Regulatory Aspects in USA (FDA) – Specific Regulations for some Medicinal Product Candidates

- Drug approval process & medicine evaluation
- Expedited programs for serious condition
- Orphan drug act
- Application types
- IND content
- FDA guidances to preclinical assessments of
  - Pharmaceuticals
  - Biotechnology-derived pharmaceuticals
  - Cellular & gene therapy products/ therapeutic vaccines
What is a drug as defined by the FDA?
A drug is any product that is intended for use in the diagnosis, cure mitigation, treatment, or prevention of disease; and that is intended to affect the structure or any function of the body.

**Drug Approval Process**

**PRE-CLINICAL**

**Drug Sponsor's Discovery and Screening Phase**

Drug Developed

Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

**Animals Tested**

Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

**IND Application**

The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from initial testing that include the drug’s composition and manufacturing, and develops a plan for testing the drug on humans.

**IND Review**

FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protections.

**CLINICAL**

**Drug Sponsor's Clinical Studies/Trials**

**Phase 1**

20-80

The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here is to determine what the drug’s most frequent side effects are and, often, how the drug is metabolized and excreted.

**Phase 2**

100’s

The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

**Phase 3**

1000’s

The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.
Who reviews new drug submissions?
A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists review the drug sponsor’s data and proposed labeling of drugs.

NDA REVIEW
FDA’s New Drug Application (NDA) Review

10 Drug Labeling
FDA reviews the drug’s professional labeling and assures appropriate information is communicated to health care professionals and consumers.

11 Facility Inspection
FDA inspects the facilities where the drug will be manufactured.

12 Drug Approval
FDA reviewers will approve the application or issue a response letter.

Application Reviewed
After an NDA is received, FDA has 60 days to decide whether to file it so it can be reviewed. If FDA files the NDA, the FDA Review team is assigned to evaluate the sponsor’s research on the drug’s safety and effectiveness.

NDA Application
The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

Review Meeting
FDA meets with a drug sponsor prior to submission of a New Drug Application.

FASTER APPROVALS
The Accelerated Approval program allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need. The approval is faster because FDA can base the drug’s effectiveness on a “surrogate endpoint,” such as a blood test or X-ray result, rather than waiting for results from a clinical trial.

The Fast Track program helps reduce the time for FDA’s review of products that treat serious or life-threatening diseases and those that have the potential to address an unmet medical need. Drug sponsors can submit portions of an application as the information becomes available (“rolling submission”), instead of having to wait until all information is available.

POST-MARKETING
FDA’s Post-Approval Risk Assessment Systems

Because it’s not possible to predict all of a drug’s effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA’s post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed.

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.

FDA’s MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug’s labeling and the public is informed of the new information through letters, public health advisories, and other education. In some cases, the use of the drug must be substantially limited. And in rare cases, the drug needs to be withdrawn from the market.

Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections.
How FDA evaluates Medicines for human Use

Analysis of target condition and available treatments

• Review of the condition of illness for which the drug is intended and evaluate the current treatment landscape, which provide the context for weighing the drug’s risk and benefits.

Assessments of benefits and risks from clinical data

• Evaluation of clinical benefit and risk information considering any uncertainties that may result from imperfect or incomplete data.

Strategies for managing risks

• All drugs have risks. Risk management strategies include an FDA-approved drug label, which clearly describes the drug’s benefit and risks, and how the risks can be detected and managed. The implementation of a Risk Management and Mitigation Strategy (REMS) may be requested.
Accelerated Approval & Drug Development Designations

**Accelerated Approval**

- Accelerated approval can be applied to promising therapies that treat a *serious or life-threatening condition* and provide *therapeutic benefit over available therapies*.

- This approach allows for the approval of a drug that demonstrates an effect on a “*surrogate endpoint*” that is reasonably likely to predict clinical benefit, or on a *clinical endpoint that occurs earlier* but may not be as robust as the standard endpoint used for approval.

**Drug Development Designations**

- Fast Track
- Breakthrough Therapy
- Priority Review
FDA Programs to facilitate and expedite development and review of new drugs* to address unmet medical need in the treatment of a serious or life-threatening condition

*all references to drugs and drug products include both human drugs and biological drug products regulated by CDER (Center for Drug Evaluation and Research) and CBER (Center for Biologics Evaluation and Research)
# Fast Track

**Get important new drugs to the patient earlier**

Facilitate development, and expedite the review of *drugs to treat serious conditions and fill an unmet medical need* (e.g. advanced cancer, congenital enzyme deficiency diseases)

**Fast Track designation is eligible for:**

- More frequent meetings with the FDA
- More frequent written communication from the FDA
- Accelerated Approval and Priority Review, if criteria are met
- Rolling Review

**Fast Track designation must be requested; FDA´s review and decision making process within 60 days**
Breakthrough Therapy

Develop evidence needed to support approval as efficiently as possible

Expedite the development and review of drugs that are intended to treat a serious condition. **Preliminary clinical evidence** indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

**Breakthrough Therapy designation is eligible for:**

- All Fast Track designation features
- Intensive guidance on an efficient drug development program, beginning as early as Phase I
- Organizational commitment involving senior managers

**Breakthrough Therapie designation must be requested no later than the end-of-Phase II meetings and also may be suggested by the FDA; FDA’s review and decision making process within 60 days**
Priority Review

• FDA aims to take *action on an application within six months compared to 10 months* under standard review.

• Overall attention and resources will be directed to the evaluation of applications of drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

• FDA decides on the review designation for every application, but an applicant may also request priority review (information by the FDA within 60 days)
Orphan designation by Orphan Drug Act (ODA)

**Definition**
- Affects <200,000 persons in the US
- Affects >200,000 persons in the US but for which there is no reasonable expectation that the cost of developing and making available a drug for such disease or condition will be covered from sales of such drug in the US.

**Incentives**
- 25% tax credit for qualified clinical trials
- No prescription drug user fee on a marketing application
- 7-year market exclusivity
- Grants to support studies of orphan products
FDA Application Types

- Investigational New Drug (IND) Application
  - Commercial
  - Research (non-commercial)
- New Drug Application (NDA)
- Therapeutic Biologics Applications (BLA)
- Abbreviated New Drug Application (ANDA)
IND Application Content

**Animal Pharmacology and Toxicology Studies:**
Is the drug reasonably safe for initial testing in humans?

**Manufacturing information:**
Does the drug substance and drug product information ensure that the company can adequately produce and supply consistent batches of the drug?

**Clinical Protocols and Investigator information:**
Will subjects be exposed to unnecessary risks?
Are the clinical investigators sufficiently qualified?
Are commitments given to obtain informed consent from the research subjects?
Guidance for Industry

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Additional copies are available from:
Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 51, Room 2201
Silver Spring, MD 20903-0002
(Tel) 301-796-3400
and/or
Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1348
(Tel) 800-877-4800 or 301-443-1800

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

January 2010
ICH
Revision 1

Guidance for Industry

S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

Additional copies are available from:
Office of Communications
Division of Drug Information, HFD-351, Room 2201
Center for Drug Evaluation and Research
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10903 New Hampshire Ave., Silver Spring, MD 20903-0002
Phone: 301-796-3400; Fax: 301-443-9114
druginfo@fda.hhs.gov
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Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
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(Tel) 800-877-4800 or 301-443-1800
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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)

May 2012
ICH

Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), HFD-40, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-877-4809 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/GuidanceDocument.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

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

November 2013
### Guidance for Industry

**M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials at Marketing Authorization for Pharmaceuticals**

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#### Maximum Duration of Clinical Trial

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials</th>
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<tr>
<td>Rodents</td>
<td>Nonrodents</td>
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<td>Up to 2 weeks</td>
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<td>Between 2 weeks and 6 months</td>
<td>Same as clinical trial(^b)</td>
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<td>&gt; 6 months</td>
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- **Primary Pharmacodynamics**
- **Safety pharmacology - GLP**
- **In vitro metabolism**
- **Plasma protein binding**
- **Exposure/ PK**
- **ADME (Phase II)**
- **Drug interactions (Phase II)**
- **Characterization of human metabolites (Phase II)**
- **Dose escalation or short-duration dose finding studies (MTD) – GLP**
- **Repeated-dose toxicity study in 2 species - GLP**

**Small molecules:**
- Timely conduct of clinical trials
- Reduce number of animals in accordance with 3R

**Local tolerance**
- Genotox
- Carcinogenicity
- Reproduction Toxicity (Phase II)
Estimation of the first human Dose (small molecules)

- All nonclinical data to be considered
  - Pharmacological dose-response
  - Pharmacological/toxicological profile
  - Pharmacokinetics.
- **NOAEL** (no observed adverse effect level) determined in nonclinical safety studies performed in the most appropriate animal species provides most important information.
- The high dose in the toxicology study should be selected to produce a **50-fold exposure margin** over the anticipated clinical exposure at the highest dose in proposed for Phase II and III studies (for Phase I smaller margins are appropriate)
• Applies to products derived from characterized cells through the use of a variety of expression systems (bacteria, yeast, insect, plant, mammalian cells)

• For in vivo diagnostic, therapeutic and prophylactic use

• Active substances: Proteins, peptides, their derivatives & products of which they are components

Monoclonal antibodies, cytokines, recombinant plasma factors, hormones, enzymes, receptors, recombinant DNA protein vaccines, plasma derived products, endogenous proteins, oligonucleotide drugs, chemically synthesized peptides
Preclinical Safety Testing – Important Aspects

- Safety concerns may arise from the presence of impurities or contaminants of the test material.
  - Presence of cellular host cell contaminants can result in allergic reactions and other immunopathological effects
  - Nucleic acids contaminants may potentially be included into the host genome
  - Risk of viral infection

- The product used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies
- The comparability of the test material during a development program should be demonstrated when the production process is modified or the formulation is significantly changed.
Preclinical Safety Testing – Important Aspects (cont.)

- Conventional approaches to toxicity testing of pharmaceuticals are not appropriate for biopharmaceuticals due to unique and diverse structural and biological properties
  - Species specificity
  - Immunogenicity
  - Unpredicted pleiotropic activities

- Selection of **relevant** animal species incl. age & physiological state
- Manner of delivery & administration dose, route and schedule
- Stability of the test material under the conditions of use.
Species Selection

- Target sequence homology
- In vitro assays: Cross-species comparison of binding affinities, receptor/ligand occupancy, kinetics
- Functional activity in species-specific cell-based systems/ in vivo pharmacology & toxicology studies
- Tissue cross-reactivity (TCR) studies by comparing human and animal tissue binding profiles.
- Use of homologous molecules
- Transgenic animals

No of animals

- 2 species for short term toxicity studies (≤ 1 mo), if product is pharmacologically active in both
- If findings are similar or the findings are understood from the MoA, 1 species sufficient for longer-term studies
- 1 species for all toxicity studies justified when pharmacological activity is given in only 1 species.
**Dose Selection**

Considering the dose-response relationship:
- Dose at maximum intended pharmacological effect or at 10-fold exposure multiple over the maximum exposure to be achieved in the clinic

OR considering PK data and available *in vitro* binding/pharmacology data

**Duration of Studies**

For chronic use products, repeat dose toxicity studies of 6 months are sufficient.

**Immunogenicity**

Assist in the interpretation of study results. ADA measurement to take place, when:
- Evidence of altered PD
- Unexpected changes in exposure
- Immune-mediated reactions
- Considering the dose-response relationship
- nADA measurements when ADAs are detected and when there is no PD marker to demonstrate sustained activity.
### Reproductive & Developmental Toxicity

- Should be conducted according to guidance S5(R2) *Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility (ICH S5)*
- Reproductive tox in relevant species
- Developmental tox studies to be conducted only in NHPs, when they are the only relevant species
- When no relevant species exist, use of transgenic mice expressing the human target or homologous protein in a species expressing an ortholog of the human target can be considered.

### Carcinogenicity

- Need should be determined regarding the intended clinical population and treatment duration
- In some cases available information can be sufficient to address carcinogenic potential
  - E.g. information from transgenic, knock-out or animal disease models
  - Information on class effects, data from chronic toxicity studies, clinical data etc.
  - MoA may raise concern: e.g. immunosuppressives, growth factors
Estimation of the first human Dose (biologics)

**Toxicology**
- Determine NOAEL
- Convert NOAEL to a human equivalent dose (HED)
  - adjust for anticipated exposure in man
  - adjust for inter-species differences in affinity/potency
- Apply $\geq 10$-fold safety factor

**Pharmacology**
- Estimate human "Minimal Anticipated Biological Effect Level" (MABEL)
  - justify based on pharmacology
  - adjust for anticipated exposure in man
  - include anticipated duration of effect
  - adjust for inter-species differences in affinity/potency

"Maximum recommended starting dose"
- define anticipated safety window based on NOAEL and MABEL
- Appropriate safety factor, if necessary, based on potential risk
Regulated by OCTGT (Office of Cellular, Tissue and Gene Therapies) and CBER (therapeutic vaccines)

Prior to the first clinical trial, “the sponsor must provide adequate information about the pharmacological and toxicological studies .... On the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigation” (21 CFR 312.23)

CGT products are often the result of novel manufacturing processes and/or contain components that have not been previously tested in formal toxicology studies or in clinical trials.

The intrinsic material composition and putative MoA(s) differ from small molecules, biologic drugs and medical devices – traditional, standardized approaches are often not appropriate for safety evaluation of CGT products.

OTGT uses a flexible, science-driven review process to address safety issues considering the biology of the product and intended clinical indication.

Early and ongoing communication with OCTGT is recommended.
Specific Expectations to therapeutic Cancer Vaccines

**Guidance for Industry**

**Clinical Considerations for Therapeutic Cancer Vaccines**

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), HFM-401, 1401 Rockville Pike, Suite 2000, Rockville, MD 20852-1444, or by calling 1-800-877-8390, or by emailing ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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- **Preclinical *in vitro* and *in vivo* PoC** studies provide the rationale for the proposed clinical trial:
  - Different administration routes and treatment schedules including vaccination booster and maintenance therapy are recommended to investigate the kinetics of the immune response.

- **Potential vaccine-related toxicities**: The presence of the target antigen in normal tissues should be determined (e.g. for peptide vaccines, sequence homology searches should be conducted).

- **Toxicology studies**:  
  - Dose levels should be based on dose levels that showed biological activity in PoC studies.  
  - Purpose is to identify a dose level (NOAEL if applicable) that can guide initiation of clinical dosing, after consideration of relevant physiological parameter (body weight, antigen expression, pathology) – there is no predefined conversion factor to enable extrapolation from a safe dose in animals to a potentially safe starting dose in human.

- **In case adjuvants are used**,  
  - Information supporting the value of adding the adjuvant should be provided.  
  - the potential toxicity of the adjuvant alone and of the vaccine-adjuvant combination should be assessed.
Any Questions or Comments?

Anke Domdey (MSc, PhD), anke.domdey@andobio.com, +45 2568 3668