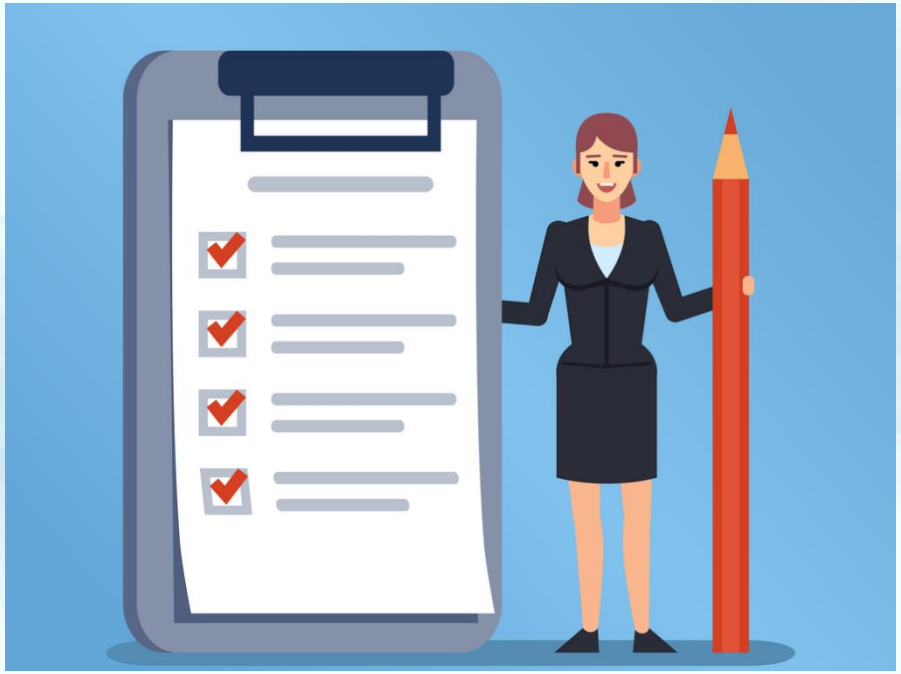
Is your Drug Ready for an IND?

Dr. Tina Rogers
Senior Technical Director, Safety Assessment
WuXi AppTec, Laboratory Testing Division



Agenda

- Where do I start?
- Regulatory Requirements
- Scientific Considerations
- The Big Picture



Where Do I Start?

IND requirements depend on…

- Status/history of drug
- Product attributes (test article type)
- Indication
- Region/country (assumes FDA)

Investigational New Drug Application (IND)

- A key milestone in a drug's development
- The document containing detailed information about your drug's safety that, if approved, will enable the first-in-human (FIH) clinical trial.
- The planned clinical trial needs to be specifically supported by the studies contained in the IND, that's why you need a clinical plan before you design pivotal studies.
- 3 general topics addressed
  - Clinical plan
  - Pharm/tox
  - CMC

Specifics – IND Content and Format Guide

U.S. FOOD & DRUG ADMINISTRATION

Search | Menu

Home / Regulatory Information / Search for FDA Guidance Documents / Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

GUIDANCE DOCUMENT

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

Guidance for Industry

NOVEMBER 1995

Download the Final Guidance Document

Final

Share | Tweet | LinkedIn | Email | Print

Search for FDA Guidance Documents

Docket Number: FDA-1995-D-0251

Issued by: Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research

Content current as of: 05/06/2020

TABLE OF CONTENTS

I. INTRODUCTION 1

II. CURRENT REQUIREMENTS AND PRACTICES 2

III. CLARIFICATIONS OF PRESENT IND REGULATIONS 2

A. Cover Sheet 3

B. Table of Contents 3

C. Introductory Statement and General Investigational Plan 3

D. Investigator's Brochure 3

E. Protocols 3

F. Chemistry, Manufacturing, and Control Information 4

G. Pharmacology and Toxicology Information 10

H. Previous Human Experience with the Investigational Drug 14

I. 21 CFR 312.23(a)(10), (11) and (b), (c), (d), and (e) 14

IV. REFERENCES 14

WHAT IS A “SUCCESSFUL” IND?

A successful IND will contain nonclinical data which supports the *SAFETY* of the proposed first-in-human clinical trial

1. Pharmacology
2. Pharmacokinetics
3. Toxicology

1. PHARMACOLOGY

A SUCCESSFUL IND WILL INCLUDE UP TO 4 KINDS OF PHARMACOLOGY STUDIES:

- Primary pharmacodynamic studies
- Secondary pharmacodynamic studies
- Safety pharmacology studies
- Pharmacodynamic drug interaction studies

1. PHARMACOLOGY
PRIMARY PHARMACODYNAMICS

- Include information on target biology, target tissue distribution and cross-species sequence homology
- Focus efficacy studies on the intended indication
- For an oncology indication:
  - Studies should characterize the mechanism(s) of action and schedule dependencies as well as anti-tumor activity of the pharmaceutical
  - Appropriate models should be selected based on the target and mechanism of action, but the pharmaceutical need not be studied using the same tumor types intended for clinical evaluation.
- Focus on conducting and submitting properly-designed and well-controlled *in vitro/in vivo* mechanistic and efficacy studies
  - Include assessments of systemic exposure in efficacy models
  - More is not better!
- Prepare and submit study reports

1. PHARMACOLOGY
SECONDARY PHARMACODYNAMICS

Broad ligand binding data to assess the potential for off-target effects

	Target	Host	Agonist	Antagonist
1	**Alpha 1a**	HEK293	(-)Epinephrine	5-Methylurapidil
2	**alpha2A**	HEK293	UK14304	Yohimbine hydrochloride
3	**ADORA2A**	CHO	NECA	CGS-15943
4	**Beta1**	HEK293	R(-)-Denopamine	(±)-Propranolol hydrochloride
5	**Beta2**	HEK293	Adrenaline	Carvedilol
6	**CB1**	CHO	WIN55212-2	SR 141716A
7	**CB2**	CHO	CP55940	SR 141716A
8	**CCKa**	HEK293	CCK-4	Lorglumide
9	**D1**	HEK293	(±)-SKF-38393	R(+)-SCH-23390 hydrochloride
10	**D2**	HEK293	Dopamine	Amisulpride
11	**ETa**	HEK293	Endothelin 1	BQ-124
12	**H1**	HEK293	Histamine	Pyrilamine maleate salt
13	**H2**	HEK293	Amthamine dihydrobromide	Cimetidine
14	**5HT1a**	HEK293	5-CT	Methiothepin mesylate salt
15	**5HT2a**	HEK293	5-CT	Methiothepin mesylate salt
16	**M1**	HEK293	Arecaidine propargylester	Pirenzepine dihydrochloride
17	**M2**	HEK293	Arecaidine propargylester	Atropine
18	**M3**	HEK293	Arecaidine propargylester	Atropine
19	**hr op-delta**	HEK293	DPDPE	Naltrindole
20	**op-kappa**	HEK293	U69593	nor-Binaltorphimine dihydrochloride
21	**op-mu**	HEK293	DAMGO	CTOP
22	**V1a**	CHO	[Arg8]Vasopressin acetate	[β-Mercapto-β,β-cyclopentamethylenepropionyl1, O-Et-Tyr2, Val4, Arg8]-Vasopressin

WuXi AppTec GPCR SAFETY PANEL

1. PHARMACOLOGY
SAFETY PHARMACOLOGY

- An IND for a NON-ONCOLOGY indication will include a full battery of safety pharmacology studies (see ICH S7A and ICH S7B)
- An IND for an ONCOLOGY indication need not include any safety pharmacology data at all (see ICH S9)
    - Safety pharmacology endpoints can be incorporated into general toxicology studies
    - In cases where specific concerns have been identified that could put patients at significant risk in clinical trials, stand-alone safety pharmacology studies could be warranted.
    - IRBs and clinicians like to see data relating to potential pro-arrhythmic risk (i.e., cardiac ion channel data)

2. PHARMACOKINETICS (ADME)

A successful IND will include:

- *In vitro* metabolic and plasma protein binding data for animals and humans
  - Key to selecting appropriate rodent and non-rodent tox species for a small molecule
- Systemic exposure data in the species used for repeated-dose toxicity
- Non-oncology [per ICH M3(R2)]
  - ADME information in test species and *in vitro* biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration (generally before Phase III).
- Oncology [per ICH S9]
  - The evaluation of limited pharmacokinetic parameters in the animal species used for nonclinical studies can facilitate dose selection, schedule and escalation during Phase I studies.
  - FDA often expects CYP induction/inhibition and transporter data to support a Phase 1 trial in cancer patients

2. PHARMACOKINETICS (ADME)
DMPK - EARLY DISCOVERY TO THE CLINIC

Chemical Screening, Optimization, Nomination

***In vitro* ADME & *In vivo* PK**

Screening

- Physico-chemical property (Kinetic Solubility, Log D)
- Plasma protein binding
- Microsomal/hepatocyte stability
- CYP inhibition
- Permeability in MDR1-MDCK or Caco2
- Rodent PK (discrete or cassette dosing)
- *In vivo* efficacy study in rodent
- Soft spot Met ID
- Reactive metabolite screening
- Plasma stability
- CYP induction screening
- SIF & SGF stability

Candidate Selection

- *In vitro/In vivo* metabolite profiling
- Bidirectional permeability in Caco2
- PgP evaluation
- PK profile at efficacious doses in efficacy animal model species
- Species specific PK (rodent and non-rodent)
- Vehicle screening (rodent and non-rodent)

Pre-Clinical Research

***In vitro* ADME & *In vivo* PK**

IND Enabling

- Plasma protein binding
- CYP inhibition/TDI/Induction
- CYP/UGT phenotyping
- PgP and BCRP assays
- Metabolite identification and profiling, cross species Met ID
- Dose proportionality PK in efficacy and TOX species
- Repeat dose PK in TOX species
- Full panels of Transporter Inhibition and Substrate assays

3. TOXICOLOGY

A successful IND will include:

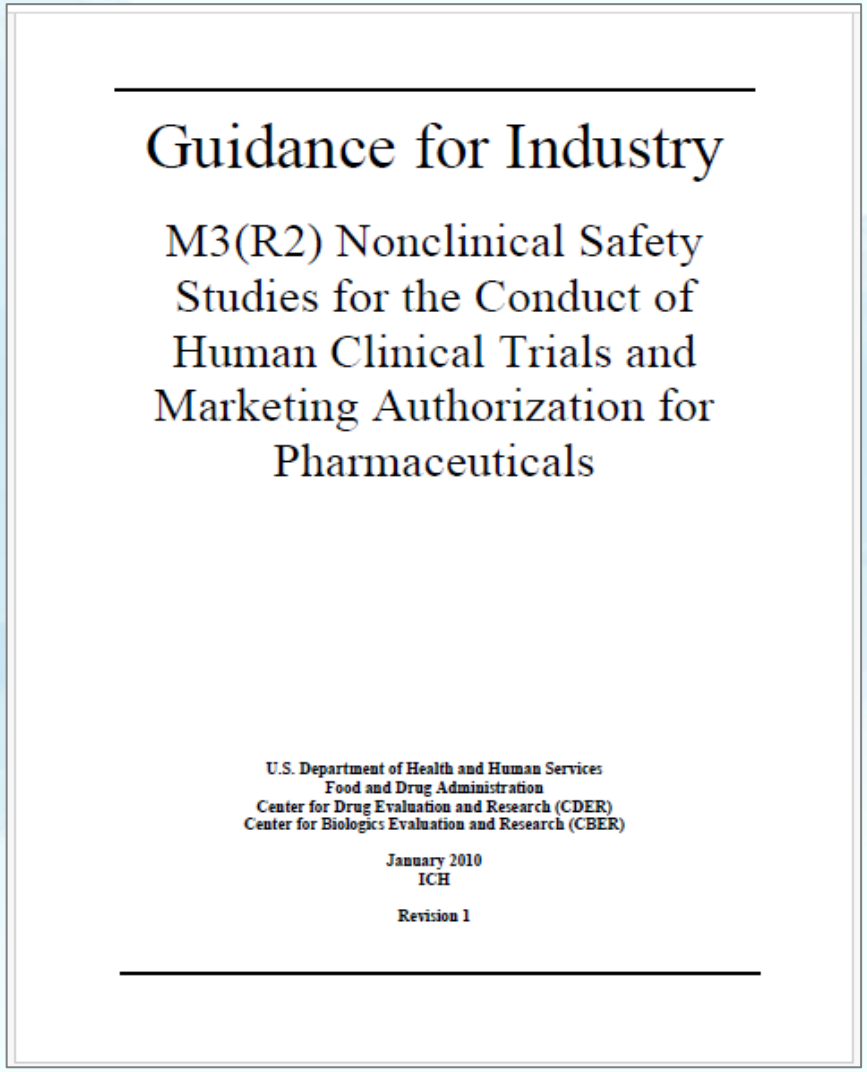
- General toxicology studies in 2 mammalian species (one of which must be a nonrodent)
  - Dose range-finding studies to support dose selection for definitive studies (nonGLP)
  - Definitive studies (GLP)
  - Studies should be conducted using a clinically-relevant route of administration
  - Studies supporting oncology indications should be conducted using a clinically-relevant schedule of administration
- Genotoxicity studies
  - *In vitro* mutagenicity and cytogenetic studies (*in vivo* study can be done prior to Phase II)
  - Not required to support clinical trials in oncology patients with advanced disease
- Other studies as necessary (e.g., skin and eye irritation for dermal products, etc.)

3. TOXICOLOGY

- Once you have justified your high-dose level, choose appropriate mid- and low-dose levels
  - The idea is to get a sense of dose-response across a wide dose range
  - Consider half-log dosing progressions (e.g., 10, 30 and 100 mg/kg/day; 20, 60 and 200 mg/kg/day)
- Deliverables from definitive repeat-dose tox studies:
  - Target organ profile
  - Assessment of dose response
  - Assessment of monitorability
  - Assessment of reversibility
  - Parameters to be monitored in humans
  - Dose levels used to set clinical starting doses:
    - Non-oncology indication: NOAELs (both species)
    - Oncology: STD10 (rodent); HNSTD (nonrodent)

ICH GUIDANCE DOCUMENTS – PRODUCT ATTRIBUTES

SMALL MOLECULES



Guidance for Industry

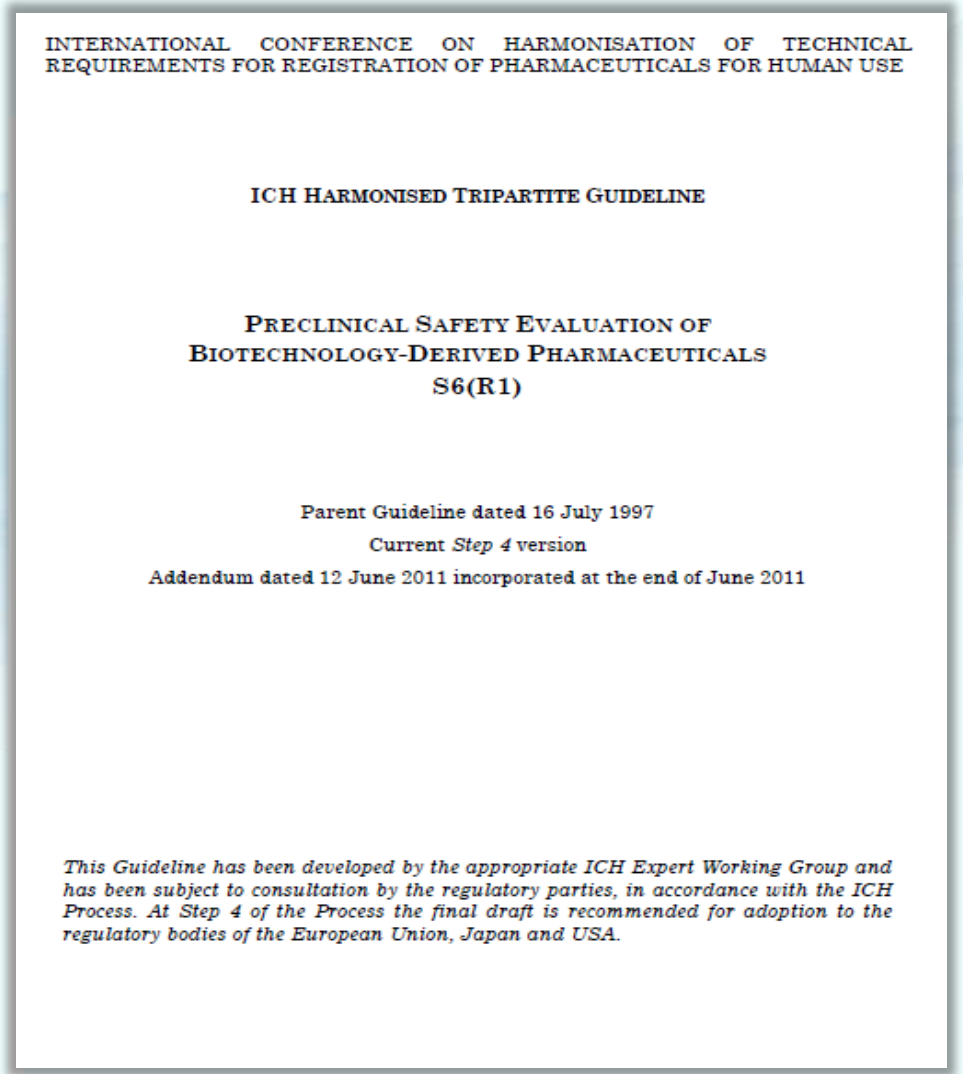
M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

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)

January 2010
ICH

Revision 1

BIOPHARMACEUTICALS



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS
S6(R1)

Parent Guideline dated 16 July 1997

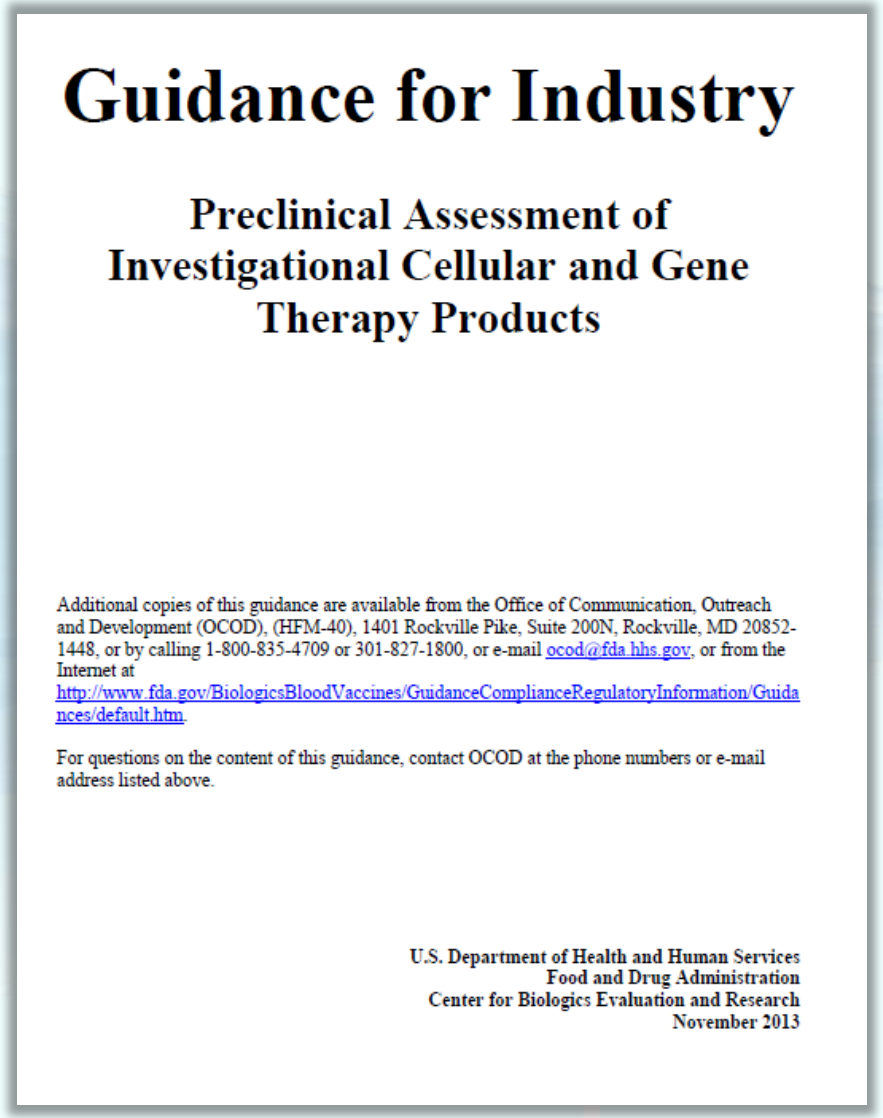
Current *Step 4* version

Addendum dated 12 June 2011 incorporated at the end of June 2011

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

ICH GUIDANCE DOCUMENTS – PRODUCT ATTRIBUTES

CELL/GENE THERAPIES



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), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.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 INFORMATION

IND Program Differences: Small vs Large Molecule

	Small Molecule	Large Molecule
Species Selection	Metabolism as a primary factor (rodent and non-rodent)	Pharmacology as a primary factor; may be only one species
Dose Selection	Based on toxicity (maximum tolerated dose)	Based on pharmacology or maximum feasible dose
Pivotal Toxicology	Two species required; duration from 2-4 weeks	One species may be sufficient; duration usually 4 weeks
Safety Pharmacology	Usually, stand-alone studies*	Incorporated in toxicology studies as needed
Genetic Toxicology	Required	May not be required

ICH M3(R2) “General guidance for drug development” 1/2

Broad Scope – Applies to “Usual Situations Encountered During Drug Development”

- Pharmacology – “safety” core battery for FIH, references **ICH S7A** and **S7B**
- Toxicokinetic and pharmacokinetic studies – see **ICH S3A**
  - Metabolic and protein binding studies and systemic exposure for FIH, ADME prior to Phase 3
- Acute toxicity studies - Short duration dose-ranging studies
- Repeated-dose toxicity studies – dose selection and duration (see below)
- Estimating 1st dose in humans – NOAEL and all relevant non-clinical data considered
- Exploratory clinical trials - approaches and nonclinical requirements based on clinical exposure
- Local tolerance studies – injection site evaluation in tox studies sufficient
- Genotoxicity (timing) – mutation and chromosomal damage prior to FIH; see **ICH S2(R1)**

Note: for biotechnology-derived products, M3R2 only addresses timing on nonclinical relative to clinical (see S6)

ICH M3(R2) “General guidance for drug development” 2/2

Broad Scope – Applies to “Usual Situations Encountered During Drug Development”

- Carcinogenicity (timing) – needed for marketing, references **ICH S1A**
- Reproductive and developmental toxicity – types and timing based on patient population: see **ICH S5(R3)**
- Clinical trials in pediatric populations – JAS only if adult data are insufficient (vs S11 WoE approach)
- Immunotoxicity – WoE approach, references **ICH S8**
- Phototoxicity – photochemical properties, chemical class and distribution; see **ICH S10**
- Nonclinical abuse liability – prior to Phase III CNS drugs w/abuse liability patterns; regional requirements (e.g., FDA)
- Combination drug toxicity testing – depends on status of individual components; see also Q&A document

Note: for biotechnology-derived products, M3R2 only addresses timing on nonclinical relative to clinical (see S6)

ICH M3(R2) – Highlight #1

High Dose Selection for General Tox Studies

- Dose levels for rodent and nonrodent species are selected independent of one another based on results of range-finding studies

- High-dose levels used in definitive studies based on specified criteria:
  - Maximum Tolerated Dose (MTD)
  - Exposure saturation
  - Maximum Feasible Dose (MFD)
  - Mean exposure margin 50X clinical

ICH M3(R2) – Highlight #2

Duration of Repeated-Dose Toxicity Studies

Clinical Trials

Table 1
Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials

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	2 weeks
Between 2 weeks and 6 months	Same as clinical trial	Same as clinical trial
>6 months	6 months	9 months

Marketing

Table 2
Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing

Duration of Indicated Treatment	Rodent	Non-Rodent
Up to 2 weeks	1 month	1 month
>2 weeks to 2 months	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months	6 months

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

"Basic framework for…biotechnology-derived pharmaceuticals"

- Applies to "proteins, peptides, their derivatives and products of which they are components"
- Principles *may* apply to recombinant DNA protein vaccines, chemically synthesized peptides, plasma derived products, endogenous proteins extracted from human tissue, and oligonucleotides
- Does not cover antibiotics, allergenic extracts, heparin, vitamins, cellular blood components, conventional bacterial or viral vaccines, DNA vaccines, or cellular or gene therapies.

S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: Content 1/3

Part I

- Specification of test material – purification to remove contaminants vs preclinical testing to qualify them
- General Principles – GLP compliance, etc.
- Biological Activity/Pharmacodynamics – *in vivo* and *in vitro* assays, receptor occupancy/affinity etc.
- Animal Species/Model Selection –variety of immunochemical and functional tests to determine relevancy
- Number/Gender – both genders, increase duration/frequency to maximize use of NHPs.
- Dose administration/selection – relevant to clinical route; dose level justification in absence of toxicity
- Immunogenicity – not translatable; needed for interpretation of nonclinical studies; collect samples, analyze?
- Safety Pharmacology – incorporate into repeat dose toxicity studies
- Exposure assessment - PK/TK, Immunogenicity
- Metabolism – classic biotransformation not applicable

S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: Content 2/3

Part I

- Single dose toxicity studies – may generate useful data for repeat dose studies
- Repeated dose toxicity studies – include recovery period to demonstrate reversibility of toxicity
- Immunotoxicity studies - routine tiered testing not applicable
- Reproductive and developmental toxicity – product, patient population, indication-dependent
- Genotoxicity – not routinely required
- Carcinogenicity studies – generally not required
- Local tolerance studies – product intended for marketing should be tested

S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: Content 3/3

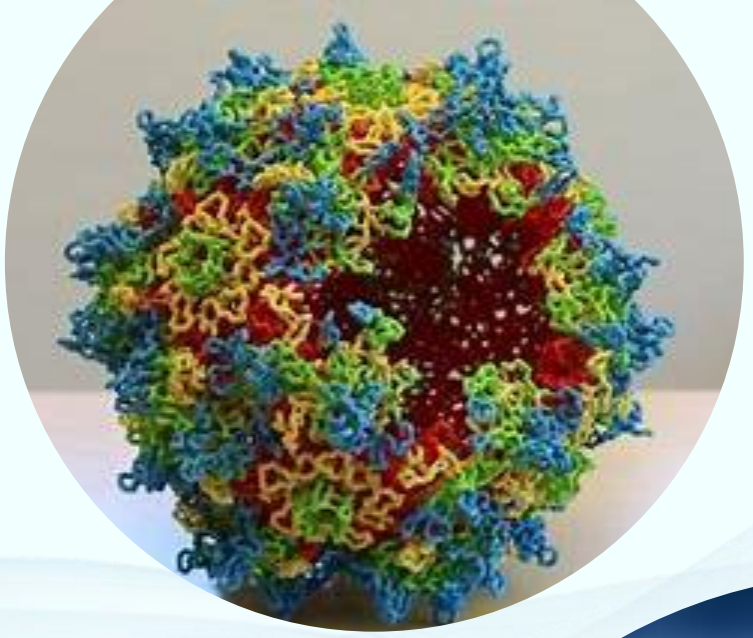
Part II (Addendum)

Provides clarification and update (supersedes Part I) on the following:

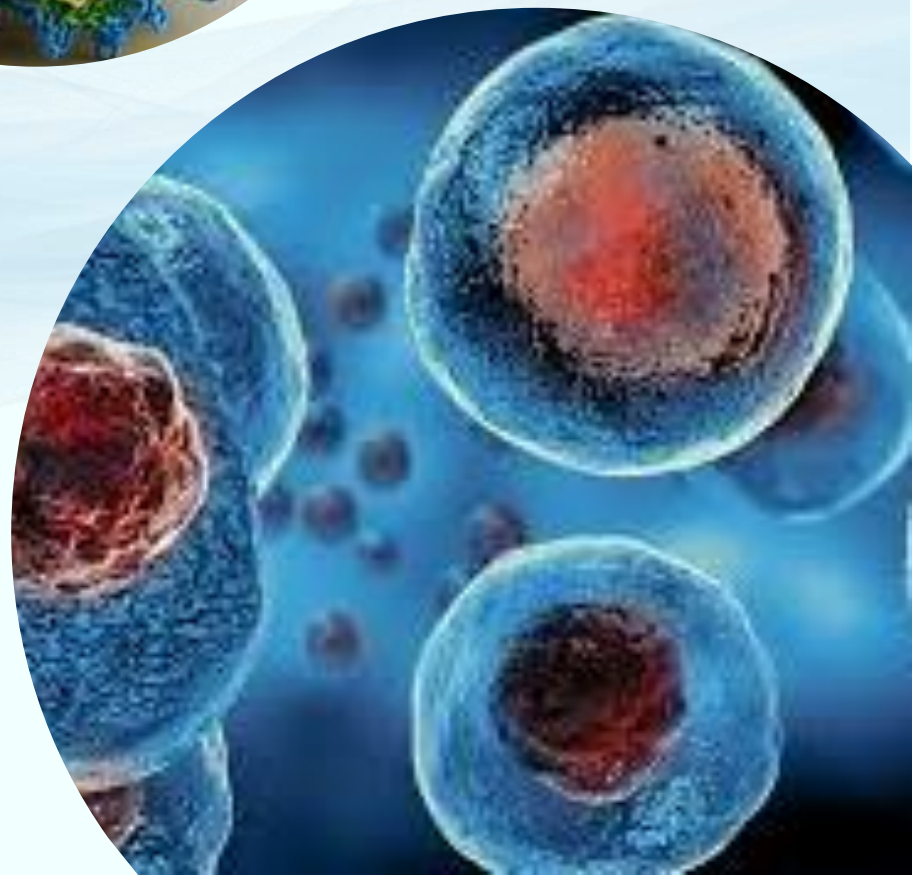
- Species selection - TCR of limited value; sequence homology, affinity, functional activity recommended
- One or Two? 2 relevant species for 1 mo studies, 1 for subsequent studies if pathology findings are similar
- Dose selection – PK/PD principles; high dose- max pharmacological effect or 10x planned clinical exposure
- Duration - 6 month repeat dose max for chronic use products
- Recovery – include in at least one dose level in one study, complete recovery not necessary
- Immunogenicity- altered PK/PD, unexpected exposure changes, immune mediated rxn; collect samples!
- Reproductive/developmental- if WoE suggests adverse effect, studies may not be needed
- Carcinogenicity – rodent bioassays not usually useful, hazard addressed using labeling and risk management

IND GUIDANCE INFORMATION

Key Differences: Gene/Cell Therapies

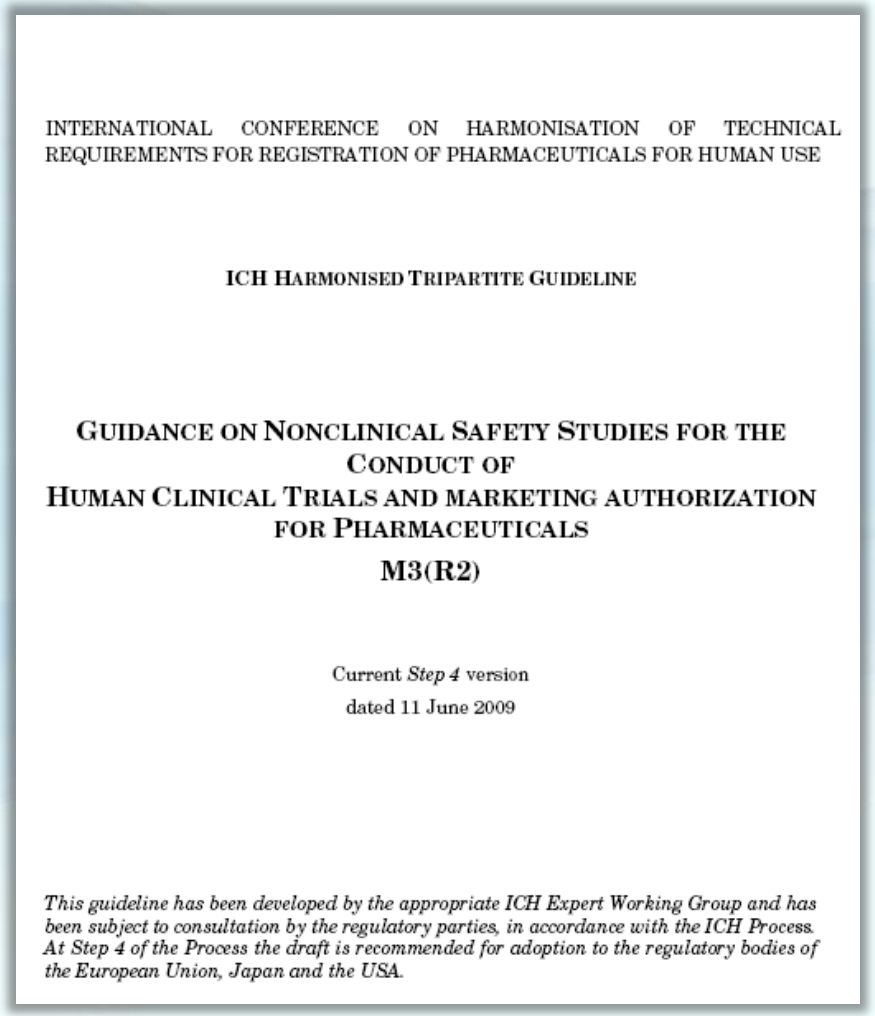


- *Nonstandard approaches are acceptable when justified. *
- Safety pharmacology, genetic toxicology not routinely required
- Stem cell therapies will require tumorgenicity studies.
- For rare disease indications, infant/juveniles may be required.
- Biodistribution (q-PCR/RT-PCR) in tissues vs. bioanalysis (LCMS, ELISA) in plasma.



ICH GUIDANCE DOCUMENTS – INDICATION-BASED

NON-ONCOLOGY



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

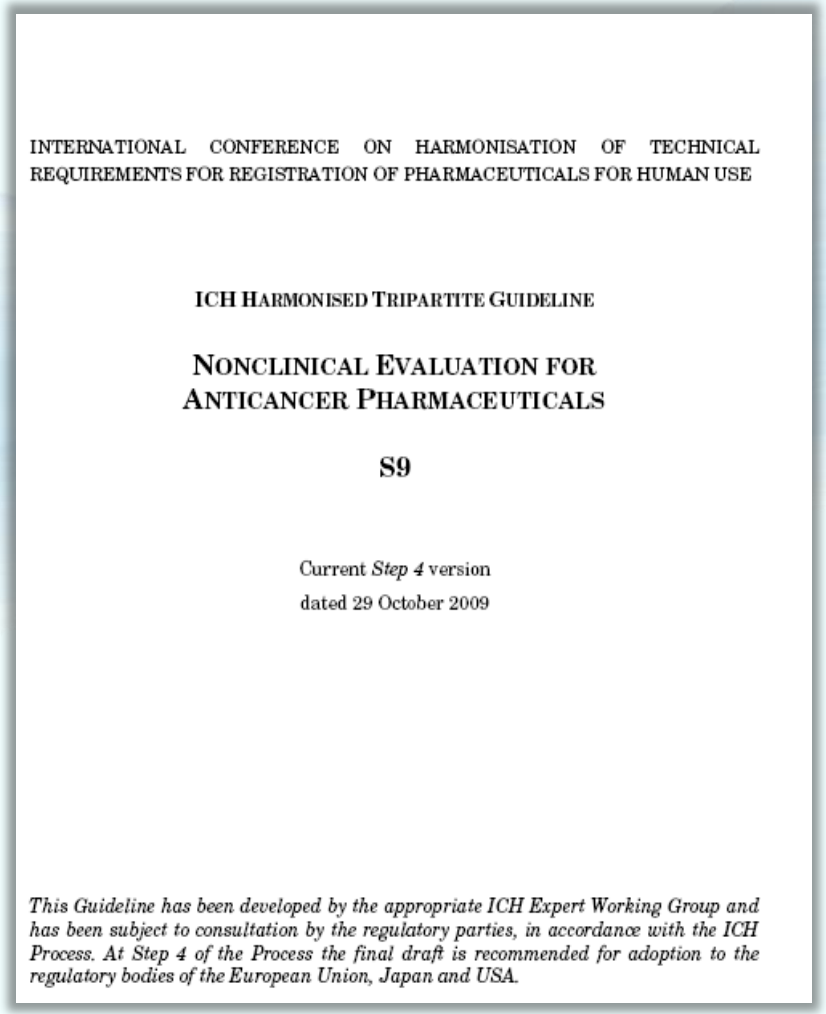
GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS

M3(R2)

Current *Step 4* version
dated 11 June 2009

This guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA.

ONCOLOGY



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

NONCLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS

S9

Current *Step 4* version
dated 29 October 2009

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Oncology vs Non-Oncology Requirements

- Stand alone safety pharmacology not generally required
- Genotoxicity not required for IND
- Clinical starting dose based on STD10 (rodent); HNSTD (nonrodent)

CLINICAL STARTING DOSE

- Based primarily on toxicology data (but all nonclinical data should be considered)
- Different approaches for non-oncology and oncology indications
  - Due to different populations to be exposed
    - Non-oncology: healthy volunteers
      - Starting dose MUST be safe
      - 100% risk:0% potential benefit
    - Oncology: patients with advanced disease
      - Starting dose must be reasonably safe and potentially efficacious
      - ~90% risk: ~10% potential benefit

SCIENTIFIC CONSIDERATIONS

"The design of safety evaluation programs should be question- and science-based, data-driven, and practical"

J Cavagnaro, Translational Medicine Chapter 7, CRC Press 2022

- Is the mechanism of action known and is it novel?
- Are animal models available?
- Can proof-of-concept be demonstrated?
- What is the optimal route/site/procedure/timing for product delivery?
- What is the proposed optimum regimen, duration?
- Where does the product go?
- What are the organs of toxicity?
- Is toxicity monitorable, delayed, reversible?

SCIENTIFIC CONSIDERATIONS (CONT.)

"The design of safety evaluation programs should be question- and science-based, data-driven, and practical"

J Cavagnaro, Translational Medicine Chapter 7, CRC Press 2022

- Are there known class effects? Are they relevant to clinical population?
- What is the risk/benefit to the clinical population? Potential to see activity in early trials?
- Is the FIH trial in a vulnerable population?
- Should drugs used to mitigate toxicity in clinical trials also be used preclinically?

A REMINDER…

A successful IND will contain nonclinical data which supports the ***SAFETY*** of the proposed first-in-human clinical trial

- Pharmacology
- Pharmacokinetics
- Toxicology

A SUCCESSFUL IND PROGRAM

Starts with the Planning

- **Begin With the End in Mind**
  - Clinical plan defines preclinical approach
- **It's all About the Details**
- **Monitor Early Studies to Allow for Adjustments**
- **Keep an Eye on the Big Picture**
  - Goal is to get drug to market, not just get into the clinic.

KEYS TO SUCCESS – THE BIG PICTURE

药明康德 WuXi AppTec

- Consider history, attributes, indication of drug
- Align program objectives with regulatory requirements
- Design a scientifically sound preclinical plan
- Select partners who can enable drug development goals

Q&A

QUESTIONS

药明康德
WuXi AppTec

Improving Health.
Making a Difference.

https://labtesting.wuxiapptec.com/