



RISK MANAGEMENT IN EARLY CLINICAL TRIALS – A CRO PERSPECTIVE

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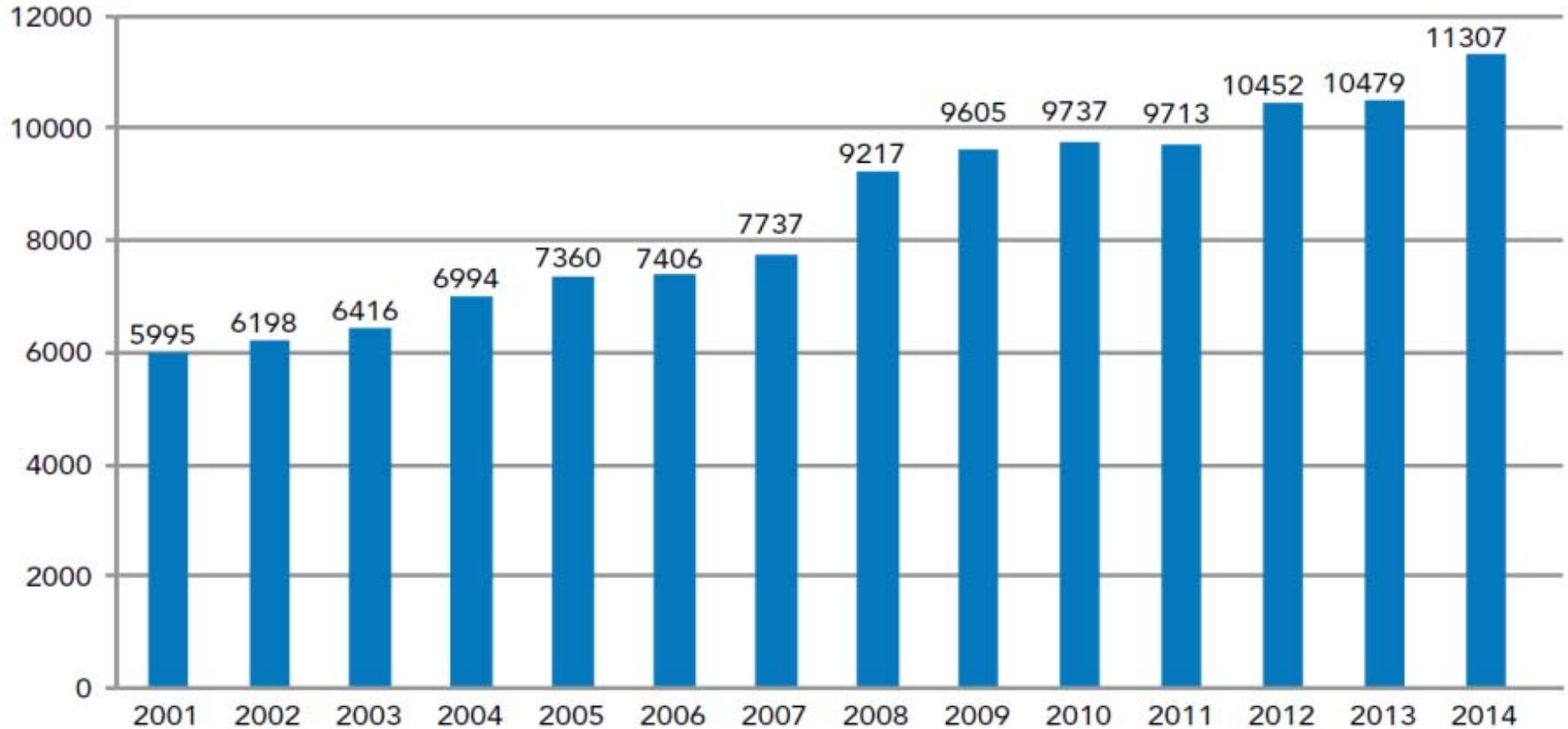
AGENDA

RISK MANAGEMENT IN EARLY CLINICAL TRIALS – A CRO PERSPECTIVE

- Introduction
- Risks in Phase I
- Safety Risk Mitigation Procedures and Requirements
- Bial/Biotrials Subject SAE/death
- Summary

R&D PIPELINE GROWS – COMPANIES AND NEW DRUGS INCREASES

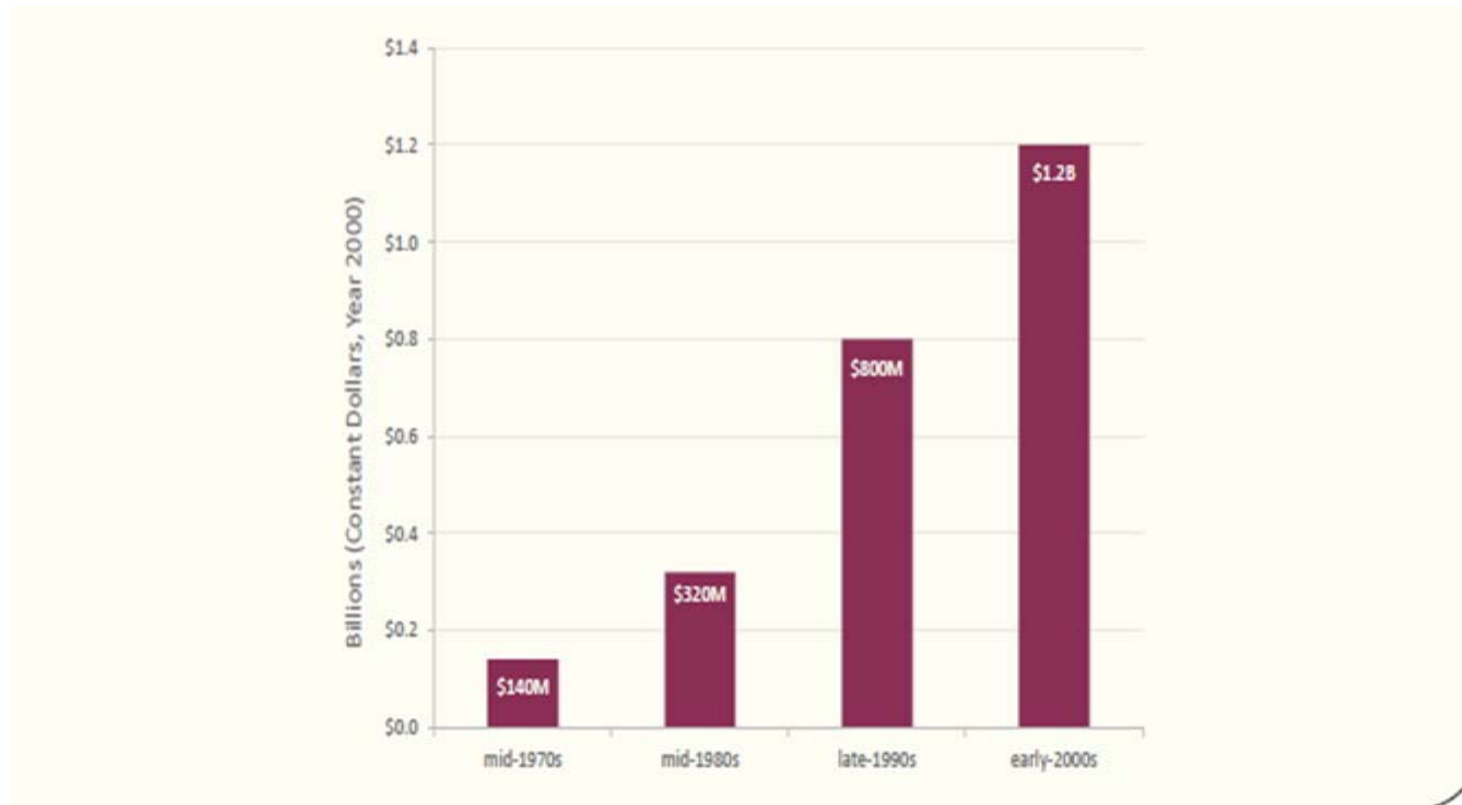
Figure 1. Total R&D Pipeline Size by Year 2001-2014



Source: Pharmaprojects® Pipeline®, January 2014

62% increase new drugs over last 15years

COSTS TO DEVELOP NEW DRUGS INCREASES



SOURCES: J.A. DiMasi, R.W. Hansen, and H.G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22(2): 151-185; J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4-5): 469-479; More recent estimates range from \$1.5 billion to more than \$1.8 billion. See for example J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203-214.

NOTE: Data is adjusted to 2000 dollars based on correspondence with J.A. DiMasi.

INCREASING COMPLEXITY OF EARLY CLINICAL TRIALS

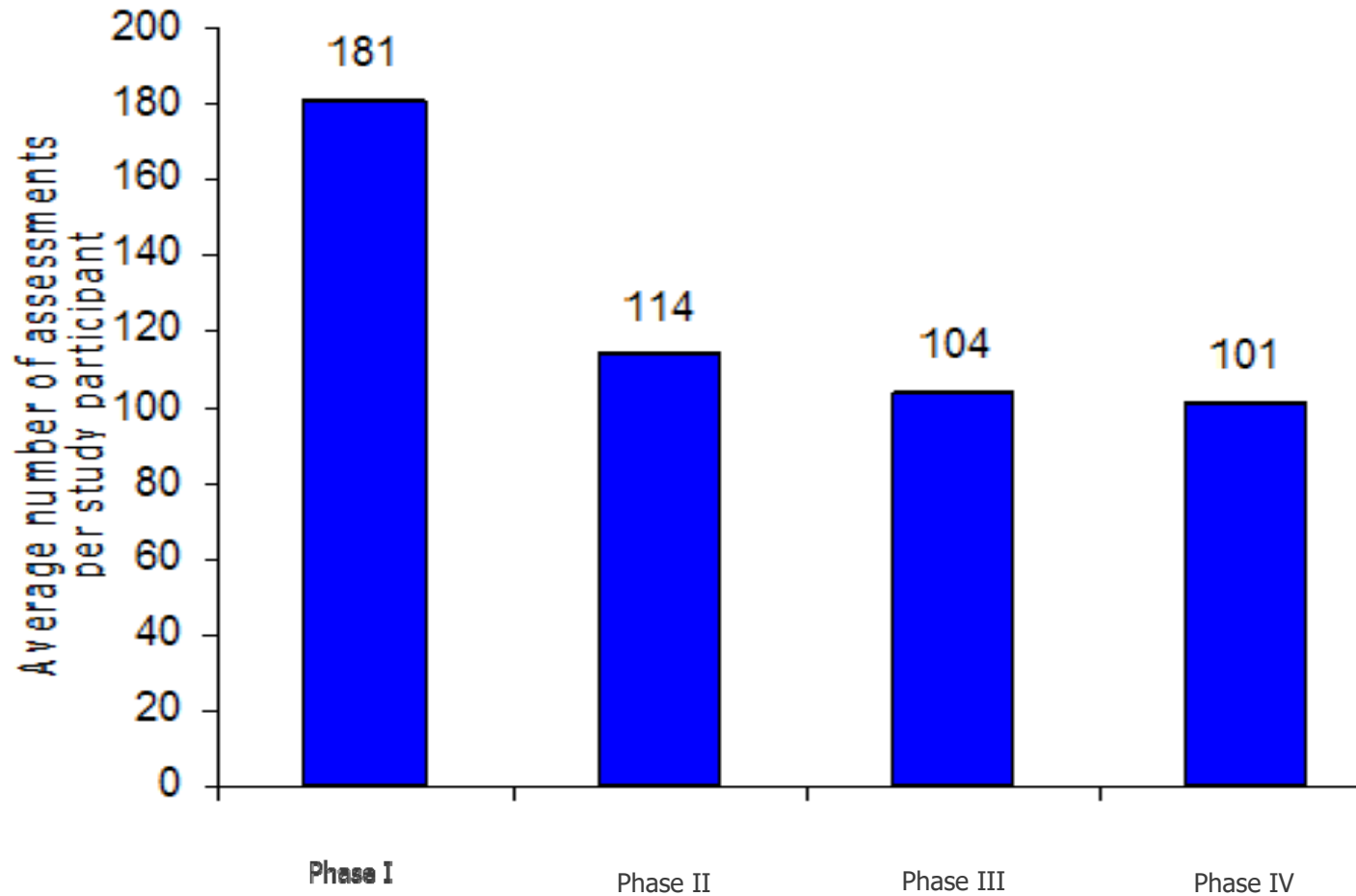
Trends in Clinical Trial Protocol Complexity

	2000–2003	2008–2011	Percentage Change
Total Procedures per Trial Protocol (median) (e.g., bloodwork, routine exams, x-rays, etc.)	105.9	166.6	57%
Total Investigative Site Work Burden (median units)	28.9	47.5	64%
Total Eligibility Criteria	31	46	58%
Clinical Trial Treatment Period (median days)*	140	175	25%
Number of Case Report Form Pages per Protocol (median)	55	171	227%

*These numbers reflect only the “treatment duration” of the protocol.

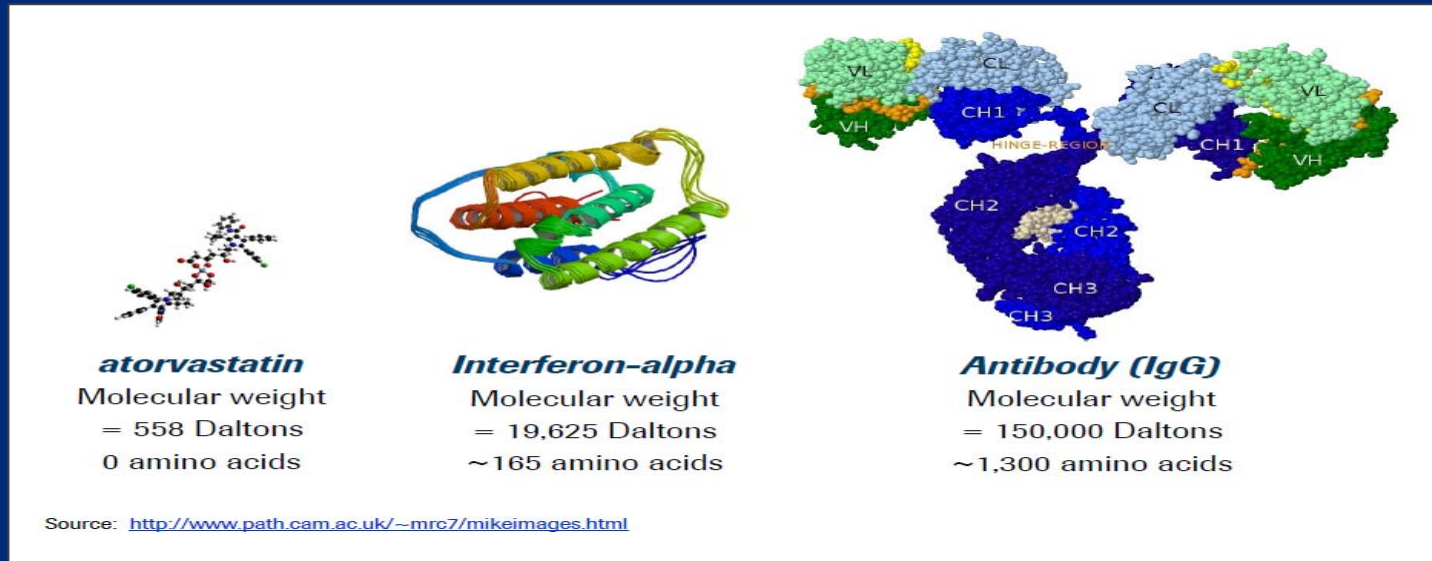
SOURCE: K.A. Getz, R.A. Campo, and K.I. Kaitin. “Variability in Protocol Design Complexity by Phase and Therapeutic Area.” *Drug Information Journal* 2011; 45(4): 413–420. Updated data provided through correspondence with Tufts Center for the Study of Drug Development.

CLINICAL STUDY ASSESSMENTS INCREASES



From PHRMA 2013 Profile

DRUGS INCREASING IN COMPLEXITY – NEW TARGETS



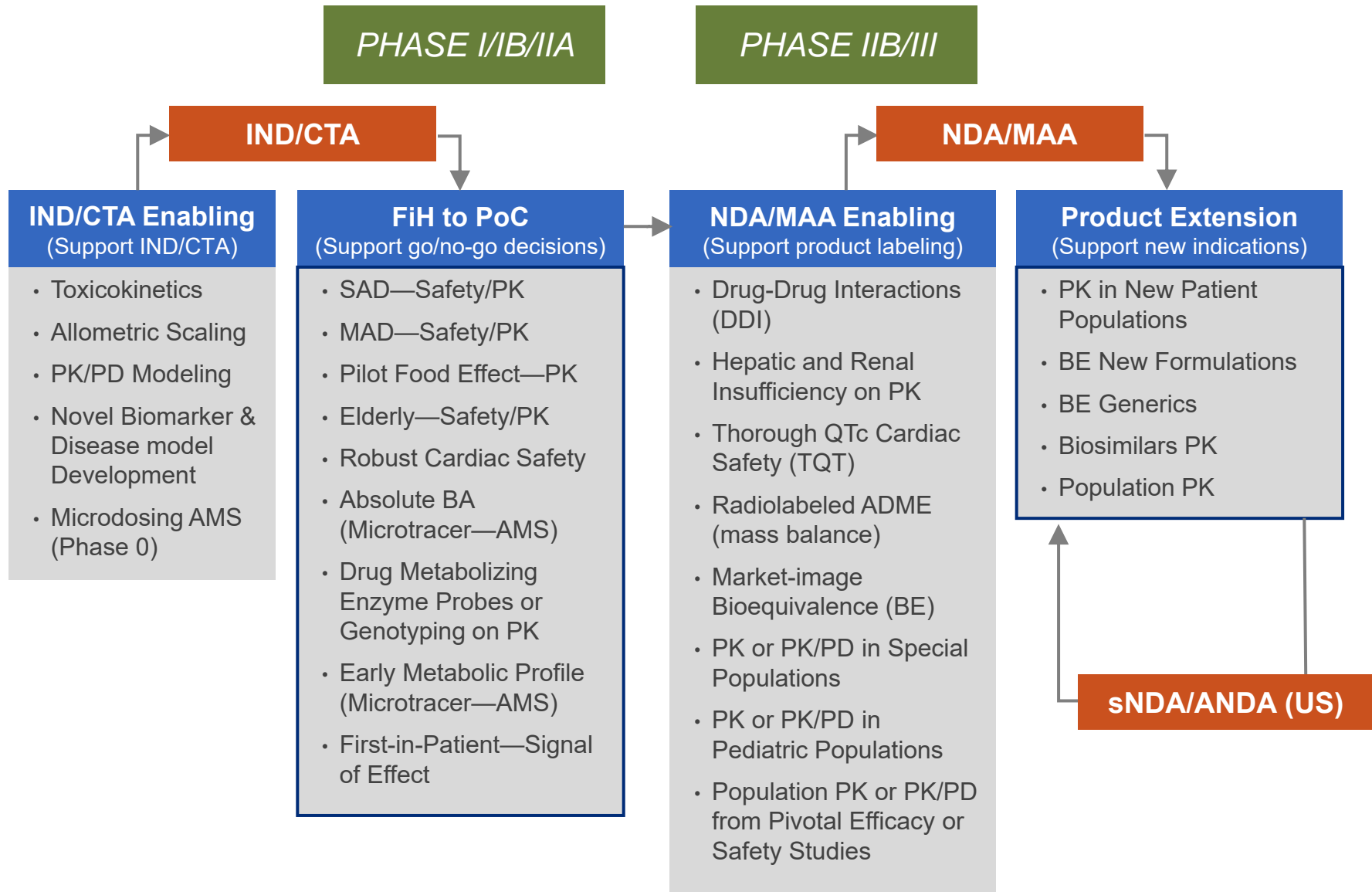
- Early clinical development complex; key aspects safety/PK/PD
- Spans First In Human healthy subjects to early patient studies
- Includes small molecules, peptides, biologicals (domain, complex bispecific mAbs, antibody conjugates), cell/tissue therapies and gene therapies - many new drug targets
- Generics and biosimilars

LIMITATION OF PRECLINICAL ANIMAL MODELS

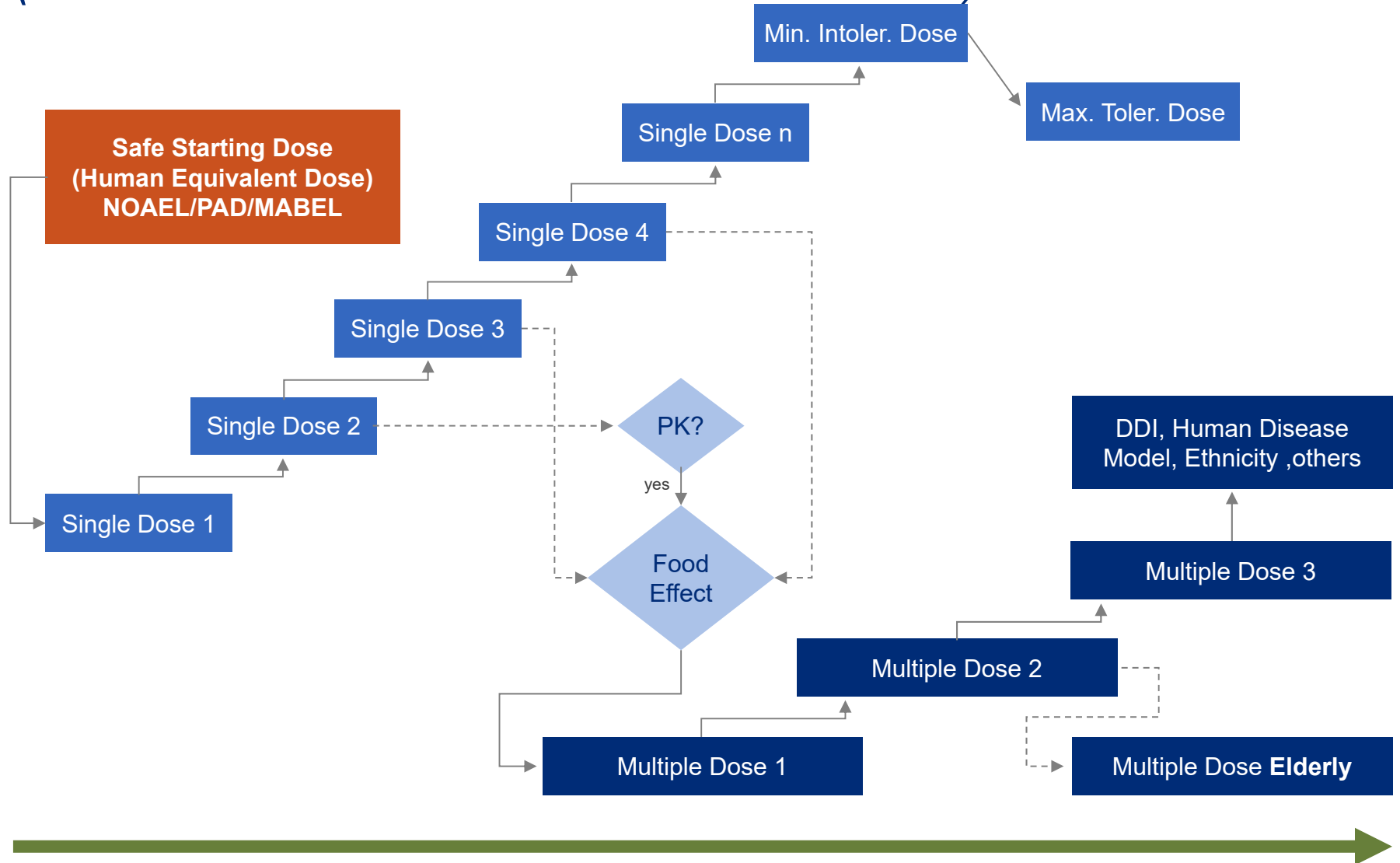


- The mouse is by far the most common animal model used in life science research
- The mouse genome reveals about 30,000 genes, with 99% having direct counterparts in humans
- Immunologically, however mouse and men are very different

CLINICAL PHARMACOLOGY STUDIES IN DRUG DEVELOPMENT



FIRST IN HUMAN COMBINED PROTOCOLS (SMALL MOLECULE - FLEXIBLE DESIGN)



RISK MANAGEMENT – REGULATORY ENVIRONMENT

Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Ann Meeker O'Connell at 301-796-3150, (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800, or (CDRH) Chrissy Cochran at 301-796-5490.

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)
Center for Devices and Radiological Health (CDRH)
August 2011
Procedural

RISK MANAGEMENT – REGULATORY ENVIRONMENT



15 April 2014
EMA/838713/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 1)

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	19 January 2012
Draft agreed by ERMS FG	24 January 2012
Draft adopted by Executive Director	20 February 2012
Released for public consultation	21 February 2012
End of consultation (deadline for comments)	18 April 2012
Revised draft finalised by the Agency in collaboration with Member States	20 June 2012
Revised draft agreed by ERMS FG	21 June 2012
Revised draft adopted by Executive Director	22 June 2012
Anticipated date for coming into effect after finalisation	2 July 2012
Draft Revision 1* finalised by the Agency in collaboration with Member States	12 March 2014
Draft Revision 1 provided to ERMS FG	2 April 2014
Draft Revision 1 adopted by Executive Director as final	15 April 2014
Date for coming into effect of Revision 1	28 April 2014

Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry

The portion of this guidance document setting forth the submission procedures for risk evaluation and mitigation strategies revisions is being distributed for comment purposes only.

Comments and suggestions regarding this document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact (CDER) Kristen Everett at 301-796-0453, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-7800.

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)

April 2015
Drug Safety

RISK MANAGEMENT – REGULATORY ENVIRONMENT



Final Concept Paper
Addendum for ICH E6: Guideline for Good Clinical Practice
dated 2 June 2014
Endorsed by the ICH Steering Committee on 5 June 2014

Type of Harmonization Action Proposed

Addition of an addendum to an existing Guideline, ICH E6, *Good Clinical Practice (GCP)*: Consolidated Guideline

Statement of the Perceived Problem

Since the adoption of the ICH E6 Guideline on *Good Clinical Practice (GCP)*, clinical trials have evolved substantially, with increases in globalisation, study complexity, and technological capabilities. To keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology we should modernise our approach to GCP to enable implementation of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that will better ensure human subject protection and data quality. Although ICH E6 generally can be interpreted as providing sponsors flexibility to implement innovative approaches, it has been misinterpreted and implemented in ways that impede innovation by, for example, emphasising less important aspects of trials (e.g., focusing on the completeness and accuracy of every piece of data) at the expense of critical aspects (e.g., carefully managing risks to the integrity of key outcome data). Modernising ICH E6 by supplementing it with additional recommendations will better facilitate broad and consistent international implementation of new methodologies. Topics to be discussed by the expert working group (EWG) to facilitate innovative approaches to clinical trials include quality risk management and quality-by-design processes which emphasizes upfront assessment of risks specific to a study design and protocol. In addition, other study operational procedures to facilitate innovative approaches should be discussed, including risk-based monitoring, focusing on critical study elements, and use of technological tools to ensure robust conduct, oversight, and reporting.

EARLY CLINICAL – RISK IDENTIFICATION & MITIGATION REVIEW SPECIFIC STUDY LIFE CYCLE

	Study Preparation				Clinical Conduct			Postclinical Services			
Project Management	resource planning, team coordination and review documents	gather documents and complete submission	organize set up meetings	organize SIV, track training compliance	organize meetings, provide status updates	track PK shipment			attend Clean Data-Review-Meeting		review CSR organize shipment and archiving of TMF
ClinBase		set up	set up	set up							
Project Quality Lead	review documents	review documents		organize trainings	perform quality checks	quality consultancy					CSR review, TMF review
Monitoring			generate Monitoring - Plan	attend SIV	monitoring	monitoring	monitoring	monitoring			
Recruitment and Enrollment Services	develop recruitment strategy	perform DB research, contact first subjects	advertising	study specific advertising	organize subject information sessions, start SCR	perform SCR	organize FUP				
Pharmacy		generate IMP manual		IMP receipt and storage	IMP preparation	IMP delivery					IMP retention, return
Clinics	review documents, capacity planning	review ClinBase set-up	resource planning, team training	IMP Manual	perform subject information sessions, conduct study	conduct study, query resolution, write safety report	conduct study, query resolution	query resolution	participate in Clean-Data-Review-Meeting	review CSR	review CSR
Laboratory (Internal and Safety Lab)	review CSP	set-up including contact with safety lab	dummy-runs	set-up	process and ship SCR samples	process and ship PK and safety samples	process and ship PK and safety samples	ship PK			
Medical Writing		generate ICD and CTA				write Interim-Safety-Report			skeleton CSR	draft CSR	final CSR
Data Management				generate DMP DVS DTA		cleaning, conversion, query resolution	query resolution	cleaning, coding, query resolution	US soft lock, conversion	US hard lock, data transfer	
Biostatistics				generate SAP		Interim analysis, TFI's				Analysis, TFI's	
Pharmacokinetics				SAP						PK calculation, PK analysis	provide PK section for CSR

Protocol No.	ABC
Sponsor Name	
PAREXEL Project No.	220848
Project Manager	
Principal Investigator	
PP Initial Release Version dated	04-Mar-15
Project Plan Version No.	Final v1.0
This section Version No.	Final v1.0

Probability or occurrence	Project impact	Risk rating
7,8,9	7,8,9	>80 = Unacceptable
	4,5,6	> 60 < 80High
	1,2,3	> 20 < 60Medium
4,5,6	7,8,9	>80 = Unacceptable
	4,5,6	> 20 < 60Medium
	1,2,3	<20 = Low
1,2,3	7,8,9	> 60 < 80High
	4,5,6	> 20 < 60Medium
	1,2,3	<20 = Low

Risk Management

Risk information				Risk impact status			Risk Management					
Risk #	Risk Statement	Risk Category	Milestone impacted	Probability 1-9	Impact 1-9	Risk Score	Risk Mgmt Required?	Planned Mitigation actions	Planned Contingency	Assigned to	Due date	Comments / additional details
1	Shortened screening window due to NCT# not being available.	Subject Recruitment	First Subject First Visit (FSFV) and First Subject First Dose (FSFD)	9	8	72	Yes	To offer subjects compensation for cancelled screening appointments. To ensure screening slots are booked at full capacity.	To delay FSFD to allow for additional screening time.	PM / Recruiter		FSFD has now been reached - within timelines.
2	Long follow-up period for the subjects	Subject Recruitment	First Subject First Visit (FSFV)	9	7	63	Yes	The study payments will be staggered across the follow up period and the ICDs will be updated. Subjects will be informed of the study schedule during recruitment.	While PXL are awaiting Ethics approval for the ICDs, subjects will be verbally informed of the change to the payment schedule. Screening visits will be overbooked for maximum attendance.	PM / Recruiter		
3	Number of dosed subjects is below target.	Other	Safety Review Meeting	5	9	45	Yes	Minimum number of subjects (six) required for Dose Escalation specified in Protocol.	Subjects being screened for the next cohort will be asked if they can reschedule and be included in a stagglor group, if the number of dosed subjects is below target.	PM / Clinical Team		Specific screening for a straggler group will not need to take place.
4	RAVE transcription one day prior to the safety review meeting.	CRF / eCRF	Safety Review Meeting	5	5	25	Yes	The data quality team are aware of the tight timelines and the requirements. Calendar reminders will be in place to ensure timely completion.	Prompt monitoring of the RAVE data.	PM / Data Quality		

2006 TEGENERO 1412 TRIAL – LESSONS LEARNT

- **Healthy volunteer first in man trial, administered to first dose cohort at 1/500 of NOAEL dose in cynomolgus monkeys and caused in 6 subjects cytokine storm and multi-system organ failure requiring intensive treatment.**
- **TGN-1412 - a humanized anti-CD28 monoclonal Ab of the IgG4 subclass.**
- A “superagonist” Mab targeting CD28, preclinical studies in monkeys and mice showed it activated and expanded resting T-cell populations without a requirement for T-cell receptor engagement as a “second signal”.
- A potent activator of “regulatory” T-cells, was non-toxic and effective in rodent models of autoimmune disease.
- **MABEL dose not considered, (except in retrospect) but human T-cells in vitro had released 1000-fold more cytokines than monkey T-cells exposed to TGN-1412 in vitro.**

THE PREDICTIVE VALUE OF AN ANIMAL MODEL

(FROM THE ABPI/BIA POST-TEGENERO TASK FORCE REPORT)

“CAREFULLY CONSIDER”:

- the target’s homology between human and animal safety species
- similar target expression / distribution between human and animal species
- differences in physiological systems and/or downstream pathways that may be affected
- a literature review of related pathways and whether there are known biological differences between the animal species and humans
- in vitro binding affinity (human and animal)
- in vitro bioactivity or functionality / potency (human and animal tissue)
- the biological effect of the antibody FC regions in the animal species and their relevance to humans. (effects on clearance, ADCC vary with species)

WHAT WAS WRONG WITH THE TGN1412 SAFETY PHARMACOLOGY/TOXICOLOGY? (OR ITS INTERPRETATION)

- Sponsor and regulators gave the safety profile in monkeys priority over exposure/response data with human immune cells. **Human *in vitro* responses were incompletely characterized** and were not conservatively interpreted.
- **Ignored receptor occupancy:** Based on data in IMPD, when binding affinities and PK modeling is considered, this product dosed at 0.1 mg/kg would achieve >90% receptor occupancy. (this is NOT a safe starting dose for an agonist)
- **Ignored published data on CD28 expression** on human neutrophils, NK cells, mouse mast cells and neutrophils, NK cells, and mast cells ignored in safety pharmacology and tissue cross-reactivity studies.

EU GUIDELINE FIRST IN HUMAN STUDIES



London, 19 July 2007
Doc. Ref: EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
AGREED BY CHMP EXPERT GROUP	4 July 2007
ADOPTION BY CHMP	19 July 2007
DATE FOR COMING INTO EFFECT	1 September 2007

KEYWORDS	First-in-human, Phase I clinical trials, identification of risk, non-clinical requirements, animal models, MABEL, risk mitigation strategies
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- **Definition of “high-risk IMP”**
 - Mode of action
 - Nature of the target
 - Relevance of animal model
- **Preclinical**
 - Relevant species
 - Human tissue/cells
- **Clinical**
 - Study population
 - Study design
 - Starting dose (HED, MABEL)
 - Dose escalation
 - Monitoring (safety)
 - Stopping criteria
 - Study site accreditation

SAFETY RISK MANAGEMENT – REGULATORY ENVIRONMENT



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

21 July 2016
EMA/CHMP/446302/2016
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMA/CHMP/SWP/28367/07)

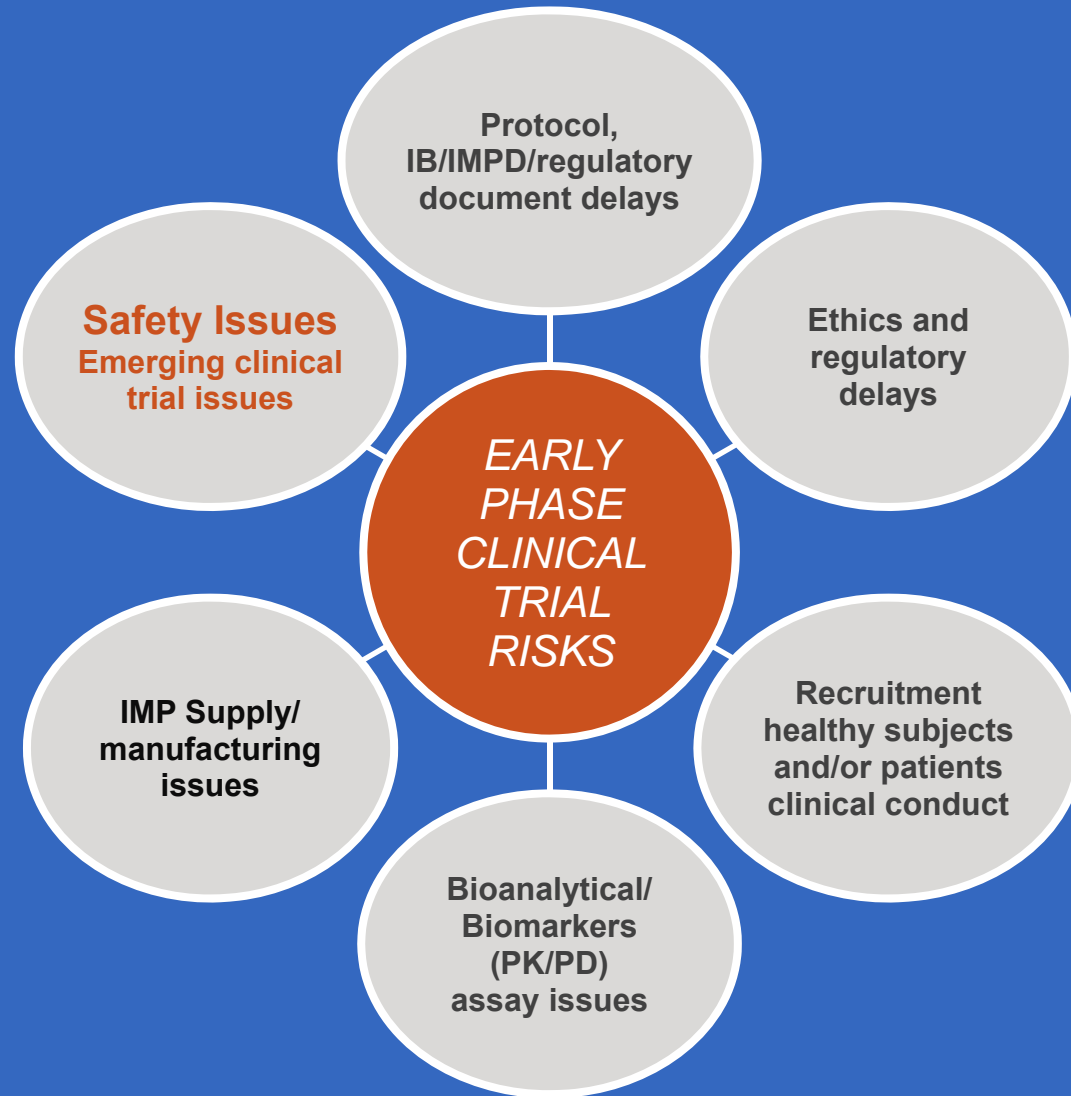
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	21 July 2016
End of consultation (deadline for comments)	30 September 2016

Comments should be provided using this [template](#). The completed comments form should be sent to FIH-rev@ema.europa.eu

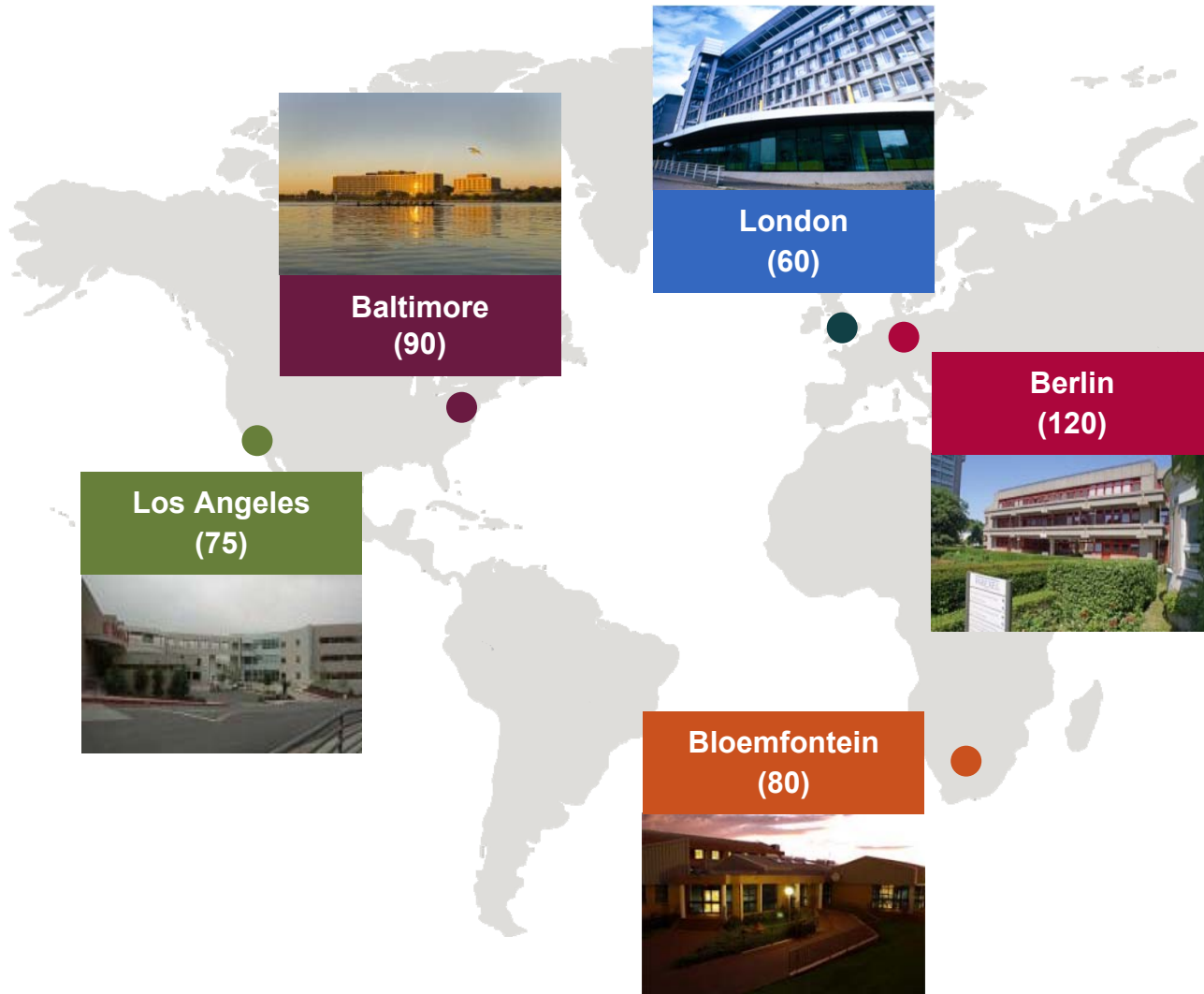
Keywords	First-in-human, early phase, clinical trials, risk mitigation, integrated protocols, multiple ascending dose.
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- EMA and similar Japanese PMDA guidelines on requirements for FIH trials – Risk assessment
- Update to the 2007 document proposed by the EMA for 2017

KEY RISKS IN A CLINICAL PHARMACOLOGY UNIT CONDUCTED STUDIES



PAREXEL GLOBAL EARLY PHASE UNITS



Five Early Phase units, 420+ beds hospital based

- 1,000+ Early Phase employees and includes 50 medical staff
- Conducts > 400 studies/year; >40 FIH studies; >20% biologicals

PAREXEL EARLY PHASE UNITS

- Conduct the **full range of Clinical Pharmacology studies**
- All units based in a **major hospital with emergency and intensive care procedures** except in Bloemfontein, South Africa
- Experienced and well trained medical and clinical operations staff
- World class facilities and equipment for complex clinical studies
- First in Human (FIH) healthy subject studies conducted in hospital based units ONLY
- **Safety Risk Identification and Mitigation processes** in place including:
 - Global FIH process for ALL PAREXEL studies overseen by Early Phase Global Medical Sciences
 - Green Light sign off process by the study Principal Investigator to insure all documents, procedures and processes adhered to including sponsors and PAREXEL insurance in place
 - Protocol defines risks and mitigation strategies

PRACTICAL SAFETY ASPECTS – FIH OR COMPLEX STUDIES

STUDY DESIGN, STAFFING, FACILITY

- Comprehensive knowledge of **preclinical information** about the compound is essential (PK, PD, toxicology, metabolism etc.)
- Careful **starting dose selection** based on **Guidelines – NOAEL/MABEL/PAD**
- Dosing of **sentinel subjects** (1 active, 1 placebo)
- Dosing interval on following days should be based on PK and PD profile
- **Maximum number of dosed subjects** should be limited to 6-8 in order to have sufficient treatment capacities in case of unexpected SAEs
- Study conducted in **hospital based facility** with adequate **well trained staff**
- Availability of general and study specific **emergency procedures**
- **Standardized safety risk identification and mitigation assessment** should be performed by qualified person -experienced medical Clinical Pharmacologist

PAREXEL SAFETY RISK OVERSIGHT

EMA/CHMP/SWP/28367/07

Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medical products



**PAREXEL Global SOP
2007**

SOP- Identification and mitigation of risk in clinical trials for ALL FIH studies (healthy subjects and patients) and other complex studies including biosimilars

RISK MITIGATION



A structured process developed by PAREXEL Global Early Phase Medical Sciences

- **3 Step approach:**

STEP 1: Prepared by Senior Clinical Pharmacologist (all FIH studies)

***STEP 2:** Prepared by Principal Investigator

***STEP 3:** Prepared by Principal Investigator

- **Overall opinion:**

High Risk – Not Known – Not High Risk

- * if conducted in PAREXEL unit

STEP 1 CARD: RISK IDENTIFICATION

Risk Identification and Mitigation (Preliminary, IMPD was NOT provided!)

Topic	Question	YES	NK	NO
IMP: Mode of Action	Biological or highly species-specific agent?			✓
	New therapeutic class?			✓
	Target is immune system or cellular-associated?			✓
	Agonist of a self-amplifying cascade system?			✓
	Multifunctional molecule (<u>pleiotropic</u>)?			✓
	New molecular structure with enhanced receptor interaction?			✓
	Evidence for non-linear pharmacokinetics?			✓
Nature of Target	Target not well established/known?			✓
	Specific human target?			✓
	Is the starting dose/dose range not justifiable?			✓
	High potential for autoimmunity?			✓
Relevance of Animal Model	Animal model not entirely adequate?			✓
	Specific human target not present in animal model?			✓
	Evidence of high species (human) specificity?			✓
	<i>In vitro</i> response different from <i>in vivo</i> response in animals?			✓

Note: If any of the above answers is YES, assume higher risk of IMP. In this case, additional precautions in the following categories may be necessary!

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STEP 1 CARD: RISK MITIGATION

Topic	Question	YES	NK	NO
Safety	Major safety concerns? If YES state which organ system:			✓
	Minor safety concerns? If YES state which organ system:			✓
	Are safety measures in adequately addressed? If YES state which organ system: If YES suggest safety measurement:			✓
	First Dosing Day: more than one subject planned?			✓
	Is observation period between dosing too short? If YES suggest observation suitable period:			✓
	No definition of stopping criteria?			✓
	No confirmatory safety pharmacodynamic parameter planned? If YES suggest a suitable parameter:			✓
Study Population	Enrollment of female subjects of childbearing potential planned?			✓
	Enrollment of minors planned?			✓
	Special Population? If YES: state what population:			✓
	Anticipated recruitment difficulties?			✓

STEP 1 CARD: RISK MITIGATION

Topic	Question	YES	NK	NO
	Are inclusion criteria in appropriate If YES state which: Number X If YES suggest change:			✓
	Are exclusion criteria in appropriate If YES state which: Number X If YES suggest change:			✓
	Number of subjects per cohort to small?			✓
	Number of subjects on placebo per cohort to small?			✓
Summary	High Risk Compound?			✓

Additional items:

- Comments and information about the compound (e.g. summary of the mode of action, preclinical data etc.) for the Feasibility Team and the PIs
- **Questions and Comments to the Sponsor:**
 - Requests for additional information, e.g. the IB
 - Suggestions for further safety assessments, design aspects etc. (methods, biomarker)

PAREXEL FIH RISK ASSESSMENTS: 2007 – 2015

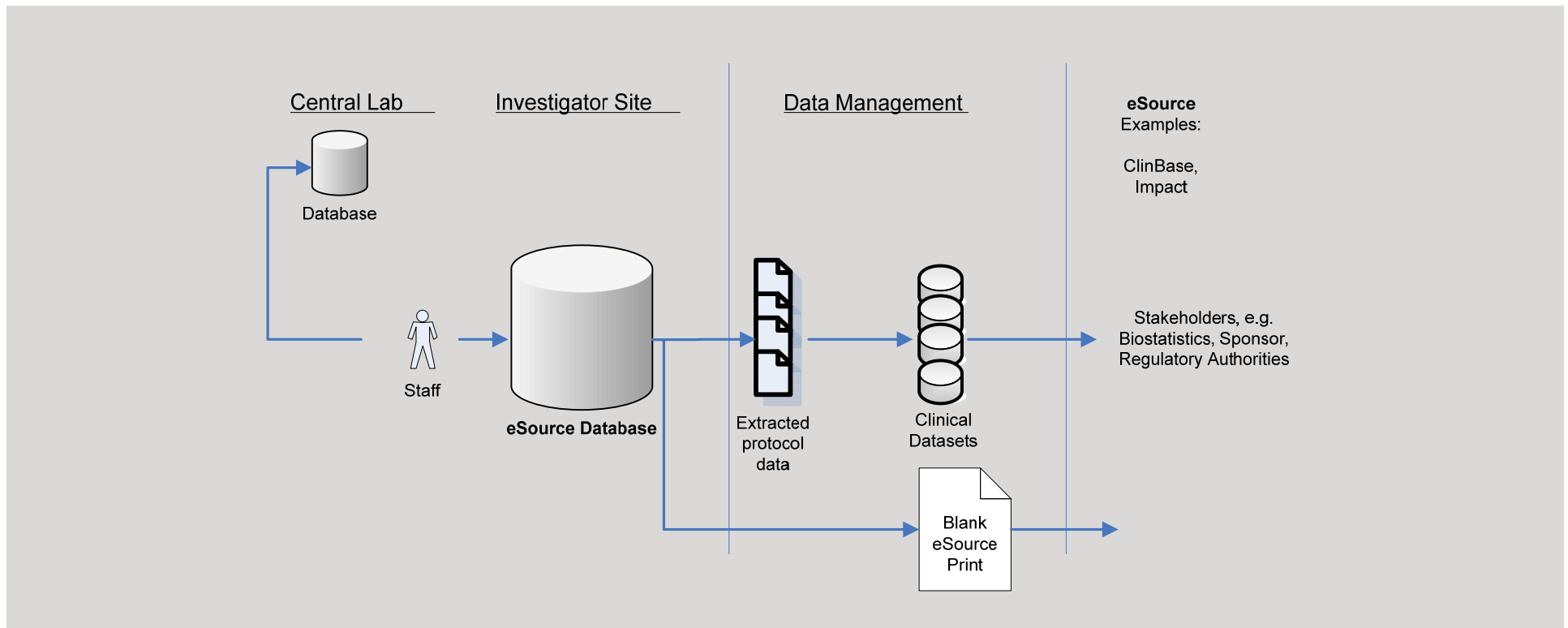
9 YEAR REVIEW

	Biologicals	Non Biologicals	Total
High Risk	15 (9%)	6 (2%)	21* (5%)
Non- High Risk	159	259	418
Not Known	25	26	51
Total	199	291	490

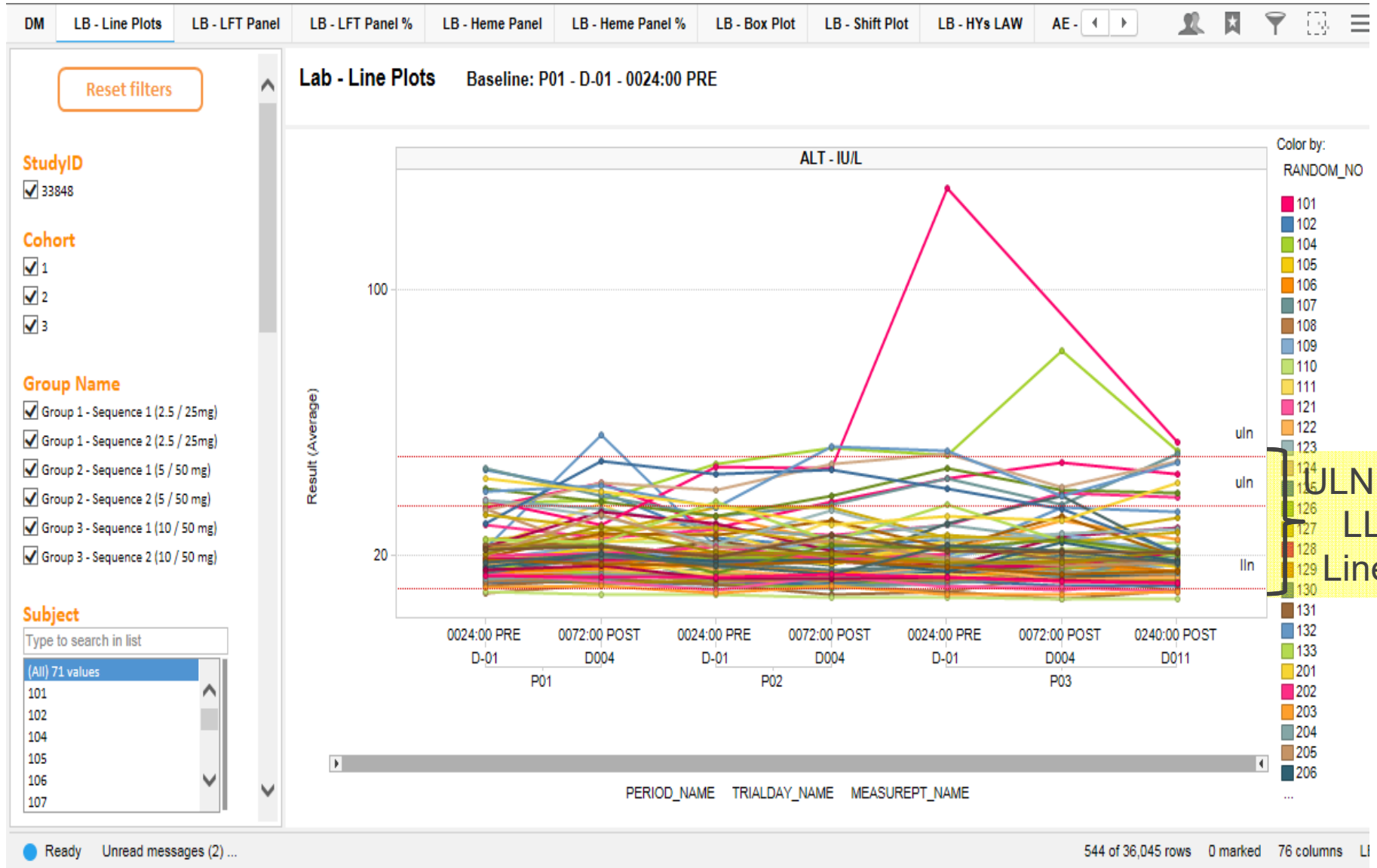
* Escalated to CMO and decision re study conduct by PAREXEL; >50% studies declined

PAREXEL ELECTRONIC SOURCE DATA CAPTURE ESSENTIAL TO MONITOR SAFETY & POTENTIAL RISKS

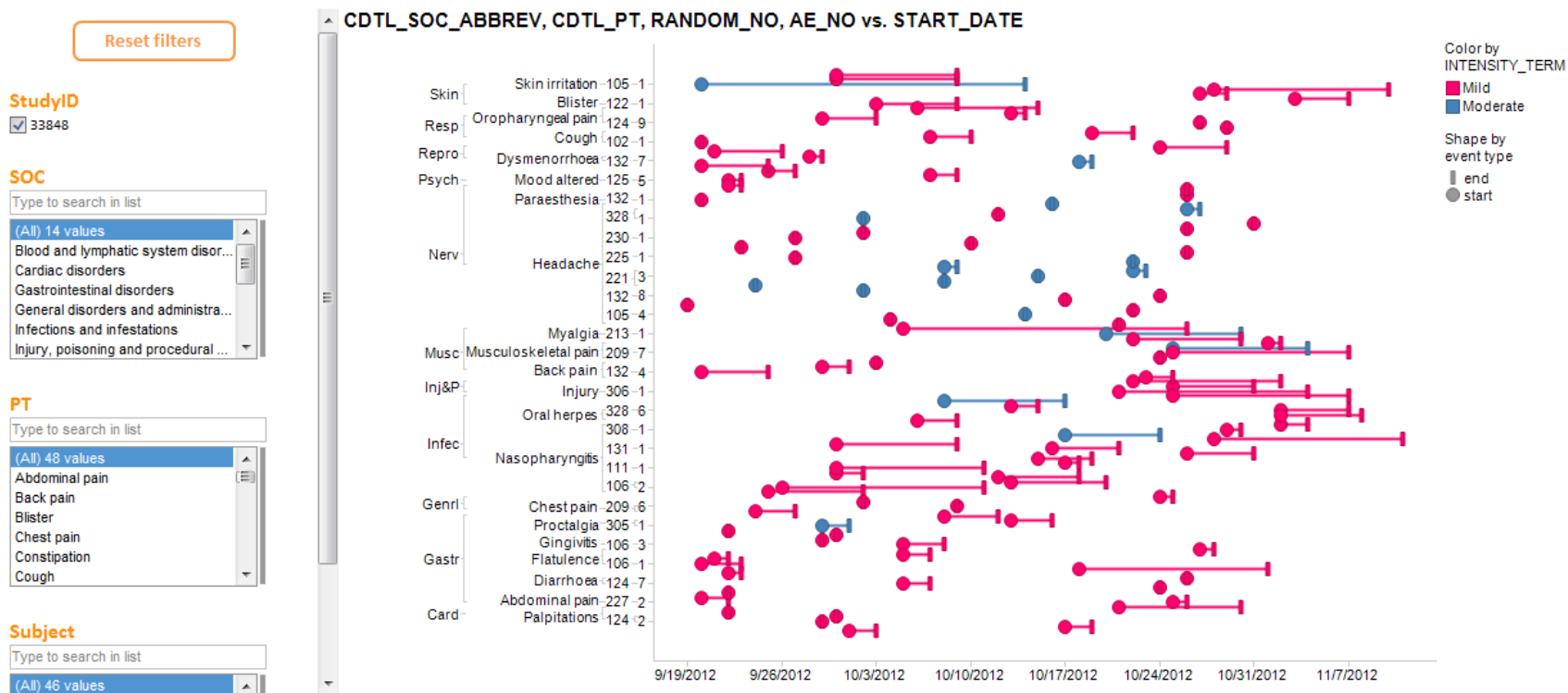
- eSource Data Flow - **ClinBase**
- eSource data and “eSource CRF” are used
- An eSource is the electronic backend of data – rapid data access, safety reviews, data analysis:
Spotfire and internal and external review (secure web portal)
- eSource database guarantees 21 CFR part 11 system compliance



LAB - LINE PLOTS

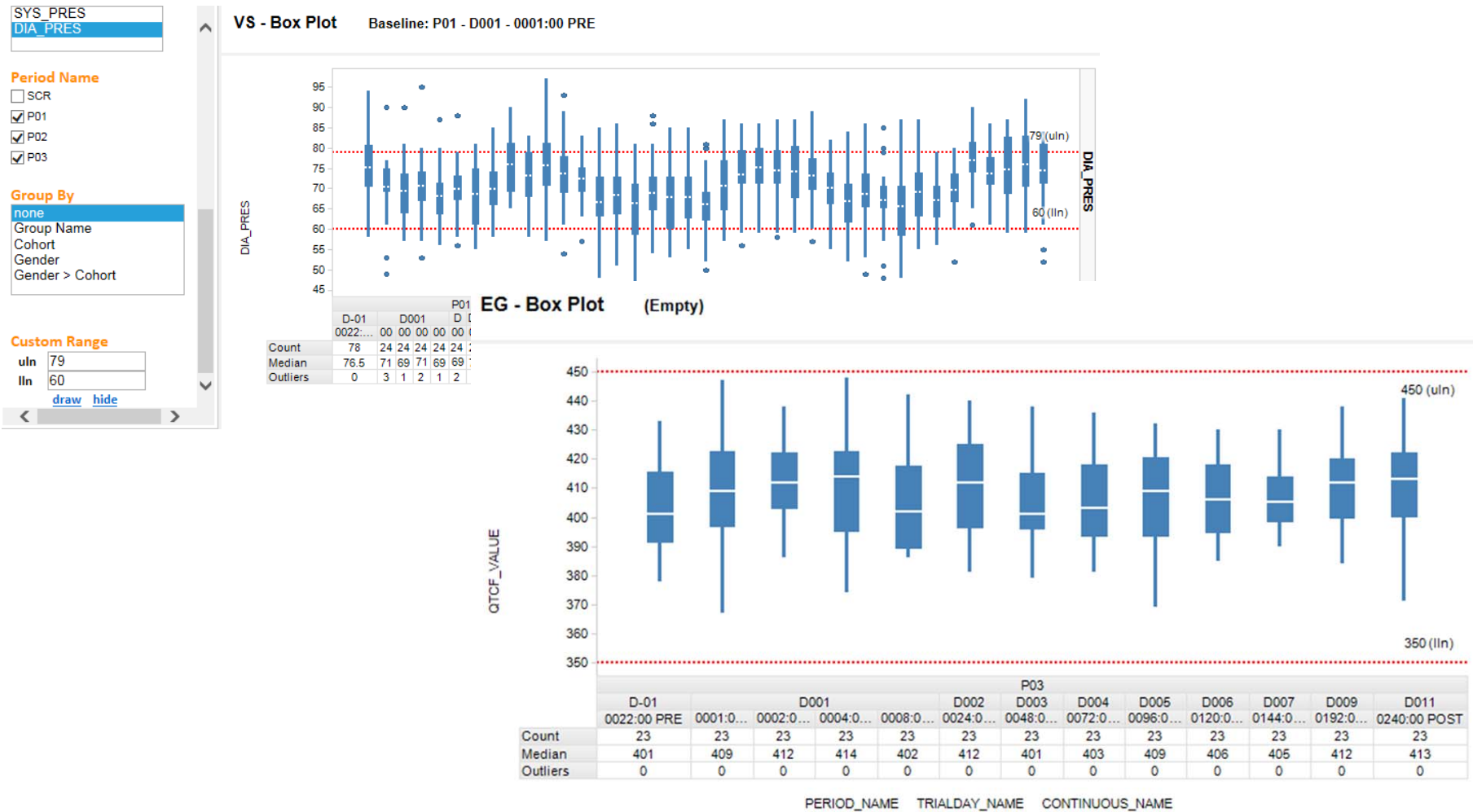


AE - TIMELINE



The AE timelines tab displays all AEs by SOC and PT and stacks them according to start and stop dates and severity. The user can see what AEs have occurred during the course of treatment during study and how they overlap. This display helps tell a story about a particular subject or subjects

VS AND ECG - BOX PLOTS



- Box plots for VS and ECG data have similar functionality as for Labs
- Note the ability to add a **custom range** to VS and ECG box plots

BIOTRIALS/BIAL INCIDENT – BIA 10-2474 SAD/MAD STUDY – DEATH OF HEALTHY STUDY SUBJECT

- **Single doses** of BIA 10-2474 administered with **no key issues or signals** up to 100mg
- **Multiple doses** (LAST and highest MAD dose 50 mg) started Wednesday, January 7, 2016 with 8 male subjects (6 active, 2 placebo). Subjects confined to the clinic.
- **Dosing Day 5 (Sunday) first subject experienced SAE**
 - Hospitalized with „stroke“?, resuscitated?, reported, brain dead“ and **died a week later**
- Further **dosing was not stopped** (next Dosing Day 6) for remaining subjects. The other subjects received one additional dose.
- Subject 2-5 hospitalized with CNS symptoms and signs
- “with three were suffering a ‘handicap that could be irreversible’ and another also had neurological problems.”
- All released from hospital, unknown condition ; one hospitalized, but NO symptoms;
- Both placebo subjects – no safety findings

Source: TSSC Report

BIA 10-2474 – A SAD/MAD STUDY WITH DISASTROUS CONSEQUENCES

- **THE IMP** - BIA 10-2474 is an inhibitor of fatty acid amide hydrolase (FAAH), increases brain concentration of anandamide, an endogenous ligand for the brain CB1 cannabinoid receptor. BIAL claimed that the inhibitor is reversible, but later data indicate that it is irreversible or very slowly reversible.
- BIA 10-2474 developed to treat pain and CNS disease
- FAAH metabolizes also
 - oleamide, a sleep-inducing lipid originally isolated from the cerebrospinal fluid of sleep deprived cats, and
 - N-acetyltaurines, which are agonists of the transient receptor potential (TRP) family of calcium channels
 - Both not discussed in the protocol or IB
- BIA 10-2474 has low selectivity for FAAH versus other targets including CNS acetylcholinesterases. Little information provided in the submission re off-target enzyme interactions.

Source: Temporary Specialist Scientific Committee (TSSC) Report April 2016

INDEPENDENT BODY TSSC FINDINGS/KEY RECOMMENDATIONS

Bial/Biotrials Issues

- Incomplete preclinical package
- Regulatory review limited
- Clinical study
 - Limited CNS monitoring
 - No use of previous data to support dose escalation steps and levels
 - Stopping rules not in place re SAEs
 - Inadequate safety monitoring during MAD
 - Study conducted in non hospital based facility

TSSC Recommendations

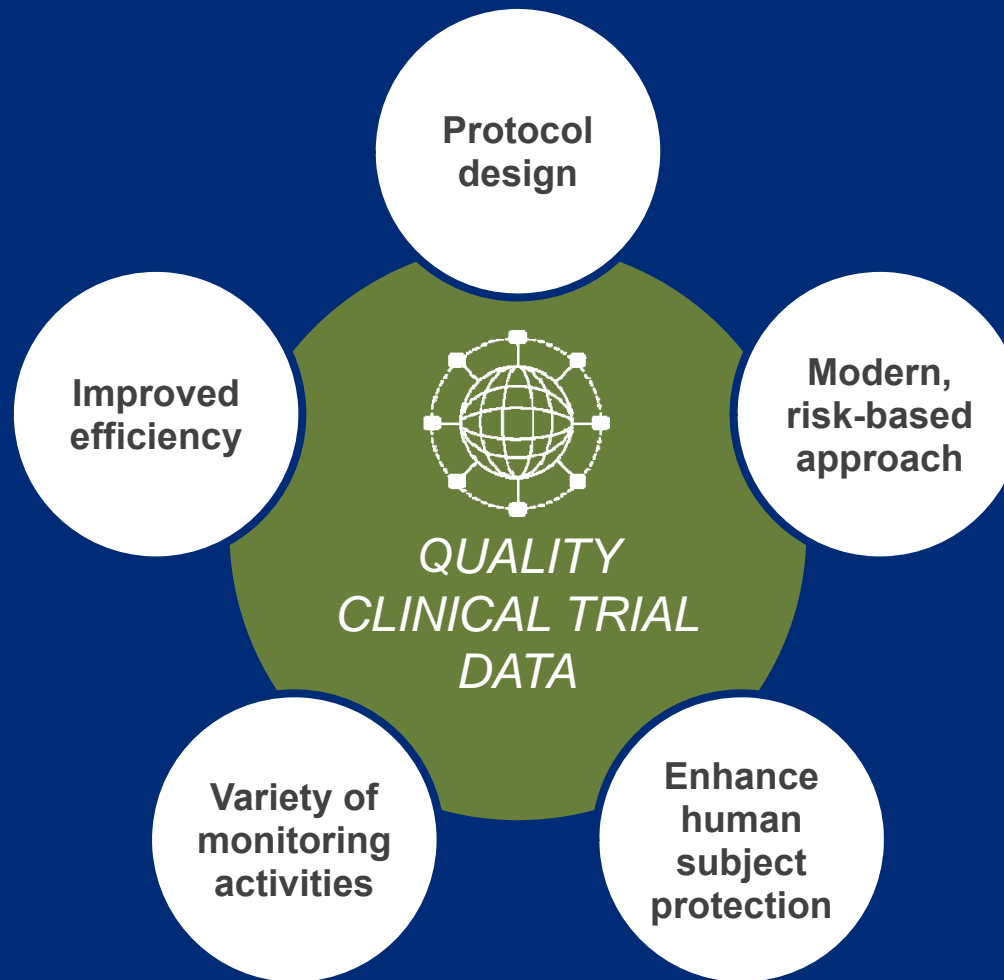
- Improved preclinical studies to establish a dose-effect curve predictive of real-life, future therapeutic efficacy.
- CNS assessments in clinical study
- Ongoing monitoring of safety, PK, PD data during the study with changes to protocol as required
- Dose adjustment to consider variability of exposure considering worst case scenario
- Global sharing of trial information

SAFETY RISKS IN EARLY CLINICAL STUDIES – SUMMARY



- Optimal **safety risk mitigation strategies** should be in place for all studies conducted by Clinical Pharmacology units
- Adequate **processes to cover clinical staff training, adverse event handling, safety risk assessment, emergency procedures, medical staff accreditation and drug preparation, handling and dosing**
- Pending updates to EMA Risk Mitigation Guidelines in 2017
- Future **new and more complex drugs and targets** will require ongoing review and updating of risk minimisation procedures by Pharmaceutical Companies and CROs

EARLY CLINICAL RISK ASSESSMENT – SUMMARY



Aim : Enhanced safety and improved data quality

THANK YOU