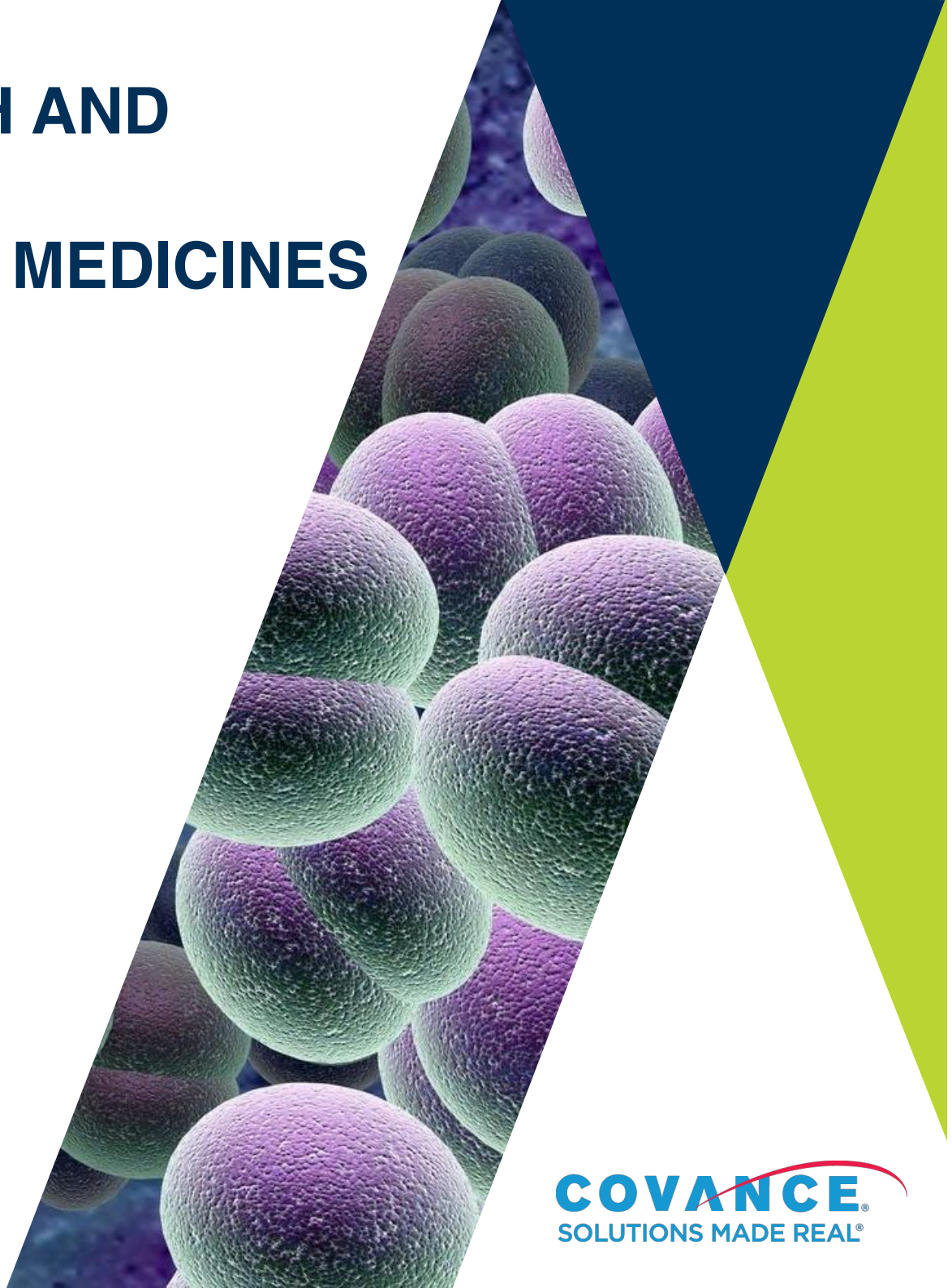
CONTRACT RESEARCH AND PRECLINICAL SAFETY ASSESSMENT OF NEW MEDICINES



Gerhard F Weinbauer, Ph.D.

Vice President, Global DART,
Covance Preclinical Services GmbH
Münster, Germany

December 17, 2018

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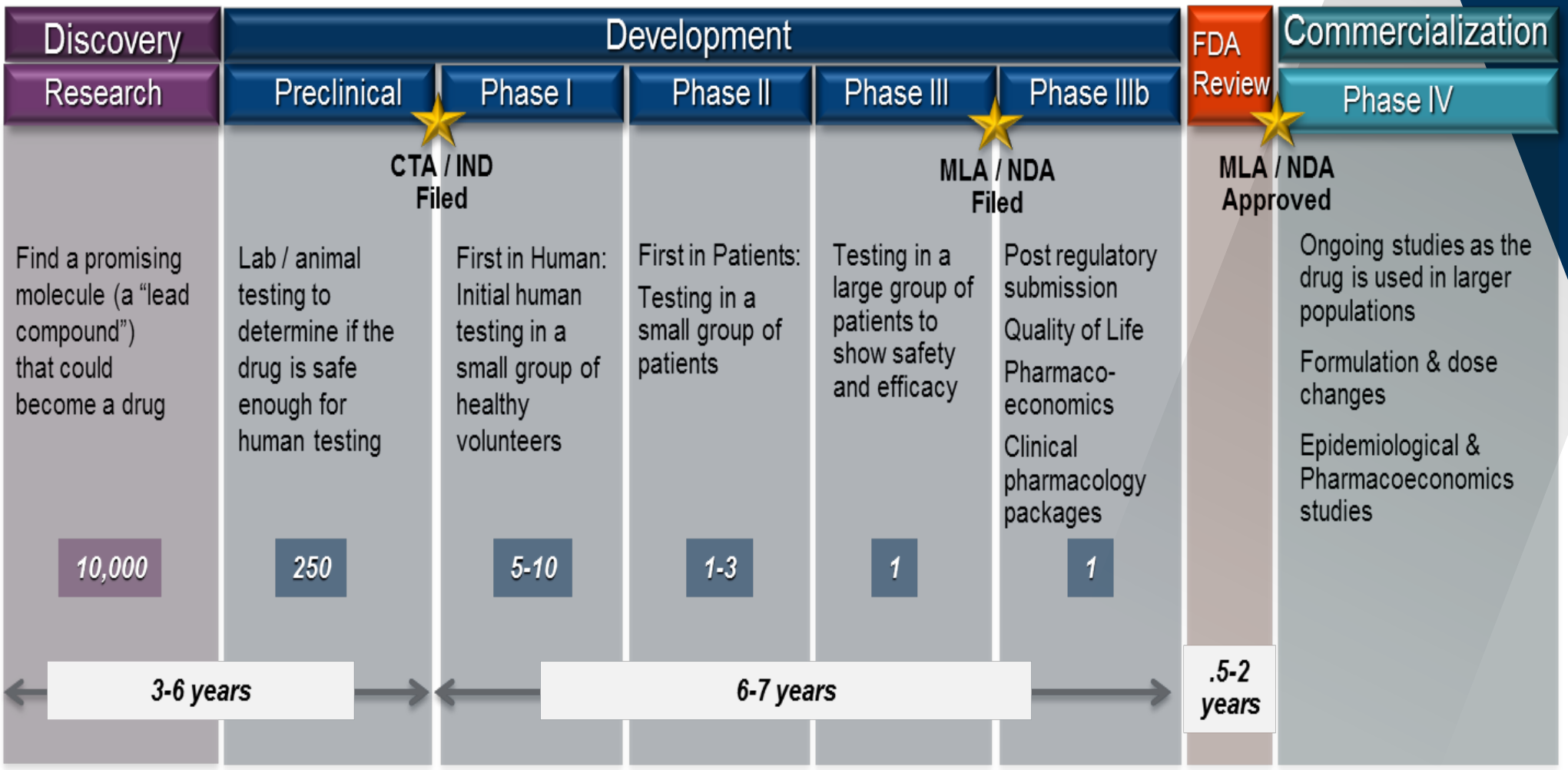
The Drug Development Process

Drug Development Overview



Outsourcing to Contract Research Organizations

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What is a Contract Research Organization ?

A Contract Research Organization (CRO) is a service organization that provides support to the pharmaceutical and biotechnology industries via research services that are outsourced (contracted)

Services may include (bio)pharmaceutical development, biological assay development, preclinical and clinical research, clinical trial management and pharmacovigilance

Depending on CRO size, services comprise selected drug development aspects or more comprehensive services including the entire drug development spectrum

Leading Contract Research Organizations

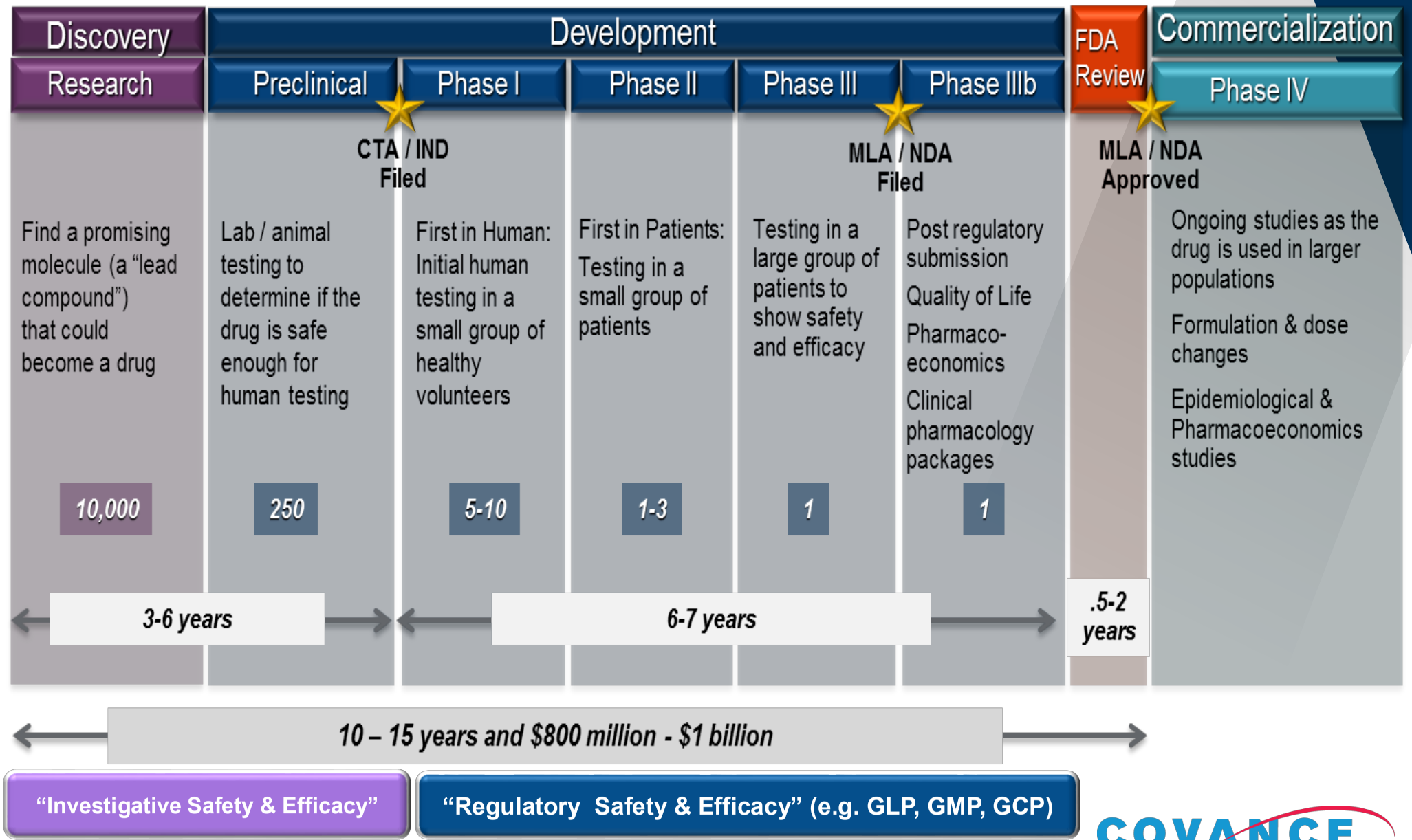
1. Laboratory Corporation of America Holdings (Covance) ($10.44B revenues in 2017)
2. IQVIA ($9.74B revenues in 2017)
3. Syneos Health ($2.67B revenues in 2017)
4. PAREXEL International Corporation ($2.44B revenues in 2017)
5. PRA Health Sciences ($2.26B revenues in 2017)
6. Pharmaceutical Product Development (PPD) ($1.90B revenues in 2017)
7. Charles River Laboratories International Inc (CRL) ($1.86B revenues in 2017)
8. ICON Public Limited Corporation ($1.76B revenues in 2017)
9. Wuxi Apptec ($1.01B revenues in 2017)
10. Medpace Holdings, Inc ($0.44B revenues in 2017)

Luca Dezzani (2018-03-15). "Top 10 Global CROs 2018". *IgeaHub Pharmaceutical Club*

Research Versus Science

- **Research**
  - Refers to actual gathering of information
  - Can be in a scientific context but not exclusively
- **Science**
  - „scientia“ (Latin) means knowledge
  - Starts with a question (e.g. hypothesis)
  - Systematic approach that finishes with a conclusion
- **Research is a step and is part of the scientific method**

Drug Development Overview



Why Good Laboratory Practice (GLP) ?

Industrial Bio-Test Laboratories (**IBT Labs**) was an American industrial product safety testing laboratory.[1][2] IBT conducted significant quantities of research for pharmaceutical companies, chemical manufacturers and other industrial clients; at its height during the 1950s, 1960s, and 1970s, IBT operated the largest facility of its kind and performed more than one-third of all toxicology testing in the United States.[3][4][5] IBT was later confirmed of engaging in extensive scientific misconduct, or more properly, fraud, which resulted in the indictment of its president and several top executives in 1981 and convictions in 1983.[6][7] The revelations of misconduct by IBT Labs led to reforms in the regulation of pesticides in the United States and Canada.

Source: https://en.wikipedia.org/wiki/Industrial_Bio-Test_Laboratories (visited Nov 8, 2018)

What is Good Laboratory Practice ?

Specifically refers to a quality system of management controls for research laboratories and organizations to ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of chemical (including pharmaceuticals) non-clinical safety tests; from physio-chemical properties through acute to chronic toxicity tests

Good laboratory practice (GLP) for safety tests on chemicals". Medicines and Healthcare products Regulatory Agency. 20 January 2017

Contract Research - 1

Contracted Research

- Legal contract (finances, time schedule)

Good Laboratory Practice

- Avoid data fraud
- Standard operating procedures (SOPs)
- Everything is quality-controlled (QC) and quality-audited (QA)

One study plan and one study director

Contract Research - 2

One study plan and one study director

- Only work according to protocol
- Every change from protocol must be autorized (amendment, deviation)
- Every deviation must be rated (criticial for study validity)

Test item administration

- Verify test item concentration in dosing formulation
- Measure test item concentration in blood during study

Final study report is a document

- Basis for regulatory submission
- Archived with limited access
- Changes to report follow a special procedure (amendments)

Drug Development – A Highly Regulated Industry

EU – European Union
UK – United Kingdom
US – United States

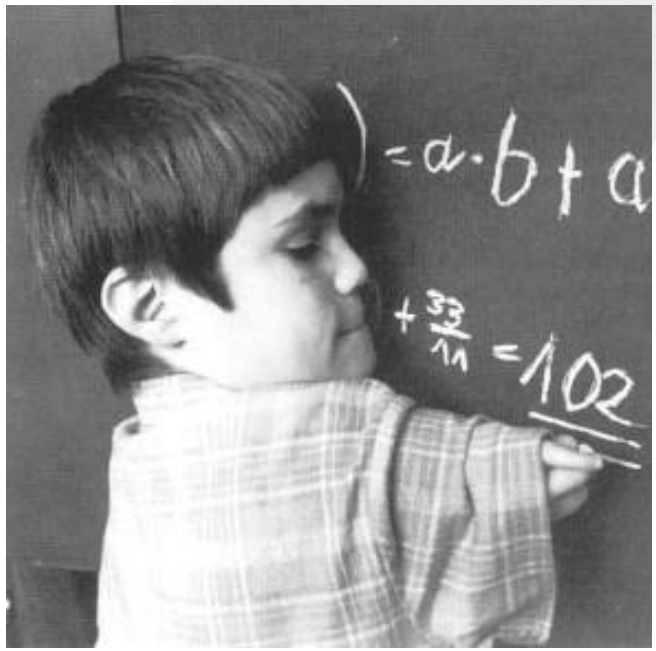
Drug Development Disasters

ELIXIR OF SULFANILAMIDE' USA 1937

- Sulfanilamide first antimicrobial drug
- Diethylene glycol used as diluent in new liquid formulation without toxicity testing
- Diluent poisonous - antifreeze
- 105 deaths (34 children and 71 adults)

Thalidomide Disaster (Contergan)

- 1954 first synthesized by Chemie Grünenthal
- 1957 launched sleeping tablet ‘Contergan’ onto market
- Sold in over 40 countries under license
- US had not given licensing approval
- Caused birth defects in 10,000 to 20,000 babies
- 1961 withdrawn from most markets



Thalidomide – Disease-based Risk-Benefit

Treatment of erythema nodosum leprosum (ENL) and multiple myeloma

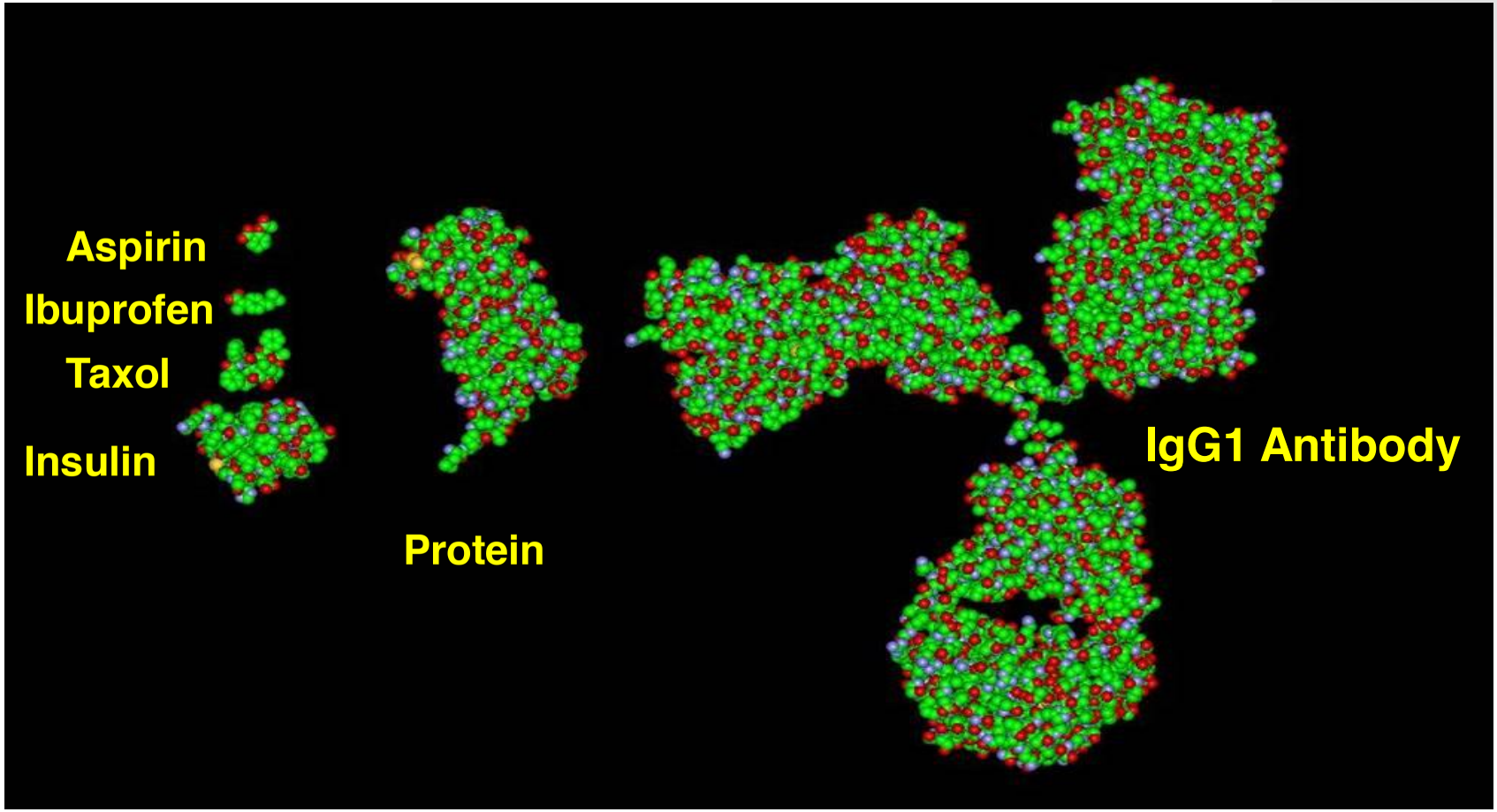
- Approved in the US in 1998 (for ENL)
- Benefit/risk much different for later indications
- Approved for Marketing under a special restricted distribution program approved by FDA
  - "SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (*S.T.E.P.S.* ®)."

Benefit/Risk acceptable for ENL and multiple myeloma

Small Molecule versus Large Molecule

Small Molecule: chemically synthesized

Biologic: Protein synthesized in a living system

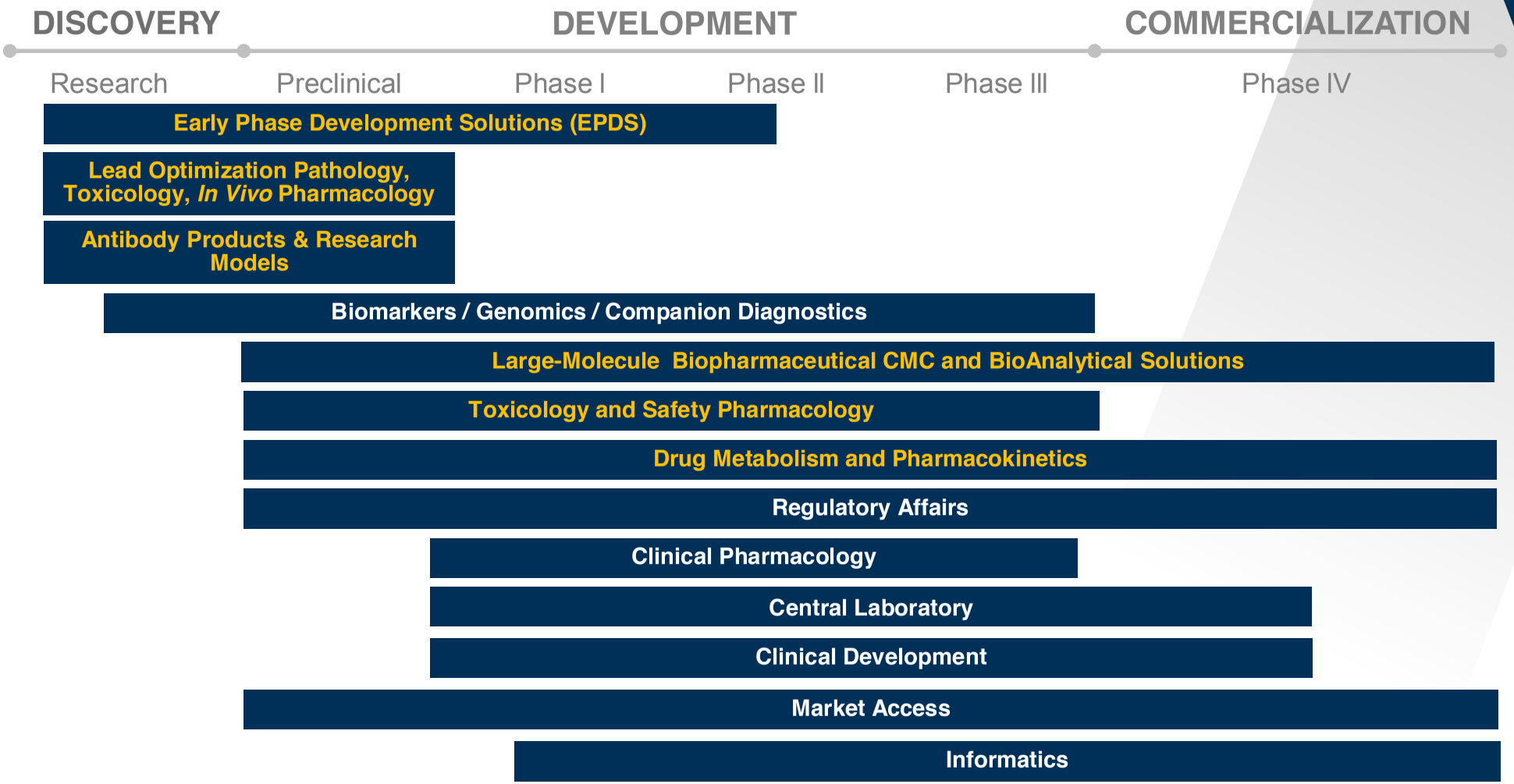


Pharmaceuticals vs. Biopharmaceuticals

Pharmaceuticals ("small")	Biolopharmaceuticals ("large")
Species independent	**Species specific**
Non-immunogenic	Immunogenic
Metabolized	Degraded (no toxic metabolite)
Short acting / short half-life	Long acting / long half-life
Chronic daily dosing	Intermittent dosing
Toxicity	**"Exaggerated pharmacology"**
Linear dose-response curves	Bell-shaped dose-response curves or plateau
Direct effects	Complex temporal relations
Application in most cases oral	Parenteral routes
Complex formulations	Simple formulations
Generics	No generics ("similar products"- biosimilars)

Covance Early Development Solutions

FROM LEAD OPTIMIZATION THROUGH COMMERCIALIZATION



Covance supports the discovery and development of more new drugs than any other company in the world

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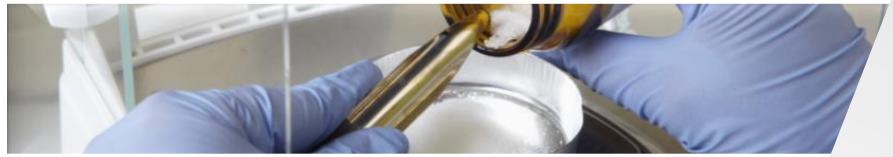
Comprehensive Safety Assessment Solutions

General Toxicology
From Single Dose to 2 years

Genetic Toxicology

Safety Pharmacology



Immunotoxicology

DART: Developmental & Reproductive Toxicology

Specialty Routes

Pathology

Animal Welfare

Providing the safety assessment insights Clients need to define the safety profile of their compounds

Regulated by the International Conference on Harmonization (ICH) Guidelines

Required Testing

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Developmental and Reproductive Toxicity/Toxicology

DART

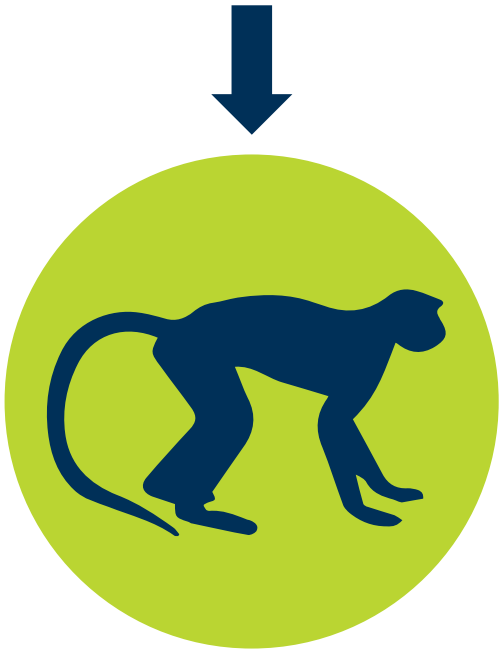
Developmental toxicity: Any adverse effect induced prior to attainment of adult life. Includes embryonic, fetal and postnatal effects/manifestations.

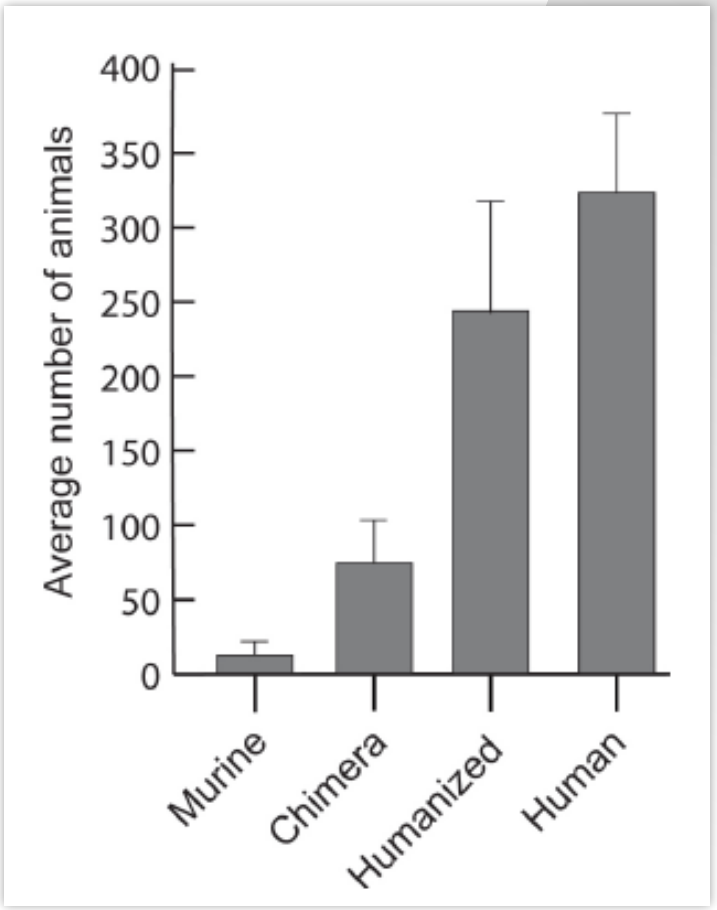
Reproductive toxicity: Effects on male or female fertility and reproductive performance

Nonhuman Primate as Relevant Animal Model

MABS HAVE EVOLVED FROM:

- mouse (100% Nonhuman)
- chimeric (33% Nonhuman)
- humanised (5-10% Nonhuman)
- fully human (0% Nonhuman)





Average use of NHP/nonclinical programme
(Van Meer et al 2013, Nat Biotechnol 31:882-883)

NHP is the only Relevant Animal Model

More than 30 mAb drugs approved by the end of 2016 in Japan and CTDs were available for 39 compounds (cancerous and non-cancerous indications)

- Cancer: 16/18 mAbs cynomolgus monkey (CM)
  - only species for 13 mAbs, CM & rhesus for 2 mAbs
- Non-cancer: 16/21 mAbs cynomolgus monkey (CM)
  - only species for 9 mAbs, CM & marmoset & chimpanzee for 1 mAb
- **32/39 mAb drugs (82%) with CM as relevant species**

Iwasaki et al (2018) Drug Mtbl Pharmacokinet S1347-4367: 30074-30075

mAbs 5:5, 1–7; September/October 2013; © 2013 Landes Bioscience

Immunogenicity of mAbs in non-human primates during nonclinical safety assessment

Peter J.K. van Meer,[1,*] Marlous Kooijman,[2] Vera Brinks,[1] Christine C. Gispen-de Wied,[3] Beatriz Silva-Lima,[4] Ellen H.M. Moors[2] and Huub Schellekens[1,2]

[1]Utrecht Institute of Pharmaceutical Sciences; Department of Pharmaceutics; Utrecht University; Utretcht, the Netherlands; [2]Copernicus Institute of Sustainable Development;

The value of non-human primates in the development of monoclonal antibodies

2013

To the Editor: the Medicines Evaluation Board in Utrecht,

Cancer Therapy: Preclinical

Clinical Cancer Research

Balancing Efficacy and Safety of an Anti-DLL4 Antibody through Pharmacokinetic Modulation

Jessica A. Couch[1], Gu Zhang[2], Joseph C. Beyer[1], Christina L. Zuch de Zafra[1], Priyanka Gupta[1], Amrita V. Kamath[1], Nicholas Lewin-Koh[3], Jacqueline Tarrant[1], Krishna P. Allamneni[1], Gary Cain[1], Sharon Yee[4], Sarajane Ross[4], Ryan Cook[5], Siao Ping Tsai[5], Jane Ruppel[1], John Brady Ridgway[2], Maciej Paluch[6], Philip E. Hass[6], Jayme Franklin[7], and Minhong Yan[2]

ORIGINAL ARTICLE

Prospective Design of Anti-Transferrin Receptor Bispecific Antibodies for Optimal Delivery into the Human Brain

ANTIBODY THERAPEUTICS

Therapeutic bispecific antibodies cross the blood-brain barrier in nonhuman primates

Y. Joy Yu,[1]* Jasvinder K. Atwal,[1]* Yin Zhang,[2] Raymond K. Tong,[3] Kristin R. Wildsmith,[4] Christine Tan,[2] Nga Bien-Ly,[1] Maria Hersom,[1] Janice A. Maloney,[1] William J. Meilandt,[1] Daniela Bumbaca,[4] Kapil Gadkar,[4] Kwame Hoyte,[5] Wilman Luk,[5] Yanmei Lu,[5] James A. Ernst,[3] Kimberly Scearce-Levie,[1] Jessica A. Couch,[4] Mark S. Dennis,[2] Ryan J. Watts[1†]

American Journal of Transplantation 2015; 15: 2825–2836
Wiley Periodicals Inc.

doi: 10.1111/ajt.13377

A Novel, Blocking, Fc-Silent Anti-CD40 Monoclonal Antibody Prolongs Nonhuman Primate Renal

Shock et al. Arthritis Research & Therapy (2015) 17:234
DOI 10.1186/s13075-015-0737-4

arthritis research & therapy

RESEARCH ARTICLE Open Access

CDP7657, an anti-CD40L antibody lacking an Fc domain, inhibits CD40L-dependent immune responses without thrombotic complications: an *in vivo* study

Anthony Shock[1*], Linda Burkly[2*], Ian Wakefield[1], Christopher Peters[3], Ellen Garber[2], Janine Ferrant[2], Frederick R. Taylor[2], Line Su[2,5], Yen-Ming Hsu[2,5], David Hutto[2,6], Ali Amirkhosravi[4], Todd Meyer[4], John Francis[4], Sarah Malcolm[1], Martyn Robinson[1], Derek Brown[1,7], Stevan Shaw[1], Roland Foulkes[1,8], Alastair Lawson[1], Olivier Harari[1], Timothy Bourne[1], Alison Maloney[1] and Neil Weir[1]

ISSN: 1942-0862 (Print) 1942-0870 (Online) Journal homepage: http://www.tandfonline.com/loi/kmab20

EC Scientific Conference Non-Animal Approaches - The Way Forward
6 – 7 December 2016, The Egg, Brussels

Increased Bile Acids Synthesis and Ileal Malabsorption of Bile Acids in Cynomolgus Monkeys

Rama Pai,*[,1] Dorothy French,† Ning Ma,* Kathy Hotzel,† Emile Plise,‡ Laurent Salphati,‡ Kenneth D. R. Setchell,§¶ Joseph Ware,|| Veronique Lauriault,||| Leah Schutt,* Dylan Hartley,* and Donna Dambach*

Reproductive Toxicology 42 (2013) 27–40
Contents lists available at ScienceDirect
Reproductive Toxicology

M Duval, A Plequet, A Cordier, G Jaral, G van Heeke, S Taplin, C Krantz, S Jones, AP Warren, FR Brennan, J Sims & P Lloyd

OPEN

Citation: Cell Death and Disease (2016) 7, e2338; doi:10.1038/cddis.2016.241
Official journal of the Cell Death Differentiation Association
www.nature.com/cddis

For this presentation:
PubMed search “cynomolgus & monoclonal antibody” since 2017 yielded over 100 papers

Jie Liu[1], Lijuan Wang[1], Feifei Zhao[1], Serena Tseng[1], Cyndhavi Narayanan[1], Lei Shura[1], Stephen Willingham[1], Maureen Howard[1], Susan Prohaska[1], Jens Volkmer[1], Mark Chao[1], Irving L. Weissman[1,*], Ravindra Majeti[1,2,*]

Oligohydramnios in Cynomolgus Macaques

A.E. Rozner, J.L. McCulloh and S. Henwood
Covance Laboratories Inc., Madison, WI, USA

Poster ACT 2016

Antibodies 2015, *4*, 426-440; doi:10.3390/antib4040426

OPEN ACCESS
antibodies
ISSN 2073-4468
www.mdpi.com/journal/antibodies

Article

Bispecific CD3/HER2 Targeting FynomAb Induces Redirected T Cell-Mediated Cytolysis with High Potency and Enhanced Tumor Selectivity

Ulrich Wuellner *, Kristina Klupsch *, Fabian Buller, Isabella Attinger-Toller, Roger Santimaria, Irene Zbinden §, Patricia Henne, Dragan Grabulovski ‡, Julian Bertschinger and Simon Brack *

Toxicologic Pathology, 41: 951-969, 2013

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623312474727

Unexpected Thrombocytopenia and Anemia in Cynomolgus Monkeys Induced by a Therapeutic Human Monoclonal Antibody

Nancy Everds[1], Nianyu Li[1], Keith Bailey[2], Madeline Fort[1], Riki Stevenson[3], Remi Jawando[1], Kevin Salyers[3,*], Vibha Jawa[3], Padma Narayanan[1], Erin Stevens[1], Ching He[1], Mai Phuong Nguyen[1], Sam Tran[1], Nancy Doyle[4], Florence Poitout-Belissent[4], Jacquelin Jolette[4], Cen Xu[3], and Katherine Sprugel[1]

COVANCE
SOLUTIONS MADE REAL®

Parathyroid Hormone Safety Evaluation for Osteoporosis Therapy

- Compound (Teriparatide) induced osteosarcoma in rat model
- Clinical study hold
- Long-term study (4.5 yrs) – 1.5 yrs treatment and 3 yrs posttreatment observation period
- Compound back on market (Forteo®)

Vahle et al (2008) J Bone Miner Res 23:2033–2039

ILARIS® (canakinumab)

- CM or rhesus monkeys were not acceptable due to lack of target binding
- Marmosets: IL-1β from marmoset shares 96% identity with human IL-1β, full cross-reactivity to marmoset IL-1β, and bioactivity of marmoset IL-1β is effectively neutralized by canakinumab
- Canakinumab has been shown to produce delays in fetal skeletal development in a marmoset PPND study
- Similar delays in fetal skeletal development were observed in mice administered a murine analog of canakinumab
- Delays in skeletal ossification are changes from the expected ossification state in an otherwise normal structure/bone: these findings are generally reversible or transitory and not detrimental to postnatal survival

FDA Medication Guide T2016-102/T2016-103 December 2016

Safety testing of monoclonal antibodies in non-human primates: Case studies highlighting their impact on human risk assessment

Frank R. Brennan, Joy Cavagnaro, Kathleen McKeever, Patricia C. Ryan, Melissa M. Schutten, John Vahle, Gerhard F. Weinbauer, Estelle Marrer-Berger & Lauren E. Black

MAbs 2018 Jan;10(1):1-17. doi: 10.1080/19420862.2017.1389364. Epub 2017 Oct 26

Acknowledgments

BIO, BioSafe Leadership, Victoria Dohnal, and many other contributions from BIO member companies, including those submitting cases. The authors were part of the Biotechnology Innovation Organization's (BIO) 3Rs Research Models and Alternatives Task Force. This task force is a committee within the BioSafe Preclinical Safety Committee, comprised of BIO members working to serve as a resource for BIO members and BIO staff by identifying and responding to key scientific and regulatory issues related to the preclinical safety evaluation of biopharmaceuticals products.

The views in this paper do not necessarily represent all members of BIO.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Approach and Outcome Parameters

Rationale

Review current approaches to the safety assessment of mAbs, and collect and analyze a cross-section of specific case examples from BIO member companies where NHP safety studies had meaningful and profound effects on clinical development.

- 18 cases (14/18 [78%] NHP relevant species, CM, BIO-6 also rhesus)
- 3 cases with NHP plus rodent, 1 case with NHP plus rabbit
- For 9 cases, detailed descriptions are provided (BIO-1 to BIO-9)
- Target, drug format, indication (if disclosed)
- Intended pharmacology
- Potential safety risk for human
- Findings in toxicity studies
- Value of NHP studies
- Impact of NHP data on clinical development

Outcomes I - Overview

- 10 cases with termination of candidate(s)/target(s)/program
- 7 cases NHP only, 2 cases NHP+rodent, 1 NHP+rabbit

- 4 cases identified new toxicities with (potential) human relevance
- 4 cases NHP only
- Clinical programme enabled/continued and enhanced/adjusted clinical monitoring

- 4 cases identified “drugged” safety
- “Target with theoretical safety liability could be drugged safely”
- 3 cases NHP only, 1 case NHP+rodent
- Clinical programme enabled/continued and enhanced/adjusted clinical monitoring

Outcome - Detailed Case Study (BIO-5)

- IgG4 mAb against a cytokine, indication inflammatory diseases
- CM only relevant toxicity species, no activity in rodents
- KO mouse and homolog mAb mouse studies without adverse findings
- NHP general toxicity studies without adverse findings
- To cover WOCBP and young infants, an ePPND study was run in CM
  - Dosing from gestation day 20 to parturition, infant monitoring for 9 months
  - mAb well tolerated, normal incidence of abortions
  - Significant prolongation of gestation in all animals, mortality at delivery
  - Dystocia caused by placental retention
  - Infant mortality likely associated with dystocia
  - Surviving infants developed normally including the immune system
- ePPND study findings not evident in KO mice and pregnant mice treated with the anti-mouse cytokine receptor mAb

Outcome - Detailed Case Study (BIO-5) - ctd

MESSAGES AND CONSEQUENCES:

- Identification of life-threatening hazard for women and infants during the latter stages of pregnancy - not predicted from literature nor from mice (KO or mAb-treated)
- The only appropriate species model for assessing DART was NHP
- Continued development in patients with autoimmune diseases without unexpected safety findings
- Informed consent form specifically warns against use in pregnancy and instructs that women who become pregnant while receiving BIO-5 must stop treatment immediately

SPINRAZA®

Spinal Muscular Atrophy (SMA) is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Ultimately, individuals with the most severe type of SMA can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing.

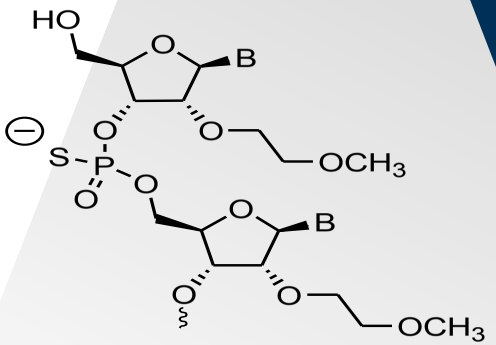
Due to a loss of, or defect in the SMN1 gene, people with SMA do not produce enough survival motor neuron (SMN) protein, which is critical for the maintenance of motor neurons. The severity of SMA correlates with the amount of SMN protein. People with Type 1 SMA, the type that requires the most intensive and supportive care, produce very little SMN protein and do not achieve the ability to sit without support or live beyond two years without respiratory support. People with Type 2 and Type 3 produce greater amounts of SMN protein and have less severe, but still life-altering, forms of SMA.

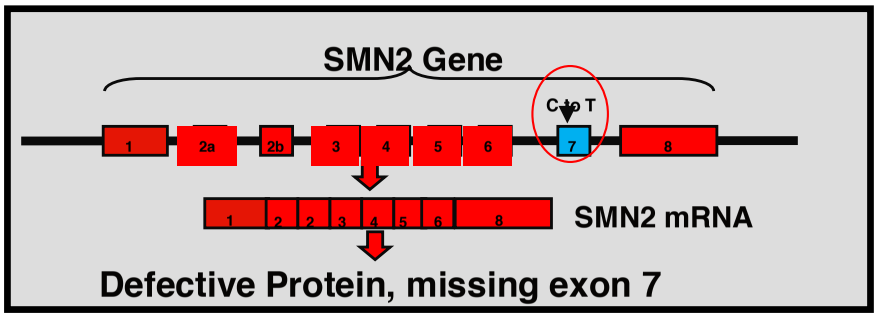
Nusinersen: Modulating Splicing of SMN2 to Increase Normal SMN Protein

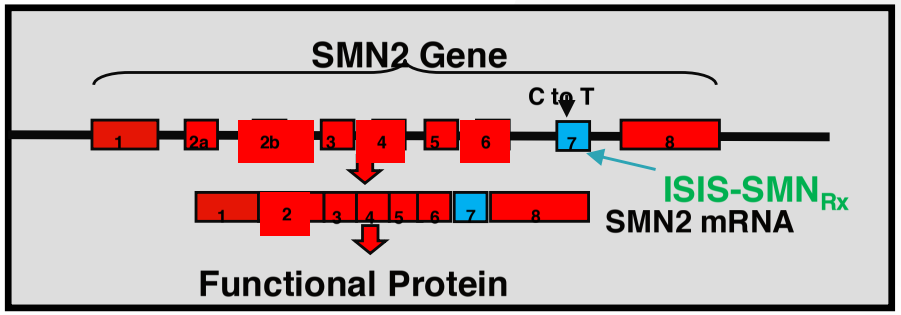
Uniformly 2'-*O*-methoxyethyl modified (MOE) antisense drug

Corrects the splicing disorder in *SMN2*, resulting in the production of fully functional SMN protein in model systems

In mild and severe mouse models of SMA provides a phenotypic and pathological benefit when delivered centrally*







*(Hua et al., Genes Dev., 2010; Passini et al., Sci Transl Med, 2011; Hua et al., Nature, 2011)

Juvenile Cynomolgus Monkey: Study Design

Group	Treatment	Nominal Dose (mg)	Total Annual Dose (mg)	Dose Conc. (mg/mL)	Dose Volume (mL)	Number of animals	
						Terminal (Day 372)	Recovery (Day 554)
						♂ / ♀	♂ / ♀
1	aCSF	0	0	0	0.75	5/5	2/2
2	Low Dose	0.3	3.9	0.4	0.75	5/5	
3	Mid Dose	1	13	1.3	0.75	5/5	
4	High Dose	4	52	5.3	0.75	5/5	2/2

Administration by IT Lumbar Puncture

5 Loading doses on Days 1, 8, 15, 22, 29 (q1w)

8 Maintenance doses on Days 71, 113, 155, 197, 239, 281, 323, 365 (q6w)

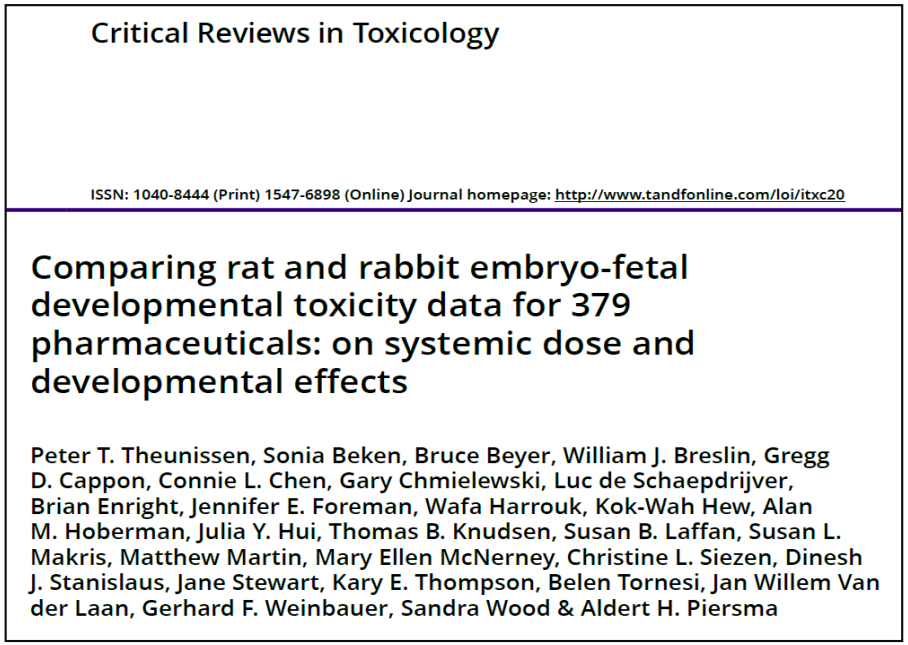
Henry et al (2017) SOT 56th Annual Meeting, Baltimore, MD

HESI Developmental and Reproductive Toxicology – 2nd Species Project

- ICH S5 guideline requests testing for embryofetal development in a rodent and a non-rodent species (typically rat and rabbit)
- Is either one species sufficient ? (379 compounds evaluated)

The use of both species recommended over single species use

http://dx.doi.org/10.1080/10408444.2016.1224807; http://dx.doi.org/10.1080/10408444.2016.1224808



Application Techniques

capsule (X Ray and magnetic controlled)

continuous i.v. infusion

oral (gavage)

dermal

intraarticular

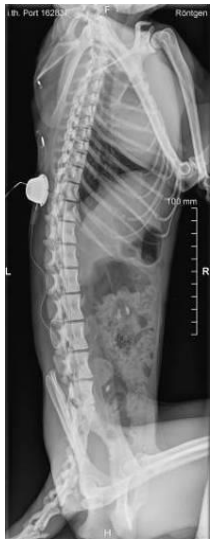
Intrabronchial (video controlled)

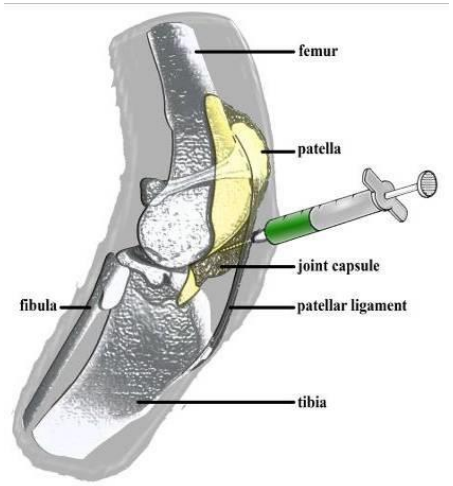
Intracavernous

Intraduodenal

Intramuscular

Intranasal





(intra)ocular:

- topical/intravitreal/intracameral

intraperitoneal

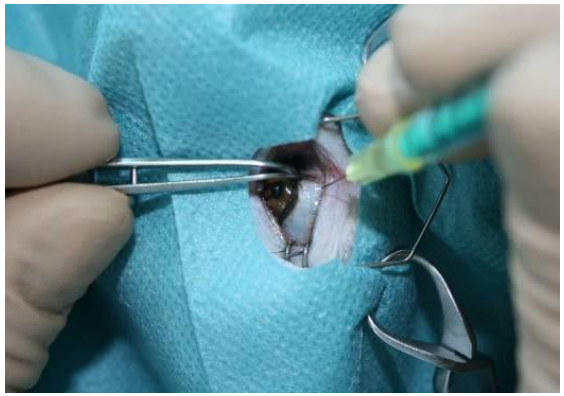
Intrathecal (also continuous)

intratracheal
(also continuous)

Intravaginal

Intravenous

subcutaneous



Diagnostic Capabilities in Macaques

bone density (DXA, pQCT)
body composition (DXA)
bronchoscopy/lavage
cardiovascular telemetry
cerebrospinal fluid (CSF)
echocardiography
electroencephalography (EEG)
electroretinography (ERG)
endometrial biopsy
geriatric diseases hormone profiling
Ethovision® (behaviour analysis)
fluorescence angiography
fat/lean body mass
high definition oscillometry
imaging (PET & SPECT, CT, MRT)
immunotoxicity (IPT, NK, KLH, etc.)
infant (neuro)behaviour
intraocular pressure
JET/BP
laparoscopy
menstrual cyclicity
modified Irwin test
nerve conductance/reflex test
pachymetry
primary cell supply
prostate biopsy/size
semen analysis
spermatogenesis staging
testis biopsy/size
ultrasonography
Wisconsin learning test
x ray (digital)

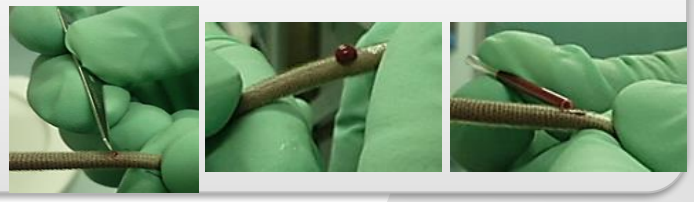
CRO Perspective on 3Rs in Biomedicine/Drug Development

- REFINEMENT
  - Opportunities
- REDUCTION
  - Opportunities
- REPLACEMENT
  - Opportunities
  - Challenging on a larger scale and from today‘s perspective

Validation and Regulatory Acceptance

CRO Perspective on 3Rs: Reduction

Microsampling (< 50 µl): ~ **65-75%** reduction in animal numbers (mouse and rat)

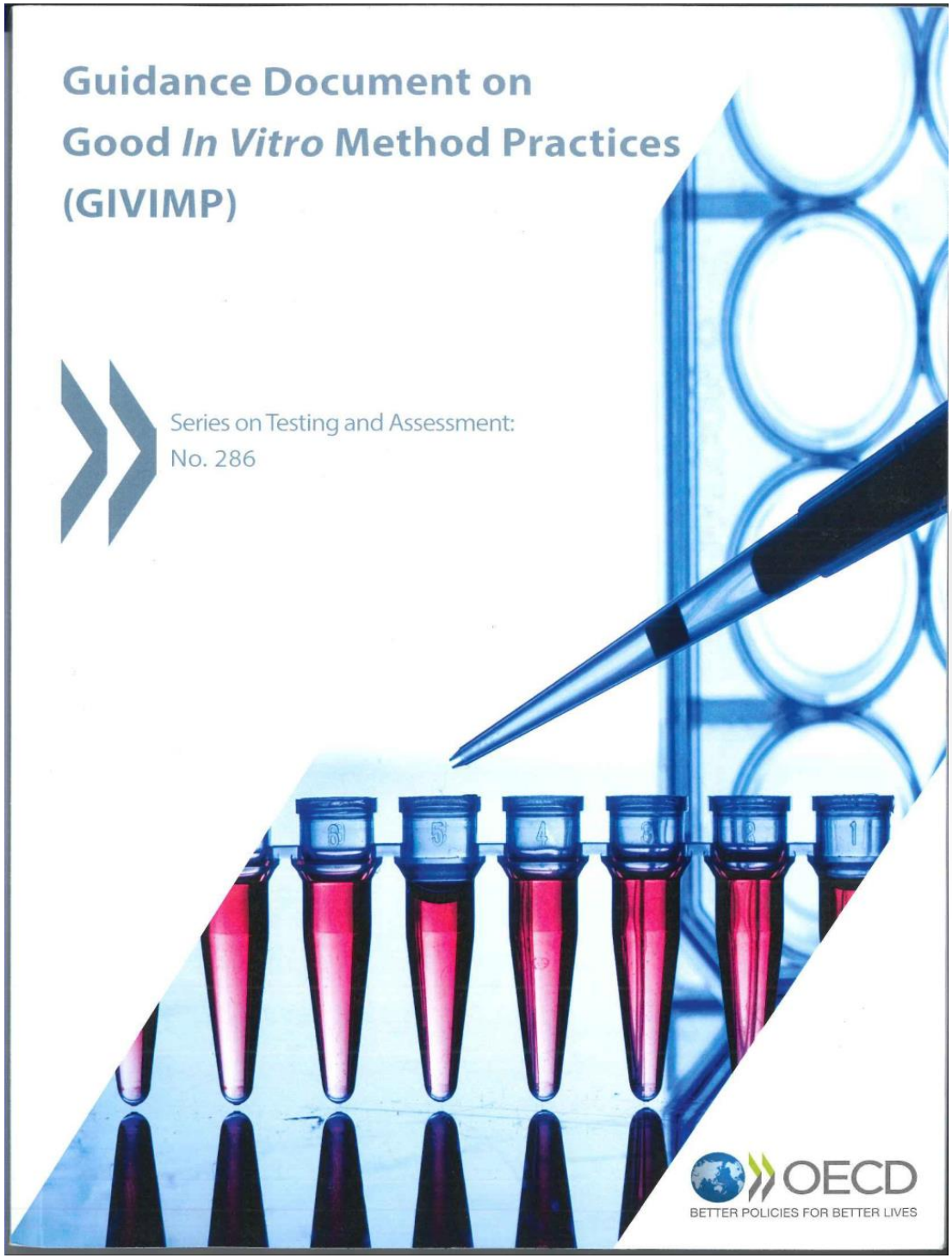


Re-use of animals:

- > **90%** reduction in minipig use for PK studies
- re-use of control animals is encouraged where possible e.g. ICH S6(R1)
- Industry challenging the need for “recovery“ animals on studies

Refined blood sampling approach: better scientific data and **>50%** reduction in rat use for PK studies

Guideline modifications and increased scientific knowledge in biopharmaceutical drug development:
~ **50%** reduction in NHP use/biopharmaceutical candidate



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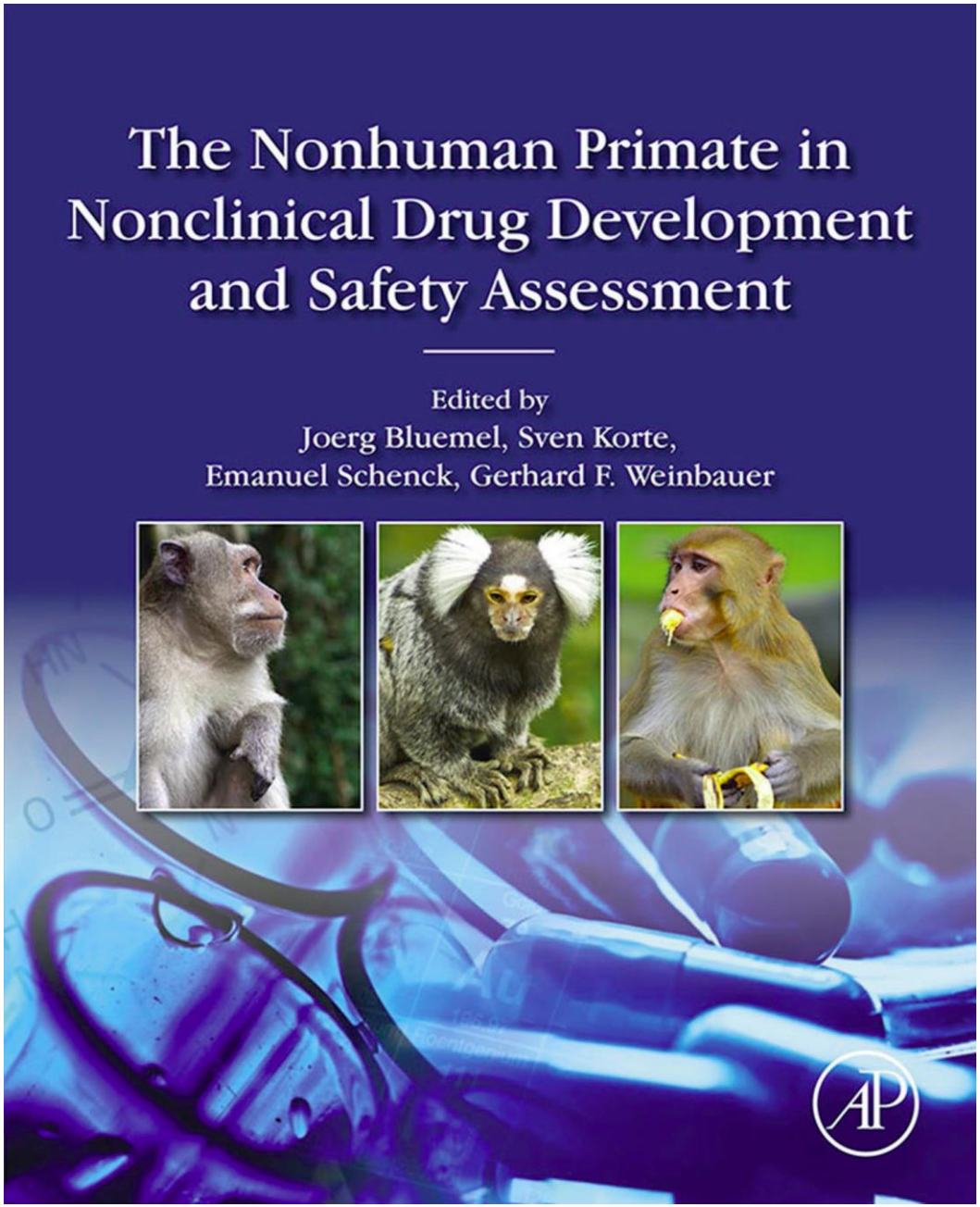

Questions !

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