PRELIMINARY AND IND-DIRECTED TOXICOLOGY STUDIES

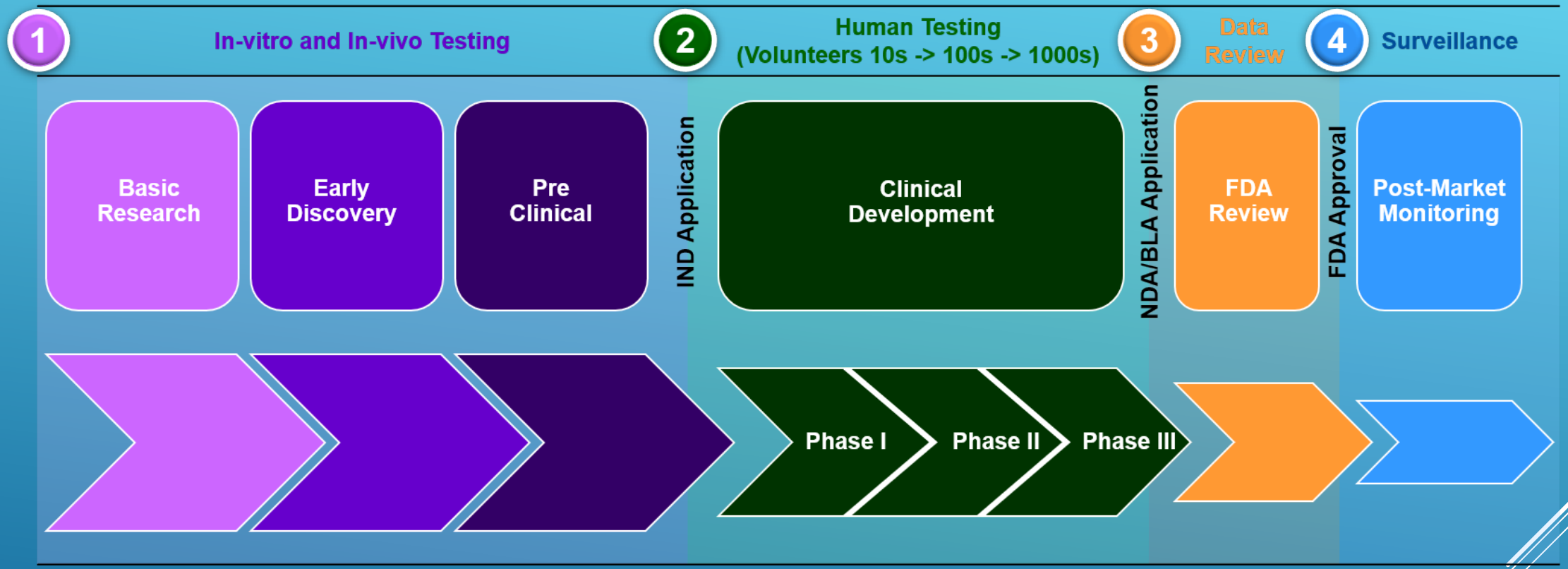
Elizabeth R. Glaze, Ph.D., D.A.B.T.
Chief, Toxicology and Pharmacology Branch
Developmental Therapeutics Program, National Cancer Institute

PRELIMINARY AND IND-DIRECTED TOXICOLOGY STUDIES

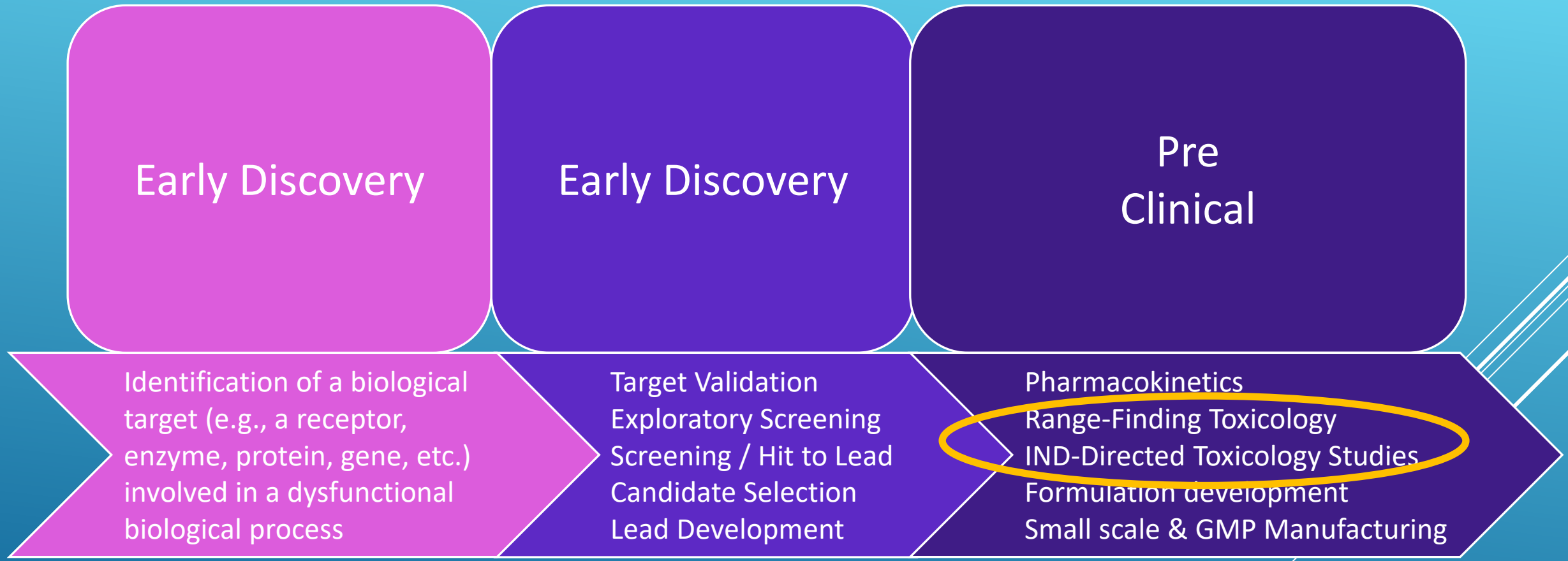
Outline

- Drug development process
- Identifying the drug indication
- Determining which studies will be required and how they should be designed
- Safety endpoints
- Data Evaluation
- Clinical dose recommendation
- Additional key points

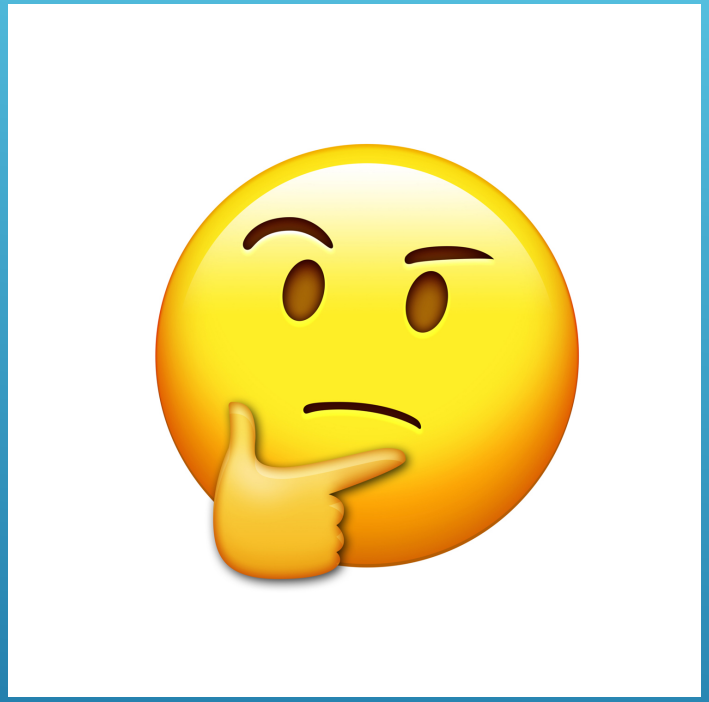
STEPS IN THE DRUG DEVELOPMENT PROCESS



DRUG DEVELOPMENT PROCESS



HOW DO YOU START?



STEP 1 – IDENTIFY THE INDICATION FOR THE DRUG

What disease/condition will the drug treat?

- Is the drug intended to treat cancer?
- Is it intended to alleviate symptoms associated with chemotherapy?
- Is the drug intended to prevent cancer?
- Other (e.g., manage heart disease)?

Is the drug a small molecule or large molecule?

STEP 1 – DETERMINE THE INDICATION FOR THE DRUG

What disease/condition will the drug treat?

- Cancer treatment
- Most other indications (e.g., heart disease, cancer prevention)

Is the drug a small molecule or large molecule? ***Yes***

FDA's Guidance for Industry ***S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*** – March 2010 https://www.fda.gov/media/73161/download

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals - Questions and Answers – Guidance for Industry – June 2018 https://www.fda.gov/media/100344/download

STEP 1 – DETERMINE THE INDICATION FOR THE DRUG

What disease/condition will the drug treat?

- Cancer treatment
- Most other indications (e.g., heart disease, cancer prevention)

Is the drug a small molecule or large molecule? ***Yes***

Guidance for Industry ***S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*** – May 2012 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals

Guidance for Industry ***S9 Nonclinical Evaluation for Anticancer Pharmaceuticals & S9 Questions and Answers***

STEP 1 – DETERMINE THE INDICATION FOR THE DRUG

What disease/condition will the drug treat?

- Cancer treatment
- Most other indications (e.g., heart disease, cancer prevention)

Is the drug a small molecule or large molecule? ***Yes***

Guidance for Industry - M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals – January 2010
https://www.fda.gov/media/71542/download

DIFFERENCES BETWEEN S9 AND M3(R2)

Study/Parameter	S9	M3R(2)
Recommended clinical starting dose	Based on the MTD of the more sensitive species	Based on the NOAEL of the more sensitive species
Genotoxicity • *In vitro* bacterial - Reverse Mutation Assay • *In vitro* mammalian - Mouse Lymphoma • *In vivo* - Chromosomal Aberration	Not considered essential	An assay for gene mutation is generally sufficient to support single dose clinical trials. To support multiple dose clinical development trials, an additional assessment capable of detecting chromosomal damage in a mammalian system. Complete battery of tests for genotoxicity should be completed before phase 2.
Safety Pharmacology (CV, CNS, Respiratory)	Stand-alone studies are not necessary	Before phase 1
Embryofetal toxicity studies	To support marketing appl	Before Phase 3
Fertility and early embryonic development	Not warranted	Before phase 1 clinical trial, or take pregnancy precautions during exposure in Phase 1 and 2 clinical trials, but before phase 3
Pre- and postnatal toxicology	Not warranted	To support marketing application
Carcinogenicity	Not warranted	To support marketing application

STEP 1 – DETERMINE THE INDICATION FOR THE DRUG

What disease/condition will the drug treat?

- Cancer treatment
- Most other indications (e.g., heart disease, cancer prevention)

Is the drug a small molecule or large molecule? ***Yes***

Guidance for Industry ***S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*** – May 2012 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals

Guidance for Industry - M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals – January 2010 https://www.fda.gov/media/71542/download

STEP 1 – DETERMINE THE INDICATION FOR THE DRUG

What disease/condition will the drug treat?

- Cancer treatment
- Most other indications (e.g., heart disease, cancer prevention)

Is the drug a small molecule or large molecule? ***Yes***

STEP 2 – DETERMINE WHICH STUDIES WILL BE REQUIRED AND HOW THEY SHOULD BE DESIGNED SMALL MOLECULE, CANCER TREATMENT

As per S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

- Animal Species? Rodent and nonrodent
- Which animal models? Use information on target, protein binding, PK, species differences in metabolism or metabolites, side effects (*e.g.,* emesis), or information from the literature; if differences between different animal models are small, then use rat and dog
- Dosing schedule? IND-directed studies - same as clinical schedule or more frequent; need range-finding studies first
- Dosing route? Same as clinical route
- Formulation? IND-directed studies – same as the clinical formulation, ***to the extent possible***
- Doses for IND-directed studies? Usually based on range-finding studies and/or PK
- Doses for range-finding studies? Use information from efficacy study and/or pk results

STEP 2 – DETERMINE WHICH STUDIES WILL BE REQUIRED AND HOW THEY SHOULD BE DESIGNED SMALL MOLECULE, CANCER TREATMENT

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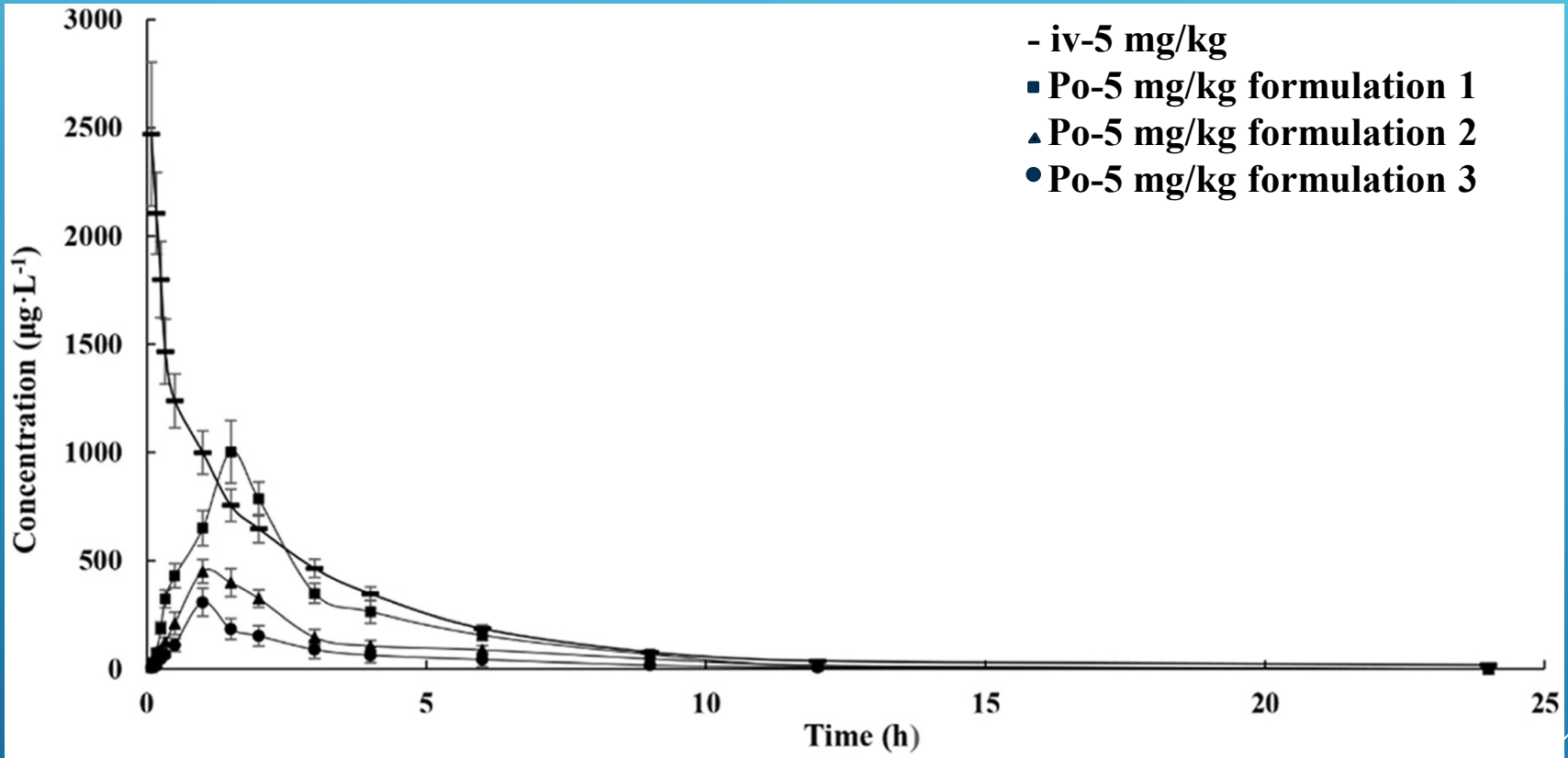
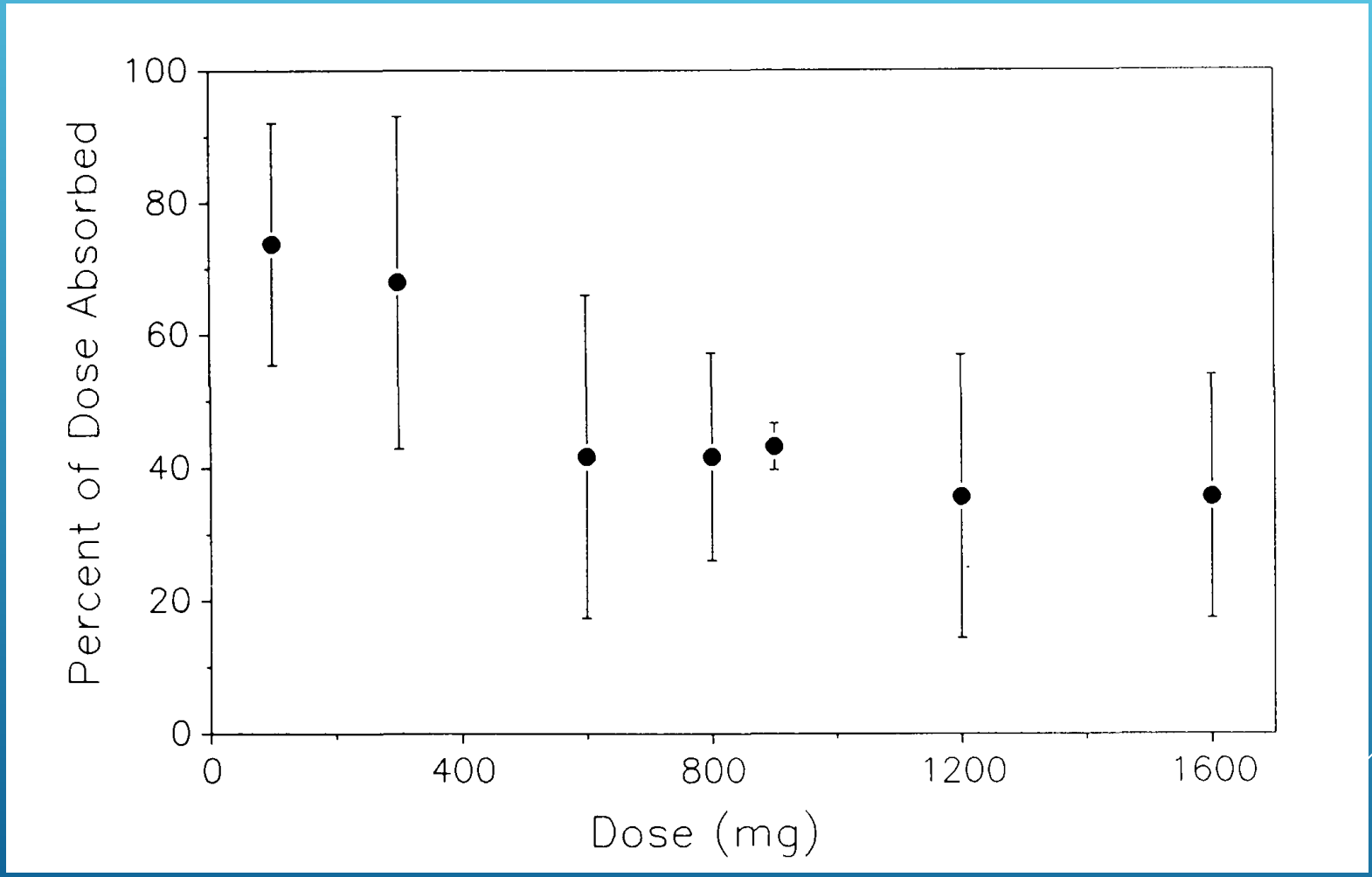
ABSOLUTE ORAL BIOAVAILABILITY



MORE DRUG ISN'T NECESSARILY BETTER!

FRACTION OF DOSE ABSORBED AS A FUNCTION OF INCREASING DOSES



STEP 2 – DETERMINE WHICH STUDIES WILL BE REQUIRED AND HOW THEY SHOULD BE DESIGNED SMALL MOLECULE, CANCER TREATMENT

As per S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

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- Dosing schedule? IND-directed studies - same as clinical schedule or more frequent; need range-finding studies first
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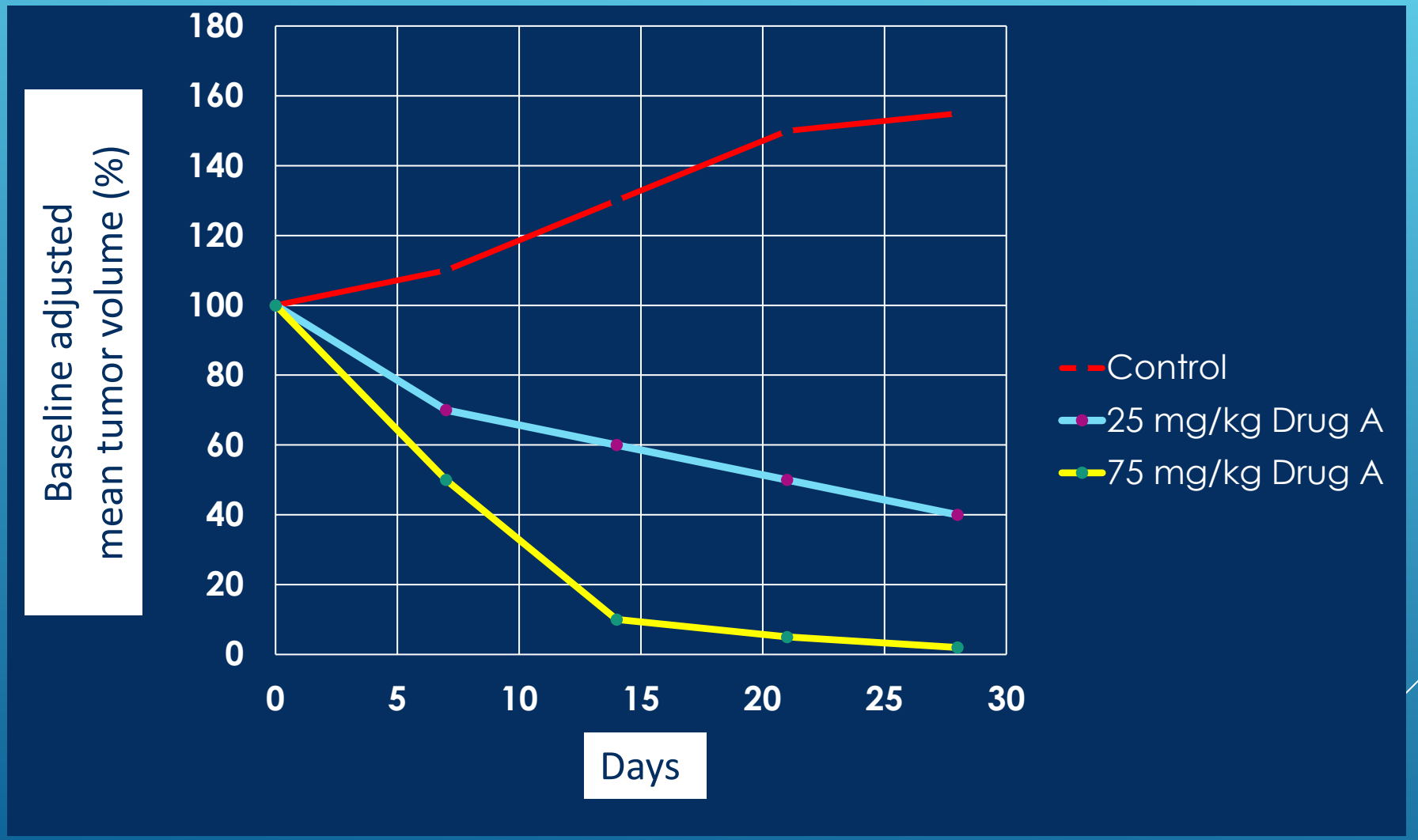
- Doses for IND-directed studies? Usually based on range-finding studies and/or PK
- Doses for range-finding studies? Use information from efficacy study and/or pk results

XENOGRAFT STUDY WITH DRUG A ADMINISTERED ORALLY TO ATHYMIC FEMALE NUDE BALB/C MICE ONCE A DAY FOR 28 DAYS



CONVERSION SCALE

(Systemically administered drugs)

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:

HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, and stumptail.

HED = Human Equivalent Dose

Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

CONVERSION SCALE

Species	To Convert Animal Dose in mg/kg to Dose in mg/m^2, Multiply by k_m
Human	37
Child (20 kg)[b]	25
Mouse	3
Hamster	5
Rat	6
Ferret	7
Guinea pig	8
Rabbit	12
Dog	20
Primates:	

75 mg/kg in mice = 225 mg/m^2 = 37.5 mg/kg in rats

225 mg/m^2 = 11.3 mg/kg in dogs

Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

STEP 2 – DETERMINE WHICH STUDIES WILL BE REQUIRED AND HOW THEY SHOULD BE DESIGNED

SMALL MOLECULE, CANCER TREATMENT

As per S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

- Animal Species? Rodent and nonrodent
- Which animal models? Use information on target, protein binding, PK, species differences in metabolism or metabolites, side effects (*e.g.,* emesis); if differences between different animal models are small, then use rat and dog
- Dosing schedule? IND-directed studies - same as clinical schedule or more frequent; need range-finding studies first
- Dosing route? Same as clinical route
- Formulation? IND-directed studies – same as the clinical formulation, ***to the extent possible; must be clinically relevant vehicle***
- Doses for IND-directed studies? Usually based on range-finding studies and/or PK
- Doses for range-finding studies? Use data from efficacy study and/or pk results
- Randomization? Typically using a computer–based body weight stratification procedure

STEP 2 – DETERMINE WHICH STUDIES WILL BE REQUIRED AND HOW THEY SHOULD BE DESIGNED

SMALL MOLECULE, CANCER TREATMENT

As per S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

- Other studies?
  - Genotoxicity? Conducted to support marketing application
  - Stand Alone Safety Pharmacology (CNS, CV, Respiratory)? ***Usually*** not warranted
  - Reproduction and Developmental Toxicology?
    - Embryofetal toxicity studies? Conducted to support marketing application
    - Fertility and early embryonic development? Not warranted
    - Pre- and postnatal toxicology study? Generally, not warranted
  - Carcinogenicity? Not warranted
  - PK? Limited (plasma concentrations, AUC, half-life) in animal models used for the toxicology studies; full ADME should normally be generated in parallel with clinical development.

STEP 1 – DETERMINE THE INDICATION FOR THE DRUG

What disease/condition will the drug treat?

- Cancer treatment
- Most other indications (e.g., heart disease, cancer prevention)

Is the drug a small molecule or large molecule? ***Yes***

Guidance for Industry ***S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*** – May 2012 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals

Guidance for Industry ***S9 Nonclinical Evaluation for Anticancer Pharmaceuticals & S9 Questions and Answers***

STEP 2 – DETERMINE WHICH STUDIES WILL BE REQUIRED AND HOW THEY SHOULD BE DESIGNED

LARGE MOLECULE, CANCER TREATMENT

As per S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

- One or two animal models?
  - Model(s) capable of demonstrating potential adverse consequences of target modulation.
  - Target sequence homology between test species and humans; relative target binding affinities, receptor/ligand occupancy and kinetics; tissue cross reactivity, when target binding is expected, but only if other approaches cannot be used to demonstrate a pharmacologically relevant species.
  - If no relevant species can be identified because the biopharmaceutical does not interact with the orthologous target in any species, use of ***homologous molecules*** or ***transgenic model***s can be considered, or include safety endpoints in the efficacy study.
  - For monoclonal antibodies and other related antibody products ***directed at foreign targets*** (i.e., bacterial, viral targets etc.), a short-term safety study (see ICH S6) in one species (choice of species to be justified by the sponsor) can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate.
  - 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.
  - Studies in two nonrodent species are not appropriate.

STEP 2 – DETERMINE WHICH STUDIES WILL BE REQUIRED AND HOW THEY SHOULD BE DESIGNED
LARGE MOLECULE, CANCER TREATMENT

As per S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

- Dosing schedule? IND-directed studies – ***may be*** same as clinical schedule, ***but it depends***; range-finding is likely not necessary
- Dosing route? Same as clinical schedule
- Formulation? Same as the clinical formulation, ***to the extent possible***
- Doses for IND-directed studies?
  - Keep in mind, the toxicity of most large molecules is related to their targeted mechanism of action; therefore, relatively high doses can elicit exaggerated adverse effects
  - There may be limitations based on the concentration of the formulated test article
  - Options
    - Dose that is equal to the anticipated human dose, based on body weight, and then 3x and, possibly, 10x higher doses
    - Maximum Feasible Dose (MFD), based on the maximum volume that can be given to animals
    - Dose that is equal to the total dose that will be given in the clinical trial
- Doses for range-finding studies? Range-finding is likely not necessary

DOSING AND BLEEDING*

A Good Practice Guide to the Administration of Substances and Removal of Blood, Including Routes and Volumes

Karl-Heinz Diehl[1], Robin Hull[2], David Morton[3], Rudolf Pfister[4], Yvon Rabemampianina[5], David Smith[6,*], Jean-Marc Vidal[7] and Cor van de Vorstenbosch[8]

J Appl. Toxicol. 21, 15-23 (2001)

Table 1. Administration volumes considered good practice (and possible maximal dose volumes)

Species	Route and volumes (ml kg^{-1})				
	Oral	s.c.	i.p.	i.m.	i.v. (
Mouse	10 (50)	10 (40)	20 (80)	0.05[b] (0.1)[b]	5
Rat	10 (40)	5 (10)	10 (20)	0.1[b] (0.2)[b]	5
Rabbit	10 (15)	1 (2)	5 (20)	0.25 (0.5)	2
Dog	5 (15)	1 (2)	1 (20)	0.25 (0.5)	2.5
Macaque	5 (15)	2 (5)	[c] (10)	0.25 (0.5)	2
Marmoset	10 (15)	2 (5)	[c] (20)	0.25 (0.5)	2.5
Minipig	10 (15)	1 (2)	1 (20)	0.25 (0.5)	2.5

[a]For non-aqueous injectates, consideration must be given to time of absorption before re-dosing. No more than two intramuscular sites should be used per day. Subcutaneous sites should be limited to two or three sites per day. The subcutaneous site does *not* include Freund's adjuvant administration.
[b]Values in millilitres per site.
[c]Data not available.

Table 3. Circulating blood volume in laboratory animals

Species	Blood volume (ml kg^{-1})	
	Recommended mean[a]	Range of means
Mouse	72	63–80
Rat	64	58–70
Rabbit	56	44–70
Dog (Beagle)	85	79–90
Macaque (Rhesus)	56	44–67
Macaque (Cynomolgus)	65	55–75
Marmoset	70	58–82
Minipig	65	61–68

[a]The recommended mean corresponds to the mid-point of the range of means.

STEP 3 - SAFETY ENDPOINTS

- Mortality
- Clinical observations
- Physical examinations
- Body weights
- Food consumption
- Clinical pathology (serum chemistry, hematology, coagulation)*
- *Additional parameters specific to product (e.g., humoral, cellular immune responses, vector biodistribution) for large molecules*
- Pharmacokinetics: bleed after the first and last dose
- Sacrifice toxicology animals 24 hours after last day of dosing and after a recovery period and collect tissues
  - Weigh select organs (brain, heart, liver, lung, spleen, adrenals)
  - Grossly examine tissues (gross pathology)
  - Evaluate tissues microscopically (histopathology)

Good Laboratory Practice (GLP)-compliance for IND-directed studies!

STEP 4 - DATA EVALUATION

- Is the effect adverse and is it related to the treatment?
  1. Is it seen in multiple animals? yes
  2. Is there a dose response? yes
  3. Is the change biologically relevant? yes
  4. Is there histological correlation? Yes
  5. Is there statistical significance? ***Not always applicable!***
- Can the adverse effect be monitored and managed non-invasively in the clinical?
- Is it reversible?

STATISTICS IS IMPORTANT, BUT IT'S NOT EVERYTHING!

28-day study with Compound A in Rats

Clinical Chemistry

10 rats/sex/group

	ALP (IU/L)	ALT (IU/L)	AST (IU/L)
Control	187 ± 41.6	46 ± 22.0	67 ± 21.3
Low Dose	164 ± 64.3	31 ± 7.5*	61 ± 6.9
Mid Dose	147 ± 57.2	31 ± 4.5*	36 ± 5.7
High Dose	148 ± 46.0	36 ± 5.7	56 ± 6.4

*$p < 0.05$

- Is this treatment-related?
  - Is it seen in multiple animals? yes
  - Is there a dose response? no
  - Is the change biologically relevant? no
  - Is there histological correlation? no

STATISTICS IS IMPORTANT, BUT IT'S NOT EVERYTHING!

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High Dose	148 ± 46.0	36 ± 5.7	56 ± 6.4

*$p < 0.05$

- Is this treatment-related? no
  - Is it seen in multiple animals? yes
  - Is there a dose response? no
  - Is the change biologically relevant? no
  - Is there histological correlation? no

STATISTICS IS IMPORTANT, BUT IT'S NOT EVERYTHING!

5-day study with Compound A in Dogs

Clinical Chemistry

2 dogs/sex/group

- Is this treatment-related?
  - Is it seen in multiple animals? yes
  - Is there a dose response? yes
  - Is the change biologically relevant? yes
  - Is there histological correlation? yes

Group	Animal	ALP (IU/L)	ALT (IU/L)	AST (IU/L)
Control	Male 1	30	29	30
	Male 2	63	28	30
	Female 1	52	42	45
	Female 2	84	27	38
Low Dose	Male 1	81	39	34
	Male 2	52	29	46
	Female 1	63	66	49
	Female 2	59	39	27
Mid Dose	Male 1	85	130	66
	Male 2	185	34	31
	Female 1	244	323	100
	Female 2	-	-	-
High Dose	Male 1	427	2132	785
	Male 2	-	-	-
	Female 1	77	69	60
	Female 2	241	108	45

STEP 5 - CLINICAL DOSE RECOMMENDATION

SMALL MOLECULES

1. Identify the *Maximum Tolerated Dose (MTD) in rodents and nonrodents*
2. Convert the MTD(s) in mg/kg to Human Equivalent Doses (HEDs, mg/m^2) *(systemically administered drugs)**

Severely Toxic Dose (STD)

MTD

Species	To Convert Animal Dose in mg/kg to Dose in mg/m^2, Multiply by k_m
Human	37
Child (20 kg)[b]	25
Mouse	3
Hamster	5
Rat	6
Ferret	7
Guinea pig	8
Rabbit	12
Dog	20
Primates:	

MTD

40 mg/kg in rats = 240 mg/m^2 humans

10 mg/kg in dogs = 200 mg/m^2 in humans

* Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

STEP 5 - CLINICAL DOSE RECOMMENDATION

SMALL MOLECULES

3. Select the HED for the more sensitive species and apply safety factor
   a) If the rodent is the more sensitive species, 1/10th HED of the MTD (mg/m^2) = FIH
   b) If the nonrodent is more sensitive, 1/6th HED of the MTD (mg/m^2) = FIH

   Dog is more sensitive
   1/6th of 200 mg/m^2 = 33 mg/m^2 = ~ 1 mg/kg = 60 mg per person

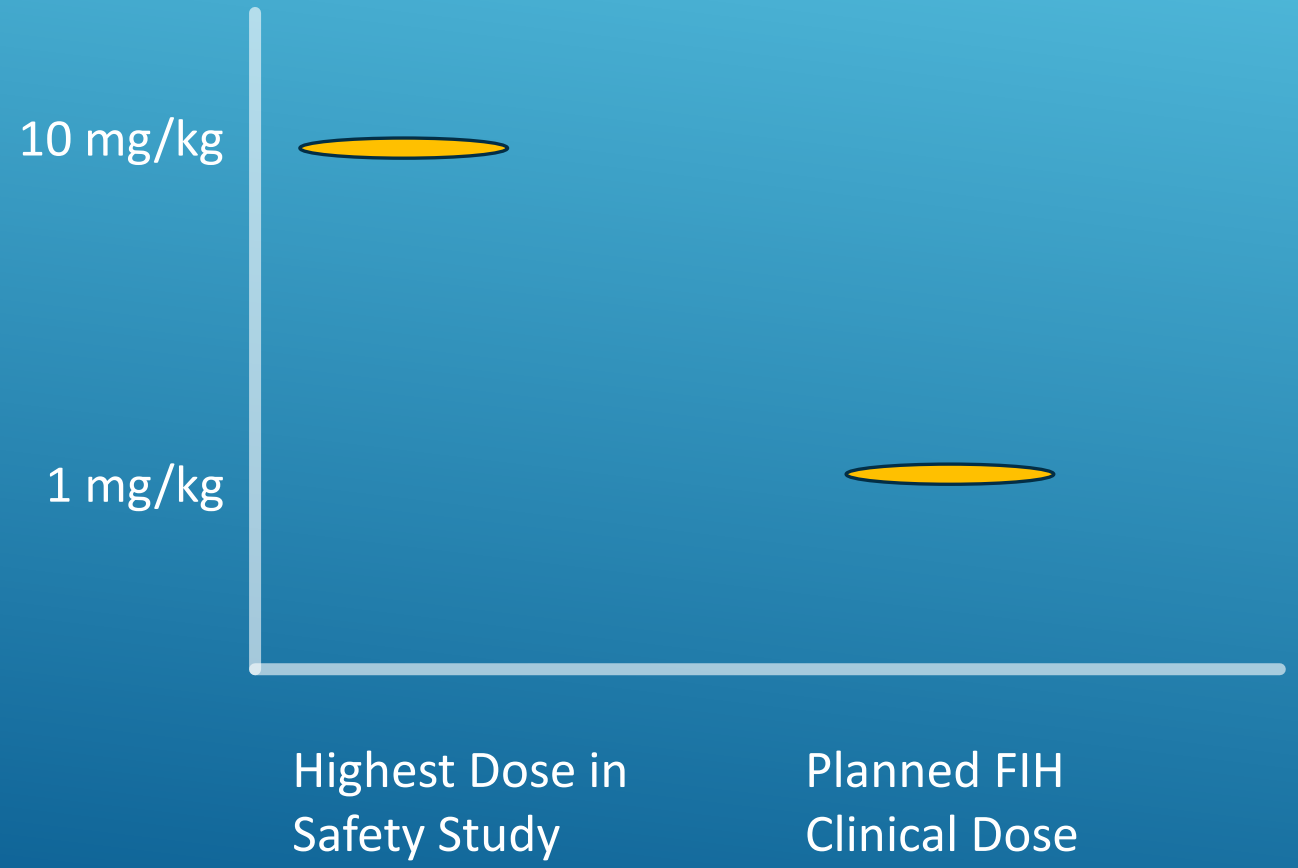
4. Recommend a starting dose of ***60 mg***

FIH = First in Human
HED = Human Equivalent Dose

STEP 5 - CLINICAL DOSE RECOMMENDATION

LARGE MOLECULES – SCENARIO 1

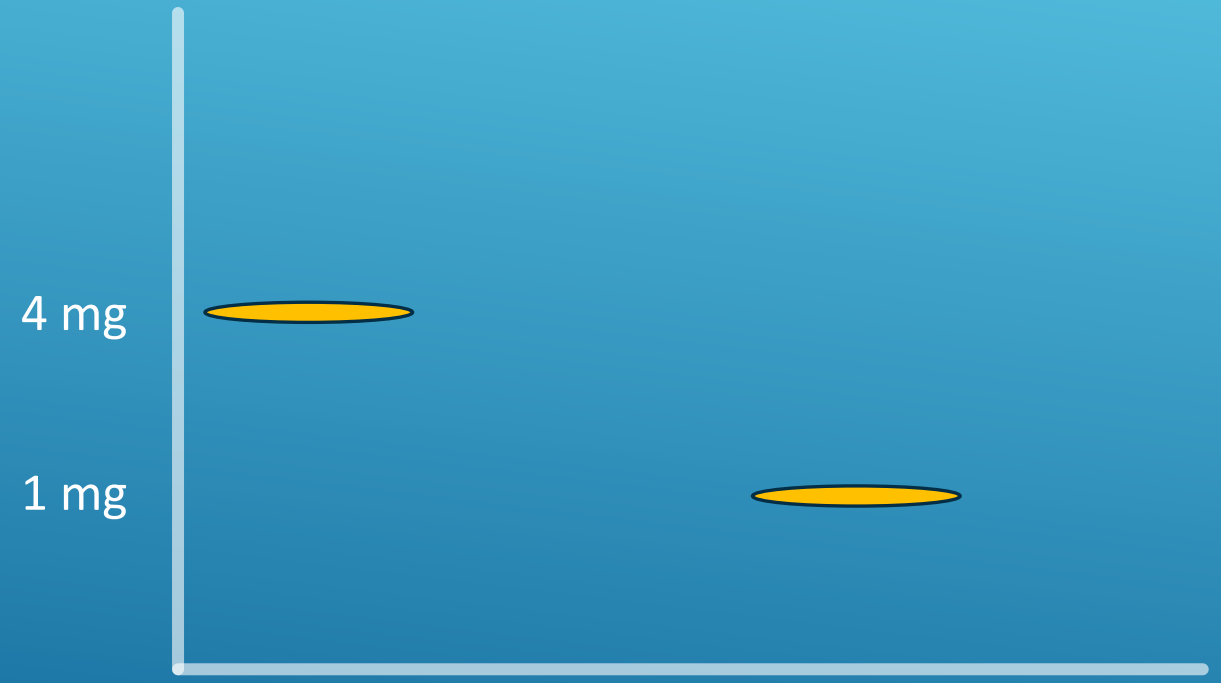
If the highest dose in the safety study is several folds higher than the planned FIH dose, based on body weight, and there was no toxicity, the starting dose recommendation ***could be*** equal to the planned FIH dose



STEP 5 - CLINICAL DOSE RECOMMENDATION

LARGE MOLECULES – SCENARIO 2

If the MFD was administered, and there was no toxicity, the recommended starting dose ***could be*** equal to the planned FIH dose

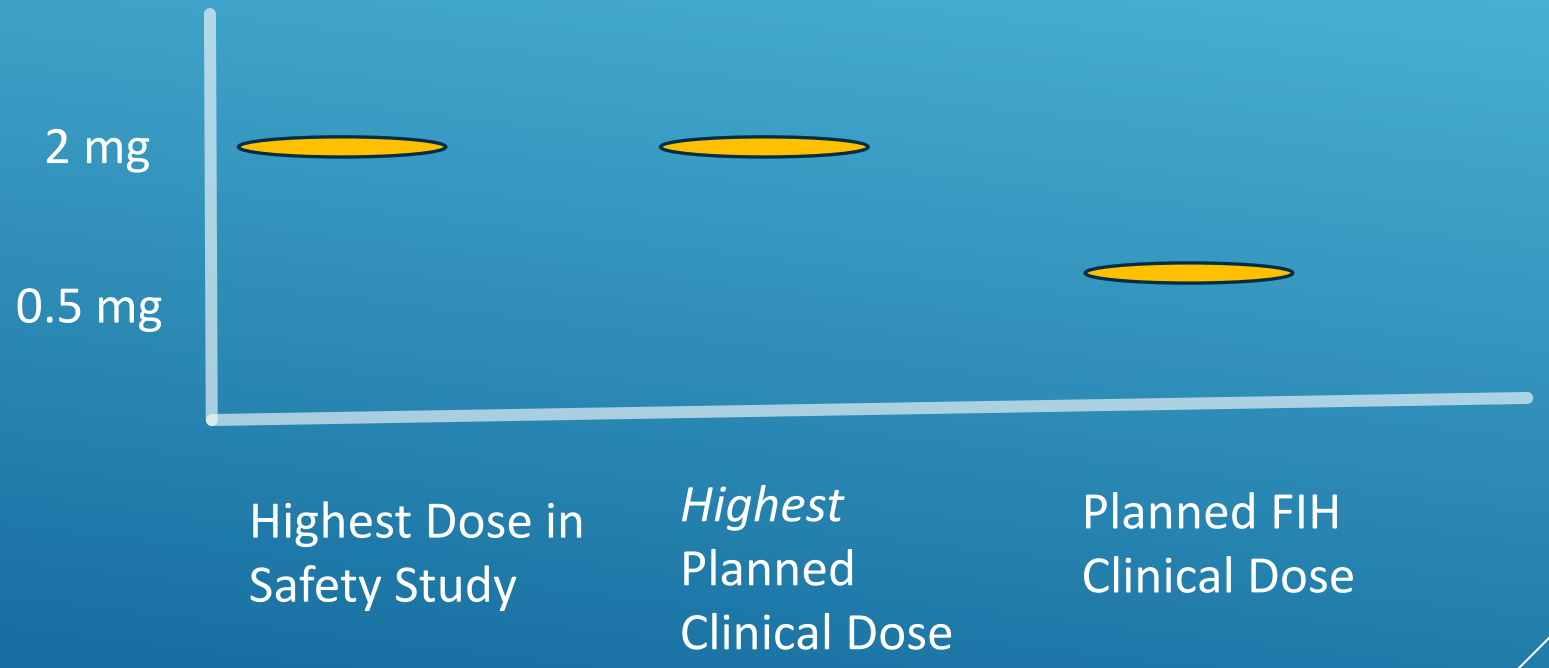


FIH = First in Human
MFD = Maximum Feasible Dose

STEP 5 - CLINICAL DOSE RECOMMENDATION

LARGE MOLECULES – SCENARIO 3

If the highest dose in the safety study is equal to the ***highest*** planned human dose, and there was no toxicity, the recommended starting dose ***could be*** equal to your planned ***FIH*** dose



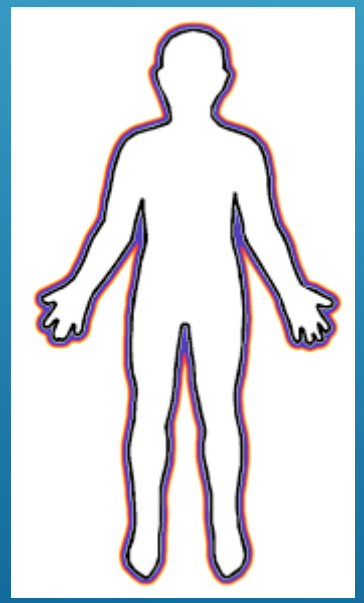
FIH = First in Human

STEP 5 - CLINICAL DOSE RECOMMENDATION

LARGE MOLECULES

2 mg = 80 mg/kg = 240 mg/m^2

200 X
(Mouse)



2 mg = 0.03 mg/kg* = 1.2 mg/m^2

*assumes a person weighs 60 kg

ADDITIONAL KEY POINTS

SHOW STOPPERS FOR CANCER TREATMENT

- Adverse effects that occur suddenly and cannot be easily managed – *e.g.,* cardiovascular, respiratory and central nervous system
- Adverse effects that are severe and irreversible - *e.g.,* cardiovascular, respiratory and central nervous system
- ***Bottom-line: cardiovascular, respiratory and central nervous system toxicities are show-stoppers!***

ADDITIONAL KEY POINTS

LIMITATIONS OF PRECLINICAL TOXICITY STUDIES

BJC British Journal of Cancer

www.nature.com/bjc

ARTICLE

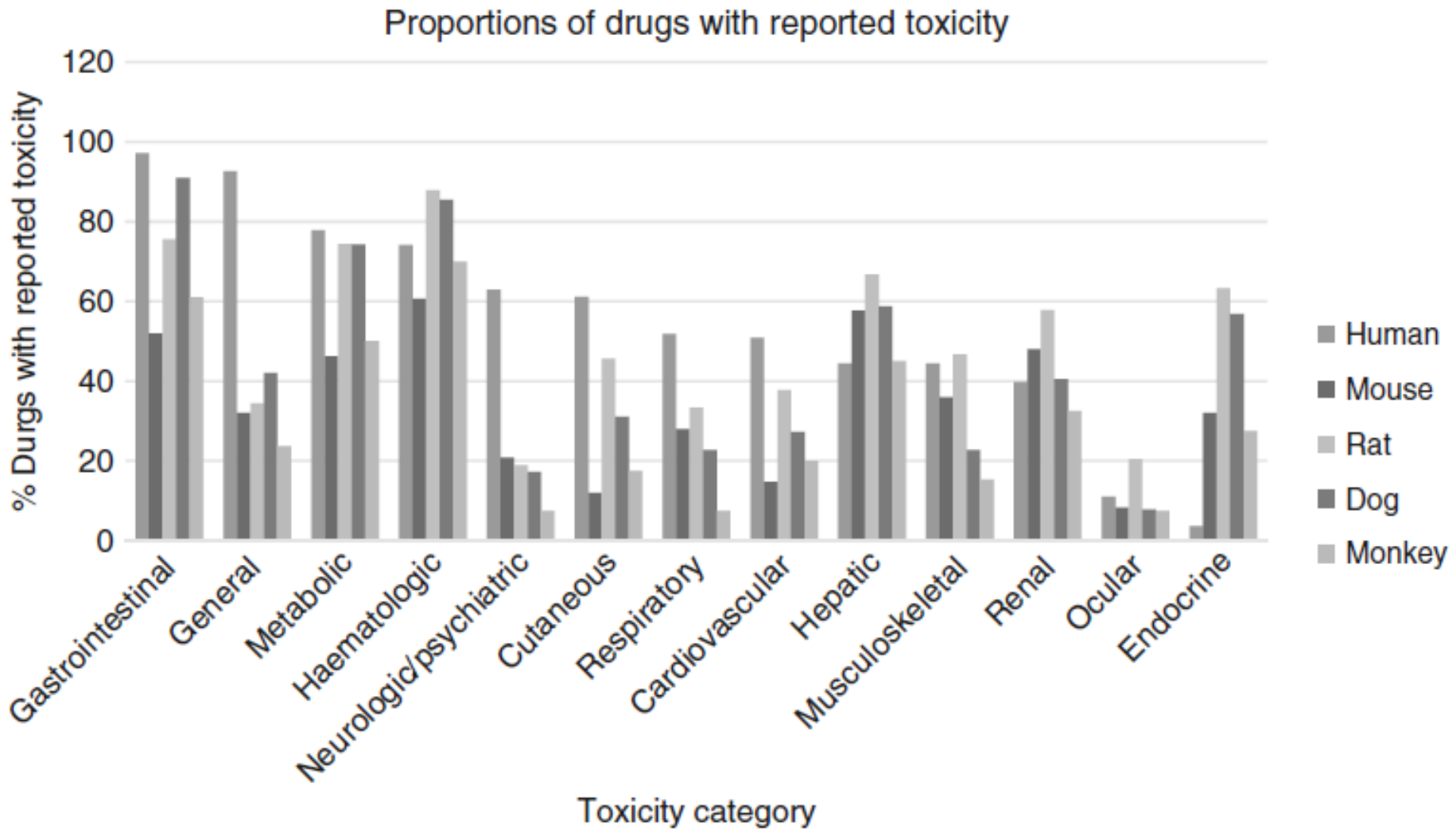
Clinical Study

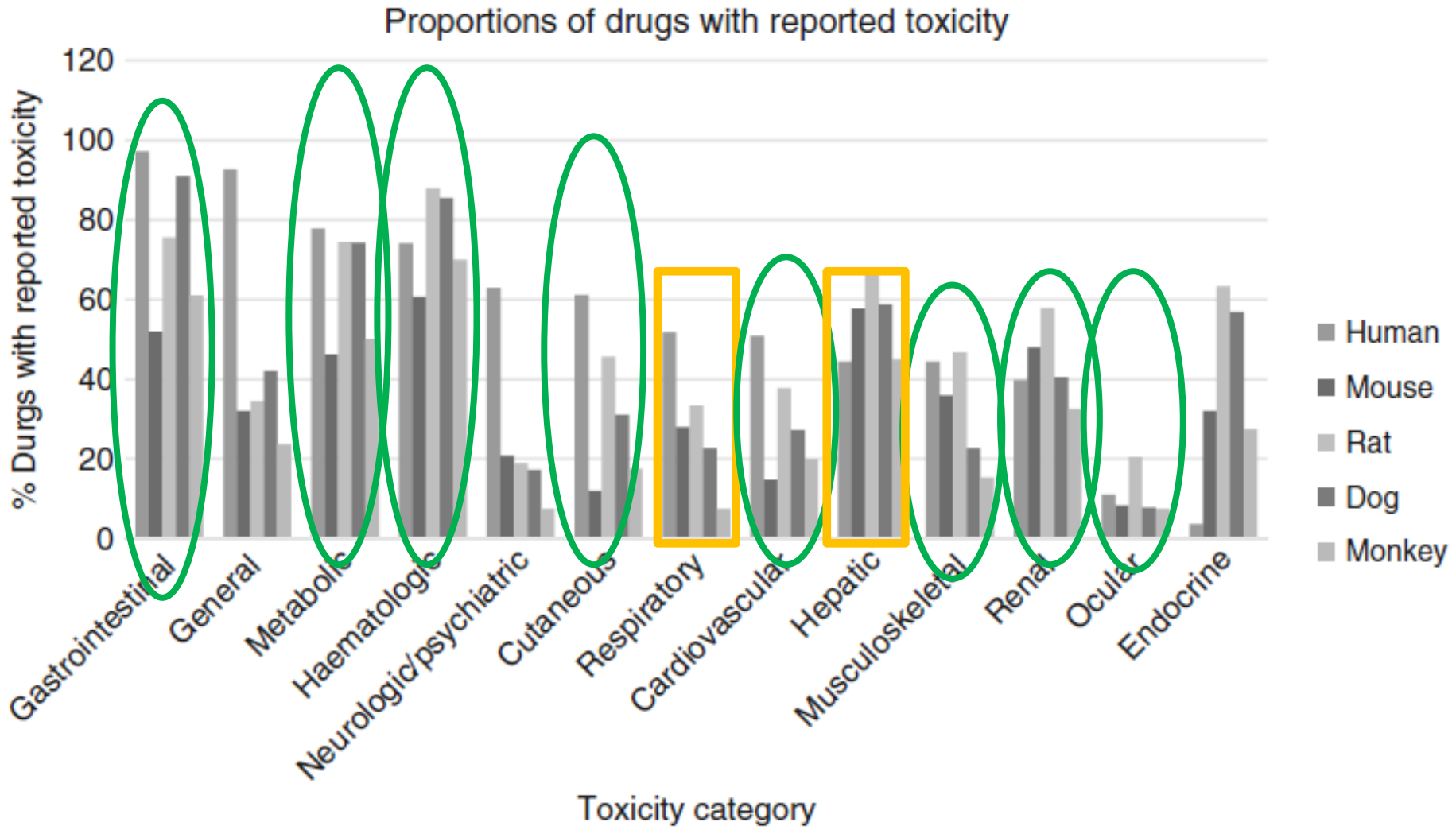
Pre-clinical animal models are poor predictors of human toxicities in phase 1 oncology clinical trials

Johnique T. Atkins[1], Goldy C. George[2], Kenneth Hess[3], Kathrina L. Marcelo-Lewis[4], Ying Yuan[3], Gautam Borthakur[5], Sean Khozin[6], Patricia LoRusso[7] and David S. Hong[8]

British J of Cancer
123:1496-1501 (2020)

- **Results**
- Most commonly reported human grade 3 and 4 Adverse Events were GI (69%) and haematologic (62%)
- Haematologic toxicities were the most commonly reported category in rats (88%), monkeys (70%), and mice (61%), and the 2nd most commonly reported for dogs (86%)
- GI toxicities were the most commonly reported category in dogs (91%) and the 2nd most commonly reported for rats (76%) and monkeys (61%)


Proportions of drugs with reported toxicity
% Durgs with reported toxicity
120
100
80
60
40
20
0
Gastrointestinal
General
Metabolic
Haematologic
Neurologic/psychiatric
Cutaneous
Respiratory
Cardiovascular
Hepatic
Musculoskeletal
Renal
Ocular
Endocrine
Toxicity category
Human
Mouse
Rat
Dog
Monkey



Green circles = rat and/or dog model(s) predicted human toxicity well
Yellow squares = rat and/or dog did an “ok” job at predicting human toxicity

ADDITIONAL KEY POINTS

LIMITATIONS OF PRECLINICAL TOXICITY STUDIES

BJC British Journal of Cancer

www.nature.com/bjc

ARTICLE

Clinical Study

Pre-clinical animal models are poor predictors of human toxicities in phase 1 oncology clinical trials

Johnique T. Atkins[1], Goldy C. George[2], Kenneth Hess[3], Kathrina L. Marcelo-Lewis[4], Ying Yuan[3], Gautam Borthakur[5], Sean Khozin[6], Patricia LoRusso[7] and David S. Hong[8]

British J of Cancer
123:1496-1501 (2020)

Authors' Conclusion

- Overall, animal toxicity did not show strong correlation with human toxicity, with a median PPV of 0.65 and NPV of 0.50.

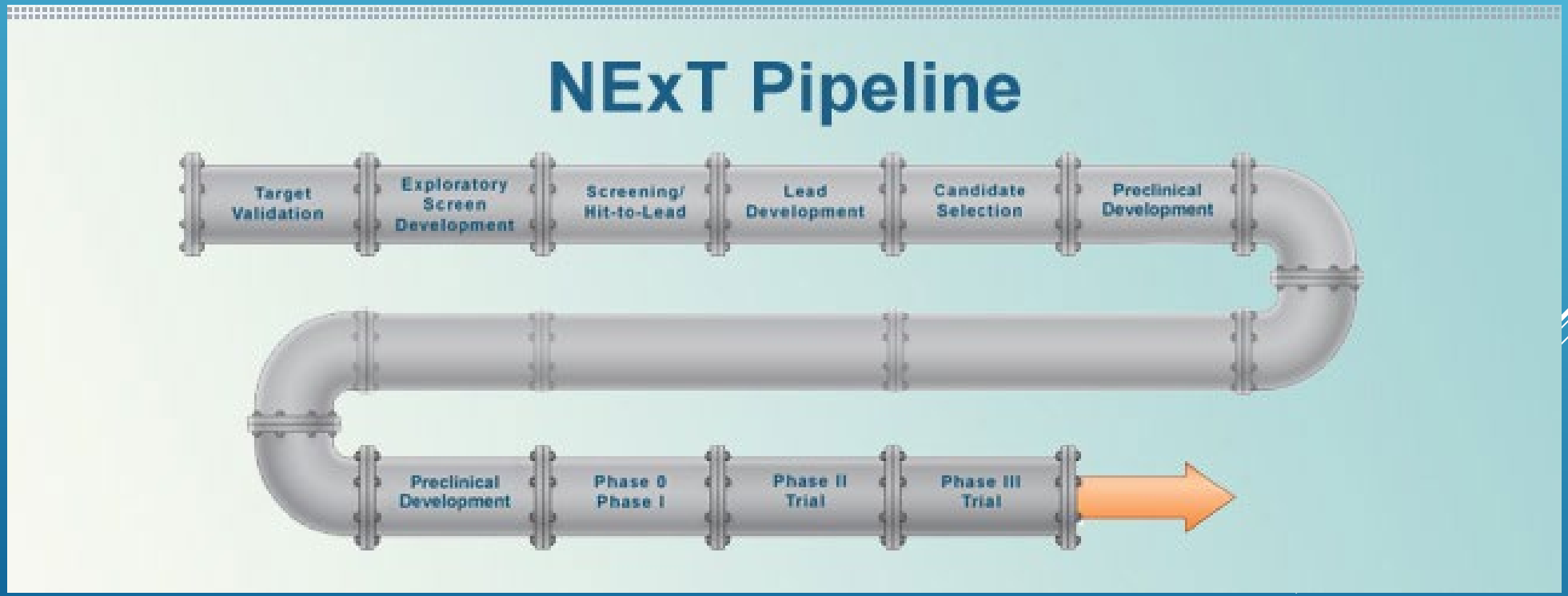
Liz's Conclusions:

- Rats and/or dogs predicted many of the human toxicities. The exceptions were general and neurological (underpredicted) and endocrine (over predicted).
- The preclinical results do not always predict human toxicity, but they can be useful predictors of human toxicity.

TPB RESOURCES

- Pharmacology Contracts (in negotiations)
- Toxicology Contracts (in negotiations)

NCI Experimental Therapeutics Program (NExT)



https://next.cancer.gov/

GUIDANCE DOCUMENTS

- Guidance for Industry S9 Nonclinical Evaluation for Anticancer Pharmaceuticals – March 2010 https://www.fda.gov/media/73161/download
- S9 Nonclinical Evaluation for Anticancer Pharmaceuticals - Questions and Answers – Guidance for Industry – June 2018 https://www.fda.gov/media/100344/download
- Guidance for Industry S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals – May 2012 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals
- Guidance for Industry - M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals – January 2010 https://www.fda.gov/media/71542/download
- Guidance for Industry - M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals – Questions and Answers - February 2013 https://www.fda.gov/media/82725/download

GUIDANCE DOCUMENTS (CONT'D)

- Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers – July 2005 https://www.fda.gov/media/72309/download
- Guidance for Industry - S7A Safety Pharmacology Studies for Human Pharmaceuticals – July 2001 https://www.fda.gov/media/72033/download
- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry - December 2017 (draft guidance) https://www.fda.gov/media/109951/download
- Nonclinical Safety Evaluation of Reformulated Drug Products Intended for Administration by an Alternate Route – Guidance for Industry and Review Staff – October 2015 https://www.fda.gov/media/72246/download

THANK YOU