and in vivo studies can contribute to this characterization

Preclinical Program Objectives



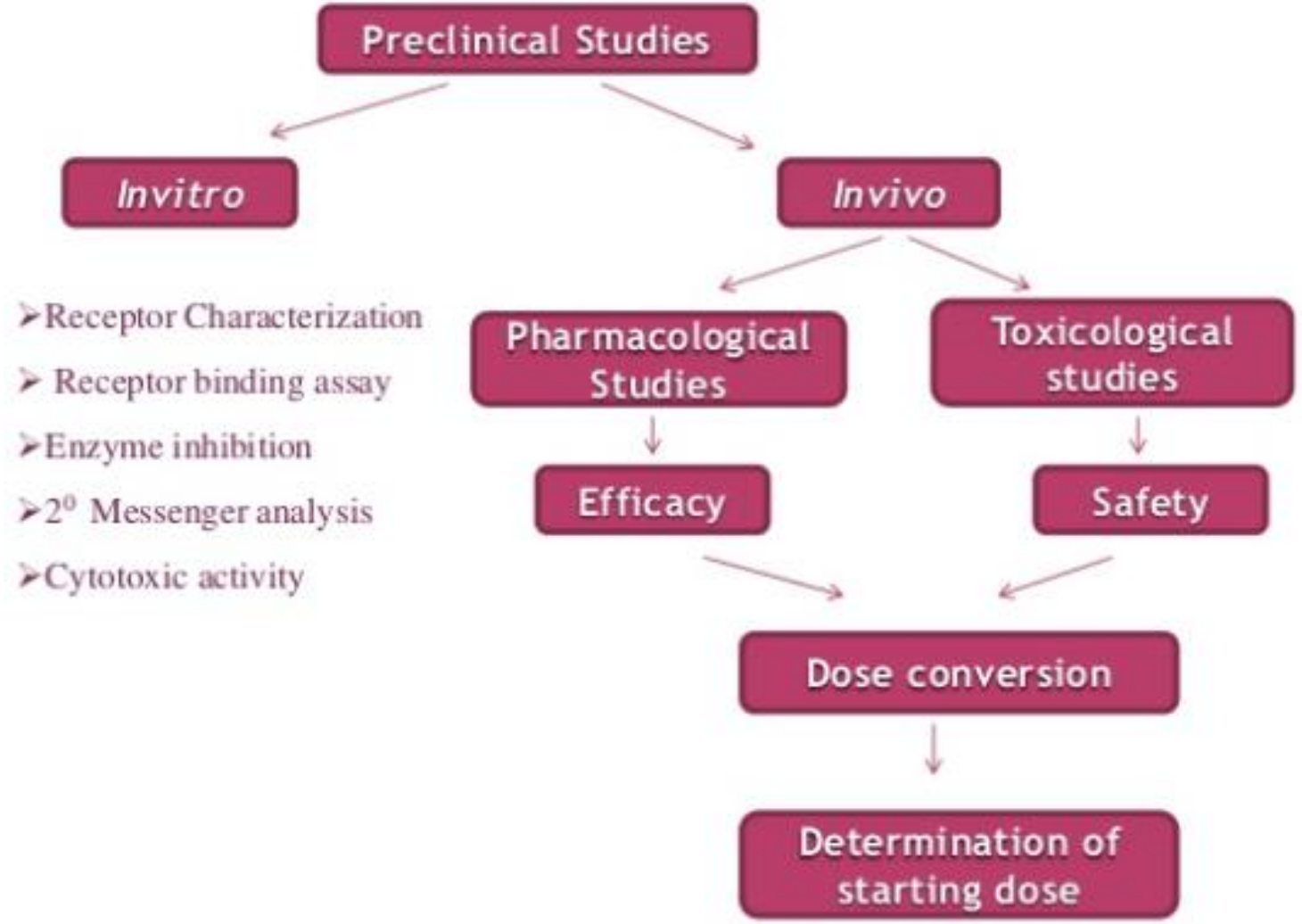
- Identification of biologically active dose levels.
- Selection of a starting dose level, dose-escalation schedule, and dosing regimen.
- Guide the design of early-phase clinical trials
- Identification of physiologic parameters that can guide clinical monitoring.
- Identify, describe and characterize hazards - reversible? - clinically monitor able?
- Establish dose-response estimation of pharmacology and toxic effects
- Assess drug distribution to organ systems
- Identify metabolic, kinetic and elimination pathways
- Assess carcinogenicity, reproductive toxicity and teratogenic potential

Proof of Concept Studies

POC studies should provide data that demonstrate:

- The pharmacologically effective dose range (i.e., minimally effective dose and optimal biological dose).
- Optimization of the ROA.
- Optimization of the timing of product administration relative to onset of disease/injury.
- Optimization of the dosing schedule.
- Characterization of the claimed MOA

A Route Map of Preclinical Studies



Considerations for Preclinical studies

- Selection of relevant animal model
- Age
- Physiological state
- ROA
- Delivery system
- Product classification and regulation
- Stability of the product
- Feasibility for mass production (manufacturing costs)
- GLP
  Non GLP
- CRO selection

Relevant Guidelines

- **The ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*** provides an overall description of the nonclinical studies generally needed for all drug development programs.

- **The ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*** provides an overall description of the nonclinical studies of biological products that sponsors should consider to support clinical trials.

- In some cases, an abbreviated or deferred program may be applicable (**The ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals***

- For recommendations on the substance and scope of nonclinical studies to support clinical trials for cell and gene therapy products, refer to the **FDA guidance for *industry Preclinical Assessment of Investigational Cellular and Gene Therapy Products, and EMA guideline for ATMPs***
- ***Specific FDA and EMA guidelines***

What Types of Studies are Needed ?

- Is the developed product a:

–Drug

–**Biologics**

–Device

–Gene/cell therapy (Advanced Therapy Medicinal Product, ATMP)

–Combination product

–Diagnostic product

- What studies are needed – dependent on product & indication

-Who are the patients ? (healthy volunteers vs. patients with the indicated disease)

-What is the unmet need ?

What is the anticipated age group ?

-What is the expected dosing – acute or chronic?

-Where will it be delivered – systemic or local?

Overview of Study Types

- **Pharmacodynamics (Mode od Action)**
- **Pharmacokinetics (Metabolism)**
- **Single dose toxicity**
- **Repeated dose toxicity**
- **Safety Pharmacology**
  - functional assessment of major systems (CNS, Respiratory & Cardiovascular)
- **Developmental and Reproductive Toxicology**
  - Male and Female fertility and reproductive performance
  - embryo/fetal development
  - neonatal development
- **Genotoxicity**
  - potential for cancer and heritable mutations
- **Carcinogenicity**
  -Depending on duration of drug treatment
- **Local tolerance**
- **ADME** (absorption, distribution, metabolism, elimination)

Product Delivery Considerations

- Drug Device Combination Products
- Involvement of NB (Notified bodies) in EMA and CDRH in FDA (Center for Devices and Radiological Health)
- The use of a large animal species
- Biocompatibility studies

Bridging Studies

- In general, the product that is used in the definitive pharmacology and toxicology studies should be **comparable** to the product proposed for the initial clinical studies.
- However, it is appreciated that during the course of development programs, changes normally occur in the manufacturing process in order to improve product quality and yields.
- The **potential impact** of such changes for extrapolation of the animal findings to humans should be considered.
- The comparability of the test material during a development program should be demonstrated when a new or modified manufacturing process or other significant changes in the product or formulation are made in an ongoing development program.
- **Comparability** can be evaluated on the basis of biochemical and biological characterization (i.e., identity, purity, stability, and potency). In some cases additional bridging studies may be needed (i.e., pharmacokinetics, pharmacodynamics and/or safety).
- The scientific rationale for the approach taken should be provided.

Consideration for Selcting your CRO

- Local or Abroad
- Costs
- Availability of required animal species and models
- Quality- GLP certification and compliance
- Experience in the therapeutic area under investigation
- Service capabilities
- Relationships - Always keep in mind that the CRO you select will be an extension of your team
- Recommendations

Species Selction

- The animal species selected for assessment of bioactivity and safety should demonstrate a **biological response** to the investigational product similar to that expected in humans in order to generate data to guide clinical trial design (cell-based assays for qualitative and quantitative cross-species comparisons).
- In some circumstances animal models of **disease/injury** may be preferable to healthy animals (mAb and related products directed at foreign targets (i.e., bacterial, viral, etc., Cell& Gene therapies)

- feasibility of using the planned:
  - clinical delivery system (e.g. pump)
  - Procedure
  - Volume dose

Species Selction

One or Two Species:

- Usually data in **two Species** is required (Species differences in response)
- However, in certain justified cases **one relevant species** may suffice:
  - ✓ when only one relevant species can be identified or-
  - ✓ where the biological activity of the biopharmaceutical is **well understood**
  - ✓ In **long term study** it may be possible to justify the use of only one species for subsequent long term toxicity studies (e.g., if the toxicity profile in the two species is comparable in the short term).
  - ✓ The regulator can exercise flexibility in nonclinical programs where the proposed clinical indications are for treatment of **rare diseases**, particularly diseases that are **serious and life threatening**

- Rodent rat or Mouse
- Non-rodent – dog, pig, non-human primate (e.g. Monkeys)

Species Selction

- When no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins should be considered.
- The scientific justification for the use of these animal models of disease to support safety should be provided.

Species Selction-Physiological State

- In recent years, there has been much progress in the development of animal models that are thought to be similar to the human disease. These animal models include induced and spontaneous models of disease, gene knockout(s), and transgenic animals.
- In certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals
- These models may provide further insight, not only in determining the pharmacological action of the product, pharmacokinetics, and dosimetry, but may also be useful in the determination of safety (e.g., evaluation of undesirable promotion of disease progression).
- When no relevant species exists, the use of homologous proteins should be considered.
- The scientific justification for the use of these animal models of disease to support safety should be provided.

Species Selction

Tissue Cross-Reactivity – Immunohistochemical examination of potential binding of monoclonal antibodies and related products to the target epitope.

✓ICH S6, Section 3.3 paragraph 2 is no longer appropriate. Tissue cross-reactivity should not be used for selection of relevant species for safety evaluation. Other techniques that assess target expression (e.g., *in situ hybridization, flow cytometry) can provide supportive* information for species selection.

✓However, tissue cross-reactivity data with human tissues can provide useful information to supplement knowledge of target distribution and can provide information on unexpected epitope binding.

✓Tissue cross-reactivity studies in nonclinical species are considered to have limited value and therefore are not generally recommended.

✓Binding to areas not typically accessible to the biopharmaceutical *in vivo i.e., cytoplasm* might not be relevant.

✓For bi-specific antibodies, evaluating each binding site separately in this assay is not called for.

Study Design

- **The route and frequency of administration** should be as close as possible to that proposed for clinical use. Consideration should be given to pharmacokinetics and bioavailability of the product in the species being used, and the volume which can be administered.
- **Dose Selection and application of PK/PD Principles**

✓ The toxicity of most biopharmaceuticals is related to their targeted mechanism of action; therefore, relatively high doses can elicit adverse effects which are apparent as exaggerated pharmacology.

✓**A rationale should be provided for high dose selection in the animal model.**

PK-PD approaches can assist in high dose selection by identifying:

- A dose which gives the maximum intended pharmacological effect in the preclinical species.

- A dose which gives an up to 10-fold exposure multiple over the maximum exposure to be achieved in the clinic.

Study Design

- Where in vivo/ex vivo PD endpoints are not available, the high dose selection can be based on PK data and available in vitro binding and/or pharmacology data. Corrections for differences in target binding and in vitro pharmacological activity between the nonclinical species and humans should be taken into account to adjust the exposure margin over the highest anticipated clinical exposure.

- For example, a large relative difference in binding affinity and/or in vitro potency might suggest that testing higher doses in the nonclinical studies is appropriate

- In the event that toxicity cannot be demonstrated by this approach, then additional toxicity studies at higher multiples of human dosing are unlikely to provide additional useful information.

Study Design

Dosage levels should be selected to provide:

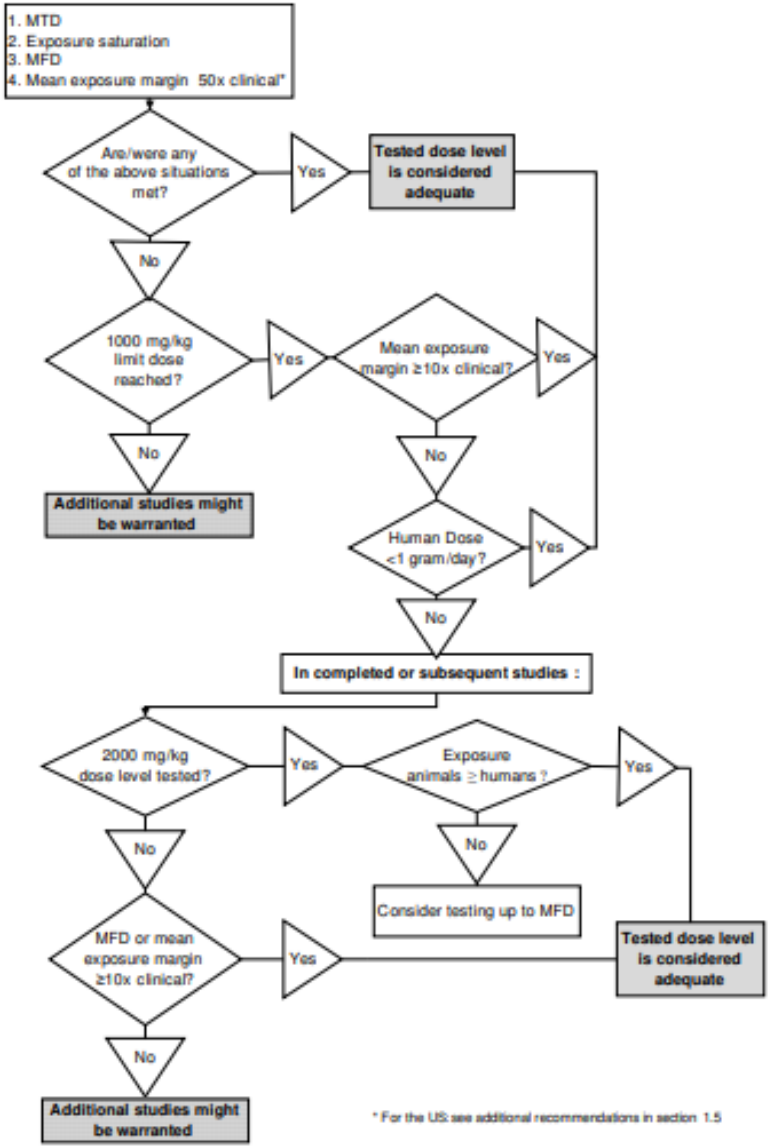
- information on a dose-response relationship,
- It is not essential to demonstrate the MTD in every study
- a no observed adverse effect level (NOAEL) (is not considered essential to support clinical use of an anticancer pharmaceutical).

- Where a product has a lower affinity to or potency in the cells of the selected species than in human cells, testing of higher doses may be important.

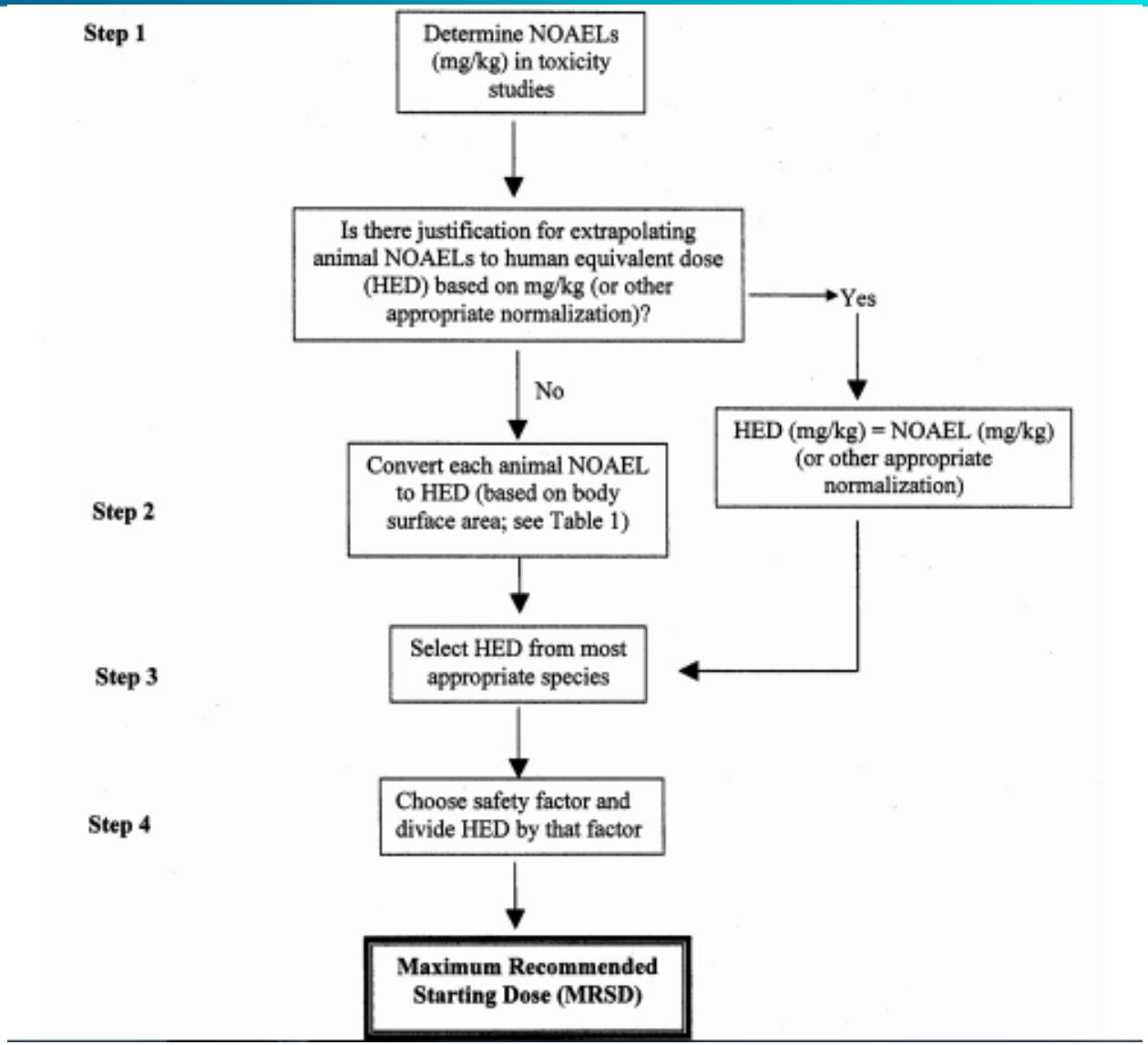
**MTD- In a toxicity study, the highest dose that does not produce unacceptable toxicity

** NOAEL- No observed adverse effect level : The highest dose tested that does not produce a significant increase in adverse effects in comparison to the control group. Adverse effects that are biologically significant, even if not statistically significant, should be considered in determining an NOAEL.

Recomended High Dose Selection For General Toxcilogy Study



Selection of Maximum Safe Starting Dose in Initial Clinical Study



Study Design

Duration of Studies

- For chronic use products, repeat dose toxicity studies of 6 months duration in rodents or non-rodents are considered sufficient
- Studies of longer duration have not generally provided useful information that changed the clinical course of development.
- For chronic use of biopharmaceutical products developed for patients with advanced cancer the treatment schedules is very short

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	Non-rodents
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months [b, c, d]

Clinical Schedule	Examples of Nonclinical Treatment Schedule[1,2,3,4]
Once every 3-4 weeks	Single dose
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5-7 days, alternating weeks	Daily for 5-7 days, alternating weeks (2-dose cycles)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Two or three times a week	Two or three times a week for 4 weeks
Daily	Daily for 4 weeks
Weekly	Once a week for 4-5 doses

Study Design

Recovery

- Recovery of pharmacological and toxicological effects with potential adverse clinical impact should be understood.
- This information can be obtained by including a non dosing period in at least one study, in order to examine reversibility of these effects, not to assess delayed toxicity.
- The demonstration of complete recovery is not considered essential.
- An evaluation of recovery is not warranted if there are no adverse effects at the end of the dosing period or sufficient scientific justification can be provided (e.g., evidence that an adverse effect is generally reversible, or an adequate margin of safety exists for the proposed clinical population).
- The addition of a recovery period just to assess for immunogenicity is not appropriate.

Immunogenicity

- Alterations in the pharmacokinetic profile due to immune-mediated clearance mechanisms may affect the kinetic profiles and the interpretation of the toxicity data.
- The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans.
- In terms of predicting potential immunogenicity of human or humanized proteins in humans, such analyses in nonclinical animal studies are not relevant .
- Many biotechnology-derived pharmaceuticals intended for human are immunogenic in animals.
- Therefore, measurement of antibodies associated with administration of these types of products should be performed when conducting repeated dose toxicity studies in order to aid in the interpretation of these studies.

Immunogenicity

Immunogenicity assessments assist in the interpretation of the study results and design of subsequent studies.

- ✓ Measurement of ADA in nonclinical studies is not routinely warranted if:

  - there is evidence of sustained pharmacodynamic activity
  - no unexpected changes in the pharmaco/toxicokinetics of the test article during the dosing or recovery phase
  - and/or no evidence of immune-mediated reactions (immune complex- related, vasculitis, anaphylaxis, etc.)

- ✓ However, it is difficult to predict whether such analysis will be called for prior to completion of the in-life phase of the study; therefore, it is often useful to obtain appropriate samples during the course of the study, which can subsequently be analyzed if needed to aid in interpretation of the study results.

  When a need occurred, according to study results, to understand immunogenicity to interpret study data, potential for **immunogenicity antibody detection assays** should be conducted to evaluate the presence of ADAs.

- ✓ When ADAs are detected, the effect on the study results should be assessed, including effects on PK and drug clearance, pharmacology effects, and toxicity.

Immunogenicity

- Characterization is generally not warranted, specifically of neutralizing potential, particularly if adequate exposure and pharmacological effect can be demonstrated by a pharmacodynamic marker of activity in the *in vivo* toxicology studies.

- In the event that neutralizing antibody assessment is deemed appropriate to interpret the study findings, assessment of neutralizing activity can be addressed indirectly with *ex-vivo* bioactivity assay, a combination of assay formats for PK-PD, or directly in a specific neutralizing antibody assay.

Preclinical Studies to be Performed Before Phase 1 Clinical Trials

- **PK &PD**
- **Pilot Tox Studies**
  - ✓ Identify MTD, dose & exposure responses, target organ toxicity; major organ system pathology; dose-limiting toxicities; repeat-dose TK
- **Single dose toxicity in two species (non-GLP)**
- **Pivotal Repeated dose toxicity in two species**
  - ✓ Should be the same as intended clinical route & schedule
  - ✓ Determine adverse effects with NOAEL & exposure ratios.
  - ✓ Provide a basis for selecting initial clinical doses & escalations
- **Safety Pharmacology**
  - ✓ Investigate potential undesirable PD effects on the physiological function of vital organs
  - ✓ Small molecule – commonly stand alone studies
  - ✓ Biological – incorporate endpoints into non-rodent tox study
  - ✓ Oncology (end stage) – waived
- **Local tolerance**
  - ✓ incorporate endpoints into tox study
- **Genotoxicity** if relevant (*in vitro* assays)

Preclinical Studies to be Completed Before Phase 2 Clinical Studies

- **Genotoxicity** studies, *In vivo* (The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed)
- **Carcinogenicity** (Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals)
- **Repeated dose** toxicity (Duration depending on duration of clinical study)

Preclinical documentation before phase 3 clinical study

- **Fertility studies:**
  - Male and Female fertility and reproductive performance
  - Embryo/fetal development
  - Neonatal development

- **Repeated dose toxicity**

- **ADME**

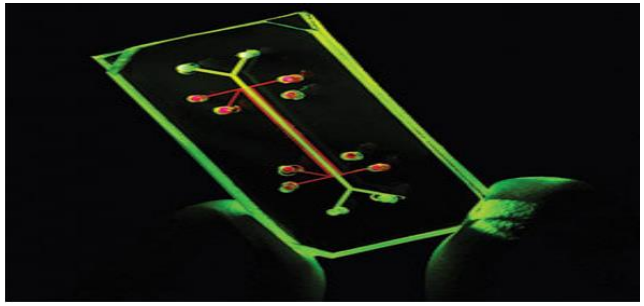
- In parallel with phase 2 and phase 3 clinical studies, other toxicity studies are completed

Juvenile Studies

- The conduct of any juvenile animal toxicity studies should be considered only when previous animal data and human safety data, including effects from other drugs of the pharmacological class, are judged to be insufficient to support pediatric studies.
- If a study is warranted, one relevant species, preferably rodent, is generally considered adequate.
- A study in a non-rodent species can be appropriate when scientifically justified.
- Generally, juvenile animal toxicity studies are not considered important for short-term PK studies (e.g., 1 to 3 doses) in pediatric populations.
- Results from repeated-dose toxicity studies of appropriate duration in adult animals, the core safety pharmacology package, and the standard battery of genotoxicity tests should be available before initiation of trials in pediatric populations.
- Reproduction toxicity studies relevant to the age and gender of the pediatric patient populations under study can also be important to provide information on direct toxic or developmental risks (e.g., fertility and pre-postnatal developmental studies).
- A chronic study initiated in the appropriate age and species with the relevant end points to address this developmental concern (e.g., 12 months duration in dog or 6 month in rodent) can be appropriate.

Moving to In Vitro Toxicity Studies

- **Toxicity studies in animal model:**
  - ✓ Ethical problems
  - ✓ Stain suitability
  - ✓ Not all toxicity issues are identified



- ***In vitro* toxicity studies are promising:**
  - ✓ Druggable genome
  - ✓ Precision medicine
  - ✓ Disease modeling, including rare diseases
  - ✓ Human-on-a-chip
  - ✓ Clinical trials on a chip
  - ✓ Microbiome, environmental toxins, infectious agents, etc.

FDA understands that human/organ-on-a-chip can be a predictive tool – but the Agency would need to have <u>confidence</u> in the data

Moving to In Vitro Toxicity Studies

- *In vitro* toxicity studies also have issues:
  - ✓ Not a fully differentiated system
  - ✓ Lack of immune/blood system
  - ✓ Not representing entire population or genetic diversity

- There are no guidelines, but FDA is willing to review such tools and methods and welcomes communication with Sponsors

- FDA is collaborating with other agencies (e.g., DARPA, NIH) through in several independent programs

- The goal is to “develop an *in vitro* platform that uses human tissues to evaluate the efficacy, safety and toxicity of promising therapies”

- This platform would have to be fully validated

Meet the Regulator- the earlier the better

- **FDA- Pre-Pre IND, Pre-IND**
  - ✓ Provide advice in response to specific queries
  - ✓ In person or by teleconference
  - ✓ Written minutes for formal meetings
  - ✓ No fee

- **EMA- Scientific advice (EMA, national), ITF**

- **Israeli MOH**
  - ✓ No formal procedure
  - ✓ However the division of clinical trials encourage meetings for new products/technologies

THANK YOU FOR YOUR ATTENTION!

QUESTIONS??

Liat Hershkovitz, Ph.D
Director Scientific & Regulatory Affairs

ADVANCED REGULATORY SERVICES LTD