

Regulatory Recommendations for Ocular Biologics Development

(IVT Monoclonal antibodies/antibody-like
molecules)

Maria I Rivera, Ph.D.

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
(ORPURM)/Office of Specialty Medicine (OSM)
Division of Pharm/Tox for ORPURM/OSM
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DISCLAIMER

The views of the author expressed in this presentation do not necessarily reflect the views or policies of the US Food and Drug Administration.

Outline

- Introduction
- Species Selection
- Studies Recommended
 - Pharmacology, PK/ADME, General Toxicology (ocular and systemic route), Immunogenicity (impact in ocular findings interpretation), Genotoxicity, Carcinogenicity, Reproductive Toxicity
- Summary

Principles to Keep in Mind

- Regulatory decisions are made on a case-by-case basis
- Decisions are based in all data submitted for each individual development program
- In addition, other factors considered include indication, patient population, clinical treatment duration, previous clinical experience, class effect knowledge, experience with similar molecules, etc.
- Recommend to consult the Agency for feedback and guidance (Pre-IND, EoP2, pre-BLA, etc.)

Key Guidances

- ICH S6 – Preclinical safety evaluation of biotechnology-derived pharmaceuticals
- ICH S6(R1) – Addendum to preclinical safety evaluation of biotechnology-derived pharmaceuticals
- ICH M3(R2) – Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals
- ICH S7A – Safety pharmacology studies for human pharmaceuticals
- ICH S5(R3) – Detection of toxicity to reproduction for medicinal products and toxicity to male fertility
- CDER - Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers
- CBER - Points to consider in the manufacture and testing of monoclonal antibody products for human use (section with recommendations for nonclinical testing)
- ICH S3A - Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
- ICH S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
- 21CFR58: Good laboratory practice for nonclinical laboratory studies
- Others as needed

Species

- Pharmacologically relevant
 - A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies).
- Toxicity testing in a pharmacologically relevant species may provide data that reflects both on-target and off-target activity.
- Toxicity testing in a species that is not pharmacologically relevant may provide only off-target activity data, limiting the toxicity profile.
- Toxicity studies in nonrelevant species may be misleading and are discouraged.

Species

- ICH Guidances for Industry S6 and S6(R1)
- Comparative assessments across potential test species and humans:
 - Target sequence homology
 - Cannot assume similar activity unless sequences are 100% homologous
 - In vitro assays of relative target binding affinities
 - In vitro assays of receptor/ligand occupancy, and kinetics
- Comparative functional activity in species-specific cell-based systems and/or in vivo
 - Binding to the desired target does not always translate to change in functional receptor activation.
- Modulation of a known biologic response or of a pharmacodynamic (PD) marker can provide evidence for functional activity

Species

- Anatomical/physiological differences
 - Eye similarity to humans: Monkey > minipig > dog > rabbit > rodents
- Target expression (ocular and systemic)
- Immunogenicity
 - Rabbits tend to be more immunogenic
 - May not be adequate for repeat-dose studies.
 - Pilot data can be collected to test utility of repeat dose in rabbit.

Species

- One or two?
 - ICH S6(R1)
 - If there are two pharmacologically relevant species for the clinical candidate (one rodent and one nonrodent), then both species should be used for short-term (up to 1 month duration) general toxicology studies
 - Ocular drugs – 2 nonrodents are typically used.
 - If the toxicological findings from short-term studies are similar or the findings are understood from the mechanism of action of the product, then longer term general toxicity studies in one species may be considered sufficient.
 - No toxicity at 1 month in either species does not allow for use of a single species in long term studies – toxicities not identified.
 - One species when there is only one pharmacologically active species

Species

- Justification for the relevancy of the species selected for toxicity testing should be included.
- If only one species is used for safety evaluation, empirical data that demonstrate the absence of additional relevant species is warranted.
- No relevant species exists - relevant transgenic animals expressing the human target antigen or the use of homologous proteins (ICH S6)
 - Hazard identification (not useful for quantitative risk assessment)

Studies Recommended

- Primary Pharmacodynamic
 - Binding assays to demonstrate target selectivity
 - In vitro/in vivo functional assays – proof of concept, prediction of active clinical dose range
 - Use same toxicology species, when feasible
 - Direct comparison of activity and adverse findings
- Secondary Pharmacodynamic
 - Test article dependent
 - ADCC
 - CDC
 - Tissue cross reactivity

Studies Recommended

- Safety Pharmacology
 - Usually incorporated in ocular toxicity study (additional arm by systemic route) and/or by conduct of systemic route toxicity studies
 - If there is negligible systemic exposure following IVT administration, studies may not be needed
 - Negligible – produces no activity in adequately conducted functional activity assays and produces no systemic effects in animal toxicology studies/clinical studies

Studies Recommended

- PK/ADME
 - These data should be collected to help define the relationship between drug concentrations in tissues and pharmacologic/toxicologic responses, thereby facilitating interpretation of nonclinical study results.
 - These data can be used to identify target tissues and select appropriate endpoints to be evaluated in subsequent nonclinical studies.
 - These data should be considered to determine adequate termination and evaluation timepoints.
 - Data may aid in determination of an appropriate dosing regimen in the clinical trials.

PK/ADME

- Some data should be collected before initiating toxicology studies

Case Example

- 12-Week ocular tox study: IVT injection on Day 0, Day 30, and Day 60
- Termination timepoint: Day 90
- Termination timepoint interval from last IVT injection is 30 days
- No PK data available

Without PK data, the duration of the full exposure period cannot be determined, and the possibility exists that the termination timepoint(s) may occur during a no-exposure period (recovery) resulting in an incomplete toxicologic profile.

PK/ADME

- Ocular tissue distribution studies
 - Conjunctiva, cornea, aqueous humor, iris, ciliary body, lens, vitreous humor, choroid, retina, optic nerve, sclera
 - Some tissues are sometimes combined: iris/ciliary body, choroid/retina
 - Plasma exposure
 - C_{\max} , AUC, T_{\max} , $t_{1/2}$ for each tissue
 - Assays sufficiently sensitive and the LLOQ adequate to capture the lowest biologically active exposure
 - Important when establishing negligible exposure level

- IV (or other systemic route) studies
 - Compare ocular vs systemic $t_{1/2}$, determine bioavailability after IVT administration
 - Help with design of systemic route studies

PK/ADME

- Species
 - Preferable to use a relevant species
 - Typically, rabbit or monkey are used
- Single/repeat administration
 - Generally, single dose
 - Repeat administration if expect accumulation

Studies Recommended

- General Toxicology
 - Ocular route
 - Same route as clinical (IVT)
 - Sufficient duration to support clinical
 - Full clinical product (clinical formulation)
 - Systemic route
 - IV, SC, IM
 - At least 1 month duration
 - No need to use clinical formulation.
 - If systemic exposure after IVT administration is $\geq 10X$ high clinical dose and adequate systemic endpoints were included in IVT toxicity studies, may justify no need to conduct

Ocular Tox Studies - Study Duration

- ICH Guidance for Industry M3(R2)
 - Recommended study duration for IND or BLA submission – note the differences

IND

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	Nonrodents
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}

BLA

Duration of Indicated Treatment	Rodent	Nonrodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months ^c	9 months ^{c, d}

Ocular Tox Studies - Study Duration

- Longer duration for marketing authorization
 - Because of the size of the population at risk and the relatively less controlled conditions in clinical practice in contrast to clinical trials, longer durations of nonclinical testing are recommended for marketing approval, as per ICH M3(R2), up to a maximum of 6 months.

Ocular Tox Studies - Formulation

- Formulation

- Full clinical product should be used.
- Novel excipients are qualified in the IVT toxicology studies, presuming a safe dose is identified
 - Vehicle control group and test-article groups
- Changes in the formulation may result in the need for additional bridging pharmacokinetic and/or toxicology studies.

Some scenarios

- If Sponsor is increasing/decreasing the amount of an existing excipient, a bridging PK study may be sufficient
- If adding a new excipient, may need a tox study
- Manufacturing changes resulting in changes in biological activity – may need a tox study

Ocular Tox Studies – Concentration/Dosing Frequency

- Concentration/dosing frequency
 - Concentration of API and/or frequency of dosing should be the same and higher (preferably 10X max clinical dose, if feasible) than intended in humans
 - Assess dose-response relationships/establish adequate exposure margin for adverse findings
 - Multiple of the maximum intended human exposure, by either using higher API concentrations and/or a more frequent dosing schedule
 - Testing lower concentrations than proposed in humans is not useful
 - Exposure margins < 10X may be acceptable provided adequate justification is presented (e.g., MFD, solubility issues/limitations on dosing volume)

Ocular Tox Studies – Dose Selection/Exposure Margins

- Dose selection should be adjusted to reflect species differences in vitreous volume and differences in pharmacological activity
- Example exposure margin calculations:
 - NOAEL = 1 mg/eye IVT
 - Low clinical IVT dose = 0.05 mg/eye; high clinical IVT dose = 0.5 mg/eye
 - Vitreous volume: 2 mL (monkey); 4 mL (human)
 - Functional assay IC₅₀ = 20 nM in monkey; 4 nM in humans (5X difference)

Nonclinical			Clinical Exposure Margins (Animal dose/clinical dose)	
Species	NOAEL (mg/eye)	NOAEL (mg/mL vitreous)	Starting Dose (0.05 mg = 0.0125 mg/mL vitreous)*	MRHD (0.5 mg = 0.125 mg/mL vitreous)
Monkeys	1	0.5	40X	4
			8X (adjusted)	0.8X (adjusted)

Ocular Tox Studies – Study Design

- 3 API dose levels are standard – sometimes see 2 dose levels
- Vehicle control group
- Doses selected to provide dose-response relationship
 - No adverse findings to adverse findings
 - NOAEL identification
 - Dose-response relationships not always observed with biologics – ADA formation, target saturation?
- Both genders

Ocular Tox Studies – Study Design

Ocular Endpoints	Systemic Endpoints
<p>Clinical signs/gross observations Slit-lamp biomicroscopy Indirect biomicroscopy/funduscopy Tonometry Histopathology (incl. macula/fovea) Electroretinography Other measurements (OCT, VEP, fluorescent angiography, fundus autofluorescence, fundus photography, PD marker [e.g., vitreous VEGF levels], test article vitreous levels, vitreous ADA, etc.)</p>	<p>Clinical signs/physical examination Body weight/weight gain Food consumption Clinical pathology Necropsy Organ weights Histopathology Toxicokinetics Immunogenicity Others (PD markers [e.g., plasma VEGF levels, complement factors, inflammatory cytokines], safety pharmacology endpoints, etc.)</p>

Note: Pharmacokinetic data should be considered to determine adequate termination and evaluation timepoints.

Ocular Tox Studies - Ocular Histopathology

- Ocular tissues, optic nerves, ocular adnexa (e.g., eyelids, nictitating membrane, Harderian glands, lacrimal glands, and adjacent muscles), and nasal mucosa at the level of nasolacrimal duct termination
- Multiple sections are often necessary to adequately characterize ocular toxicity at the cellular/tissue level.
- Macula/fovea or species equivalent should be fully assessed for IVT products.
- Data/images from ophthalmic exams also can be used to guide histologic sectioning of the eye.

Ocular Tox Studies - Systemic Histopathology

- Standard battery of systemic tissues is recommended.
- If the species/strain used in ocular toxicity studies is the same as that used in systemic-route general toxicity studies, and a sufficient margin of exposure was established over maximal intended clinical dose in the systemic-route study, then histopathology of systemic tissues may not be necessary in an ocular toxicity study of a similar or shorter duration.

Ocular Tox Studies - Recovery phase

- Recommend evaluate at least in control and high-dose groups and read down for observed findings
- Inclusion is optional. However,...
- In the absence of recovery group data, the default assumption is that the toxicity is not reversible. That factors into safe dose calculations.
- Pharmacokinetic data should be considered to determine adequate duration of recovery phase.
 - The half-life of the mAb influences the duration of the recovery period.
 - It takes approx 5 half-lives to eliminate almost all of the antibody following cessation of antibody administration.

Systemic Route Tox Studies

- A systemic-route general toxicity study should be conducted, unless the ocular toxicity study provides at least a 10-fold exposure margin over the maximum clinical exposure/dose.
 - In some cases, see addition of one arm with systemic route administration in IVT tox study (at dose $\geq 10X$ high IVT dose)
 - However, single dose studies can be difficult to interpret when systemic toxicity is observed (without dose response all observed effects will be considered treatment related)
- As noted earlier, exposure margin calculations should take into account animal-human differences in binding affinity or pharmacodynamic potency.
- Use TK data when clinical PK data is available.

Systemic Route Tox Studies

- The duration of systemic-route general toxicity studies is generally guided by the planned duration of clinical exposure [ICH M3(R2)].
- If negligible systemic exposure is demonstrated following ocular administration in short- and long term/chronic ocular-route toxicity studies and there are no findings of concern, systemic-route general toxicity studies of longer duration (e.g., chronic systemic-route studies) may not be needed.
 - Under these conditions, duration is generally at least 1 month
- Usually one species – because of negligible systemic exposure and sufficient systemic endpoints evaluated in IVT tox studies, or only one relevant species exists (monkey).
 - Sponsor needs to justify the use of one species.
- Recovery groups may also be included.

Systemic Route Tox Studies – Study Design

Systemic Endpoints

Clinical signs/physical examination
 Body weight/weight gain
 Food consumption
 Ophthalmology – slit-lamp/indirect ophthalmoscopy
 Clinical pathology
 Necropsy
 Organ weights
 Histopathology – standard panel of systemic tissues
 Toxicokinetics
 Immunogenicity
 Others (e.g., PD marker, safety pharm endpoints)

Immunogenicity

- Many biologics intended for humans are immunogenic in animals.
- Ocular inflammation is generally observed after IVT administration.
- Important to determine if inflammation is ADA related or a direct test article related effect
 - MoA support test article may cause direct inflammation?
 - Classical findings of ADA response (may also be observed with direct inflammation):
 - Cell infiltrates (mixed, mononuclear, plasma cells), perivascular sheathing, vitreous/aqueous cells, vitreous haze, keratic precipitates, others
 - Timing of ADA compared to ocular inflammation
 - e.g., ADA present at 2 weeks postdose, prior to development of ocular inflammation
 - All eyes with inflammation – ADA positive
 - All eyes ADA negative – No inflammation
 - Immune complex formation and deposition (immunohistochemistry)

Case Study

- Humanized antibody
- Initial IND – 2-week and 2-month ITV/IV tox studies in monkeys; 2-week study in rabbits
- Severe ocular inflammation (rabbits & monkeys)
- Heart findings (rabbits & monkeys)
 - Preliminary IHC data in monkeys supported immune complex deposition in the aorta (consistent with ADA formation), but similar data not provided in the eye.
 - Safety concern of direct severe ocular inflammation remained.
 - Mechanism of action supported a direct pro-inflammatory effect.
- Sponsor concluded findings secondary to ADA response - not relevant to humans

Case Study

- Nonclinical data supported the starting dose, but not the high dose due to safety concerns of severe ocular inflammation. It was not known if the inflammation was a direct or indirect inflammation through an ADA response in the eye
- It was recommended that the clinical protocol be adjusted to accommodate safety concern.

Case Study

- 6-month IVT tox monkey study
 - Severe ocular inflammation observed at 2 highest dose levels.
 - NOAEL provided no exposure margin (<1X intended clinical dose).
 - Most endpoints were affected (ophthalmology, fundus photography, OCT, histopathology).

Case Study

- Question was: Are these findings related to ADA response or a direct effect of the test article?
- To aid in the assessment, looked into the correlation of some key ocular findings with the presence of ADA in the vitreous and/or serum.

Findings Correlation with ADA in Vitreous and Serum

Dose	Animal #	Keratic precipitate – Slit lamp	RNFL-OCT	↑Blood vessel size - OCT	Perivascular Sheathing – indirect ophthalmoscopy/fundus photography	Vitreous haze 3+,4+/Degraded view fundus – indirect ophthalmoscopy	Mixed-cell infiltrate-histopath	ADA Titer		
								Vitreous ^b	Serum (Day 141)	
1.5 mg	M114							N	0.0205	
	M115	X	X		X	X	X	2.84	3.05	
	M116		X				X	0.488	3.10	
	M117	X	X		X	X		QNS	3.05	
	M118							N	0.0210	
1.5/3.0 mg	M119							N	0.0235	
	M120							N	3.00	
	M121							N	0.0210	
	M122		X	X	X		X	0.364	3.10	
	M123							0.0795	3.18	
	M124							N	0.0215	
	M125							N	0.134	
	M126	X	X	X	X	X		2.71	3.11	
	1.5 mg	F135							N	0.0215
		F136							N	0.0470
F137								N	3.13	
F138								N	0.0210	
F139								N	0.0996	
1.5/3.0 mg	F140							N	1.82	
	F141		X	X			X	QNS	3.09	
	F142	X	X	X	X		X	2.82	3.09	
	F143		X	X	X		X	2.78	3.08	
	F144		X					N	0.0575	
	F145							N	0.0190	
	F146							N	0.0215	
	F147							N	0.0215	

Case Study

- In addition, to support that the ocular inflammation was primarily related to the formation of ADAs, the Sponsor conducted immunohistochemistry evaluation in ocular tissues of high-dose animals.
- Granular deposits containing test article (human IgG), monkey IgG, IgM and/or C3 were observed in the ocular tissues with mixed cell infiltrates and in retina blood vessels (consistent with immune complex formation and complement activation).
- The overall data support that the ocular findings were primarily related to ADA formation and not a direct pro-inflammatory effect of the test article.

When Ocular Inflammation is ADA Related

- ADA formation in animals is not always predictive of ADA formation in humans.
- Careful monitoring for ADA formation in clinic
- Careful monitoring for toxicities observed
 - e.g., Inflammation affected all parameters:
Ophthalmoscopy, ERG, tonometry, OCT
- Extend evaluation time between subjects/dose escalation

Genotoxicity

ICH S6(R1)

- The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.
- Studies in available and relevant systems, including newly developed systems, should be performed in those cases where there is cause for concern about the product (e.g., because of the presence of an organic linker molecule in a conjugated protein product).

Carcinogenicity

- Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals (ICH S6).
- Generally, recommend Sponsor submit a waiver request along with a justification to omit the studies and address the topic of carcinogenicity (e.g., based on mechanism of action) in the BLA.
- Decision for the need of the studies is not made until BLA is fully reviewed.

Reproductive Toxicity Studies

- The general conduct of developmental and reproductive toxicology (DART) studies for biologics discussed in ICH Guidance S6(R1) is appropriate for ophthalmic drugs.
- EFD studies are recommended even if systemic exposure is negligible.
 - There is a potential for developing tissues/organs of the embryo and fetus to be much more sensitive than adult tissues.
 - Tools are not available (relevant embryos cells) to assess negligibility.

Reproductive Toxicity Studies

- A waiver request may be appropriate for fertility and PPND studies.
 - If negligible systemic exposure is demonstrated in ocular-route toxicity studies, and confirmed in clinical studies, stand-alone fertility studies could be waived in lieu of adequate assessment of reproductive tissues in general and ocular toxicity studies.
 - Pre-/postnatal developmental studies might be waived if negligible systemic exposure is demonstrated, and EFD studies show no toxicity at clinically relevant doses.

Reproductive Toxicity Studies

- **Sponsor position:** *“Mechanism of action suggests potential risk for reproductive capacity and/or embryofetal development – no studies planned”*
- Approach seems to be supported by statements in guidances:
 - *S6(R1): “When the weight of evidence (e.g., mechanism of action, phenotypic data from genetically modified animals, class effects) suggests that there will be an adverse effect on fertility or pregnancy outcome, these data can provide adequate information to communicate risk to reproduction, and under appropriate circumstances, additional nonclinical studies might not be warranted”.*
 - *S5(R3) – “Alternatively, there can be adequate information to communicate risk without conducting EFD studies. Evidence (e.g. pilot, DRF data, MoA, genetically modified animals) suggesting an adverse effect caused by the intended pharmacological mechanism on EFD at clinically relevant doses can be sufficient to communicate risk”.*
- We want dose-response relationships to determine risk (vs hazard) and inform in label at what dose effects are produced compared to MRHOD.

Reproductive Toxicity Studies

- Systemic route preferred
 - Want to maximize exposure to detect an effect.
 - Lucentis – EFD by IVT route (HD 13X human exposure at recommended clinical dose)
- A multi-dose study design is generally used to allow for evaluation of dose-response relationships.
 - Saturation of target should be considered when designing a study and selecting study doses.
 - Lack of consideration for target saturation may result in artificially increasing exposure margins for toxicities observed.
- At least one arm should be tested at clinically relevant exposures.
 - If high multiples of clinical doses only evaluated, and if no NOAEL identified, relevance of high LOAEL to clinical safety may be unclear.
- Measure TK
 - Use AUC/C_{max} levels to compare to human exposure at the recommended clinical dose to enable a meaningful estimate of risk.
 - Exposure margins based on dose would overestimate risk (i.e., presumes 100 percent absorption).

Reproductive Toxicity Studies

- Species
 - 2 species (one rodent, one nonrodent) if both pharmacologically relevant
 - Rodent not relevant, single nonrodent species
 - Rat, mouse or rabbit – commonly used if pharmacologically relevant
 - NHP discouraged if other species are relevant
 - Other species – Minipig, dogs

Reproductive Toxicity Studies

- Further details on dose levels, human dose multiples, species selection (pros and cons), animal numbers, study design, strategies for evaluation, principles of risk assessment, etc. – ICH Guidance S5(R3)
- When ADA is a concern
 - Rapid ADA response may necessitate staggered groups (i.e., to cover the exposure window before ADA depletes exposure)
 - E.g., dose one group of rabbits GD6-12, and a second group GD12-18.
 - ADA response may preclude testing in a species

Reproductive Toxicity Studies

Commonly, Sponsors:

- Conclude no test article related effects for findings with no dose response.
 - The lack of dose dependency is quite common when it comes to biologics and reproductive toxicity data.
 - For rare malformations, the absence of increased frequency with dose does not always alleviate concern.
- Use historical control data to support no test article-related effect, surpassing concurrent control
 - Interpretation of study data relies primarily on comparison with the concurrent control group.
 - Historical data used to assist in data interpretation, especially in the case of rare events (occurs at <1% incidence, e.g., malformations).

Summary of Studies Recommended to Support

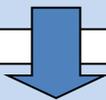
Initial IND

- Pharmacology
 - 1ry/2ry PD
 - Species selection
 - Safety Pharmacology
- PK/ADME
 - Ocular tissue distribution
 - Systemic exposure
- Ocular Toxicity
 - 2 species
- Systemic Toxicity
 - 1 species
- ADCC/CDC
- Tissue cross-reactivity

Further Development/BLA

- Longer-term ocular toxicity
 - 2 species (→ 1)
- Ocular tissue distribution

- Longer-term systemic toxicity
 - 1 species
- Reproductive and Developmental Toxicity
- Carcinogenicity
 - waiver/assessment of carc potential
- Others



Extent of evaluation depends on systemic exposure, and presence/lack of systemic effects

Questions



