AHPPI MEETING

RISK MANAGEMENT IN A CRO PHASE I UNIT

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PAREXEL International

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AGENDA

- Introduction - Risk Management
- Regulatory Considerations
- Risk Management Early Phase versus Late Phase
- Safety Risk Identification and Mitigation in Early Phase
- Summary and Discussion

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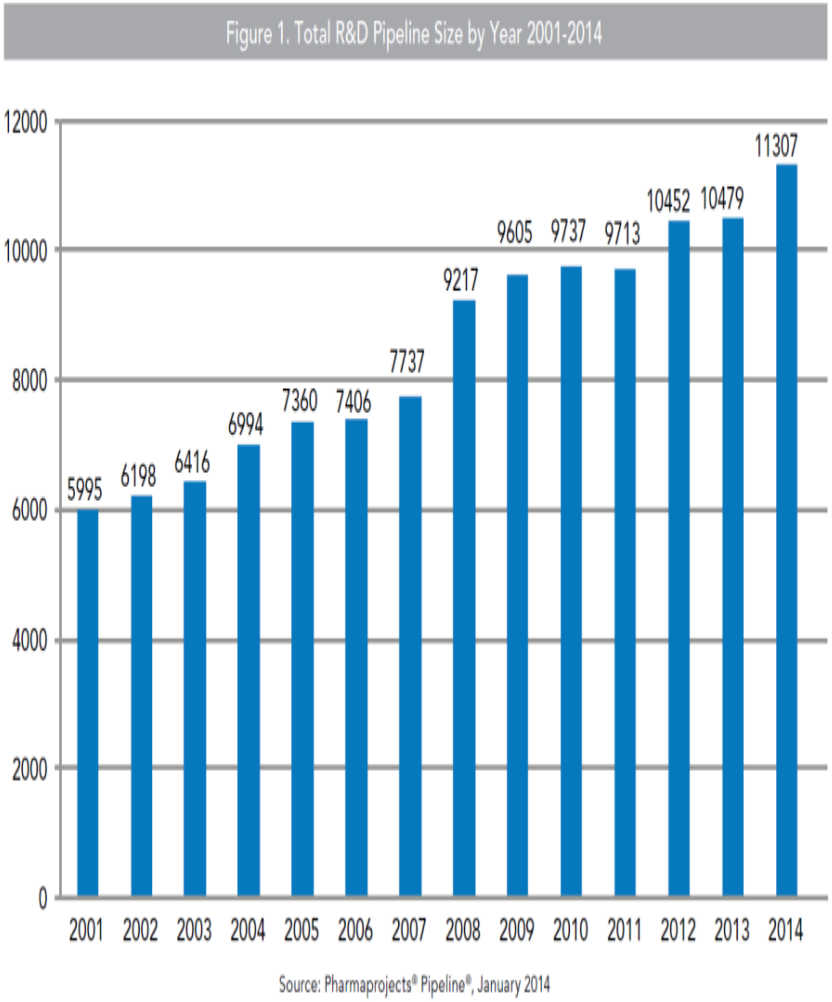
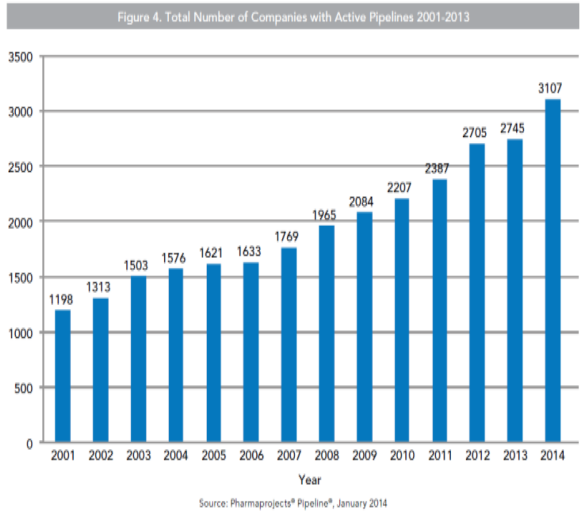
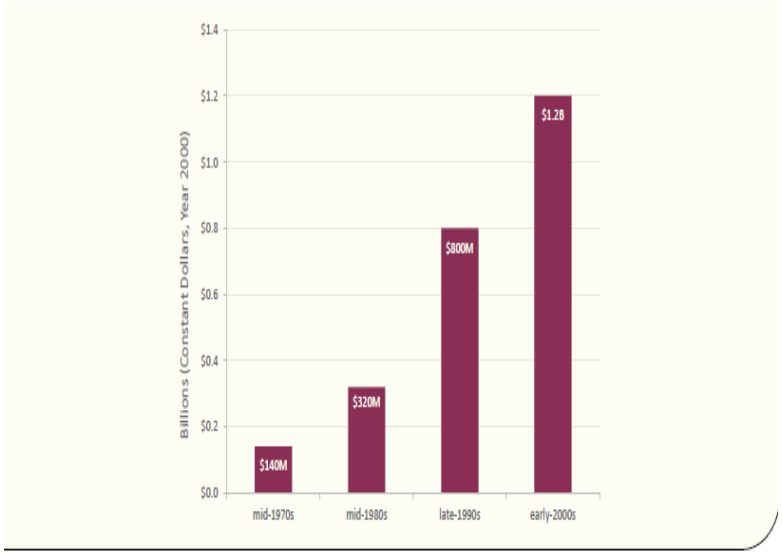
R&D PIPELINE GROWS – COSTS/NEW DRUG INCREASES



62% increase new drugs over last 15years





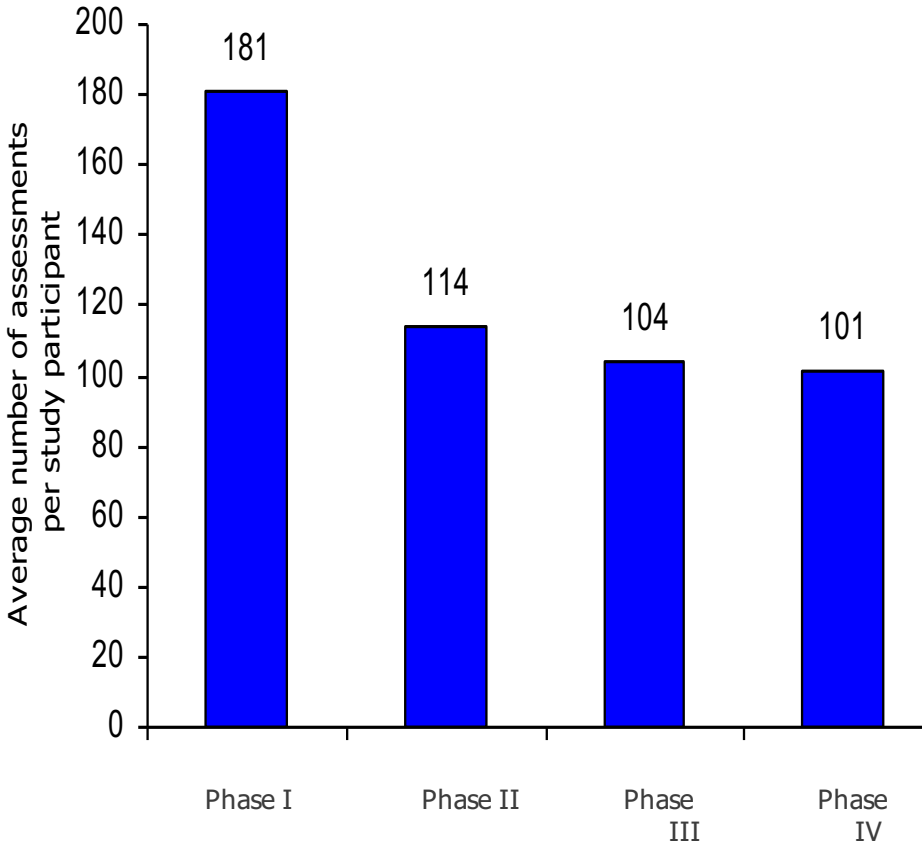
SOURCES: J.A. DiMasi, R.W. Hansen, and H.G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22(2): 151–185; J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 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.

From PHRMA 2013 Profile

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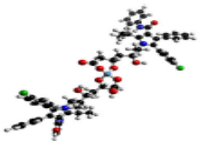
RISKS IN CLINICAL TRIALS - INTRODUCTION

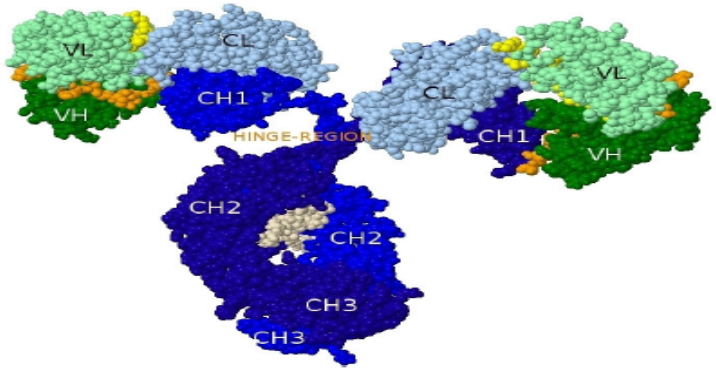
- Development of new drugs and devices in clinical trials associated with risks to
  1. patient **safety** and
  2. trial conduct to meet the required standards

  (GCP/GMP/GLP/others) - to provide high standard of **data integrity**
- 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; many new drug targets



atorvastatin
Molecular weight
= 558 Daltons
0 amino acids

Interferon-alpha
Molecular weight
= 19,625 Daltons
~165 amino acids

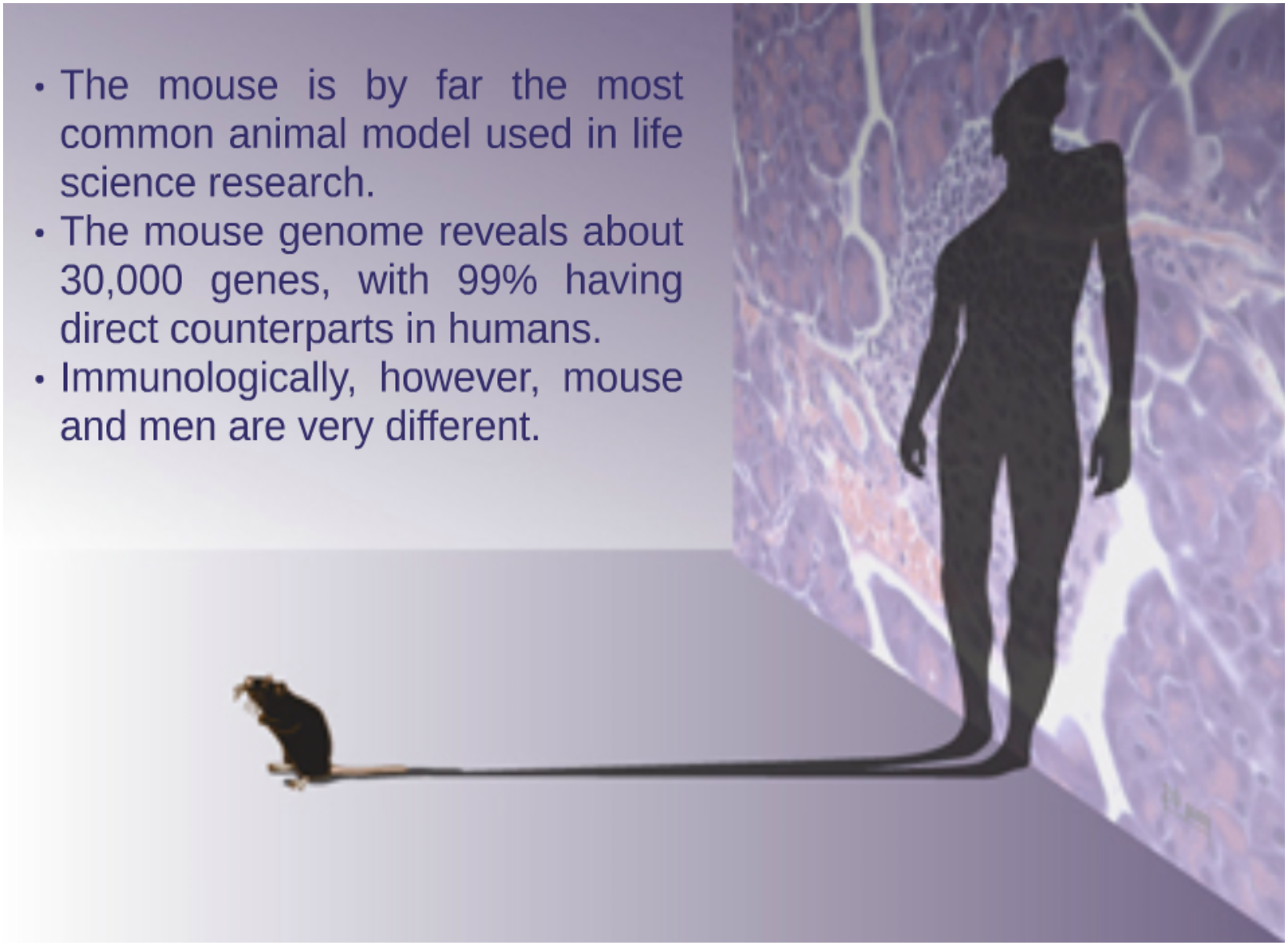


Antibody (IgG)
Molecular weight
= 150,000 Daltons
~1,300 amino acids

Source: http://www.path.cam.ac.uk/~mrc7/mikeimages.html

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.



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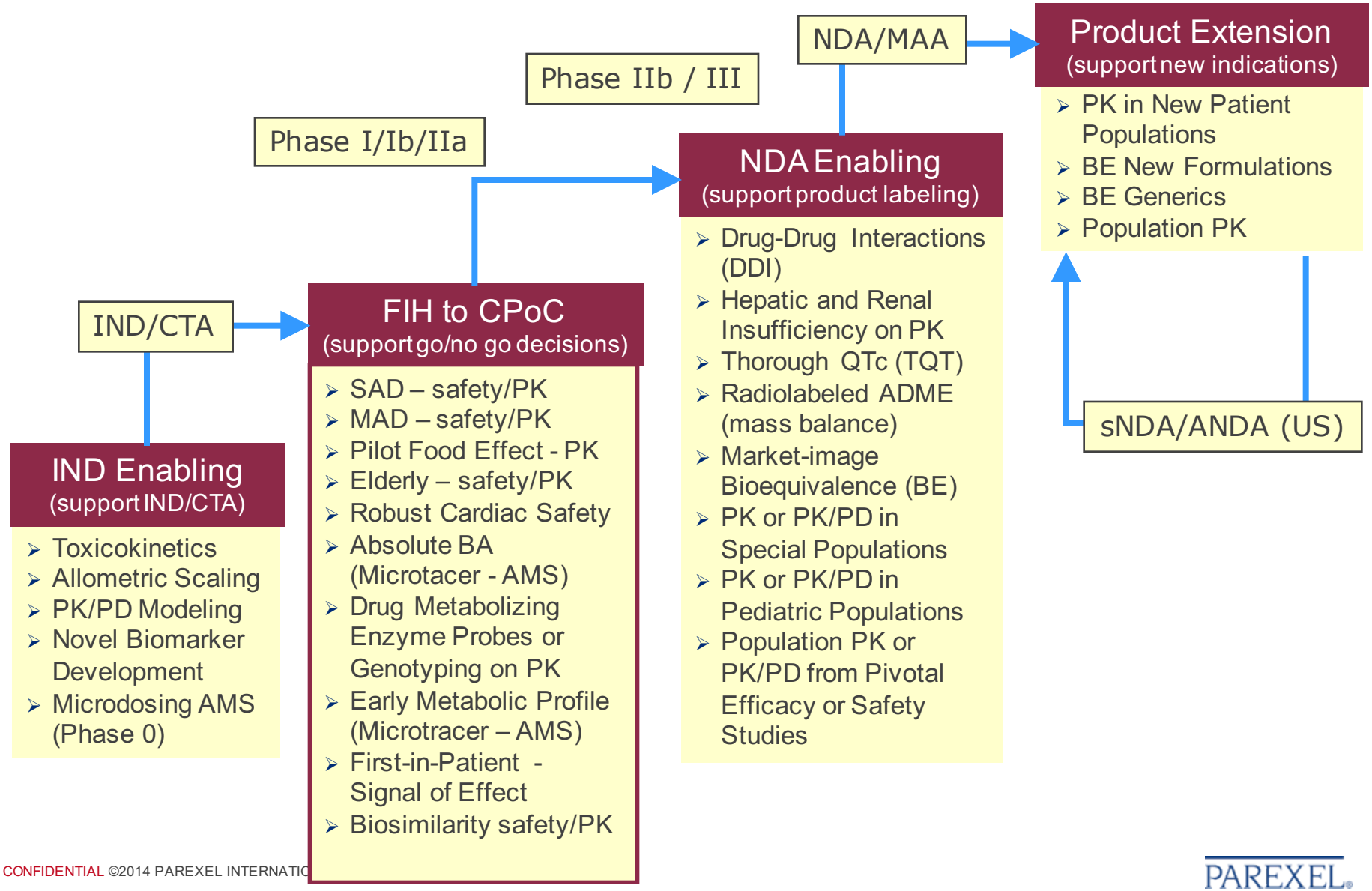
CLINICAL PHARMACOLOGY STUDIES IN DRUG DEVELOPMENT



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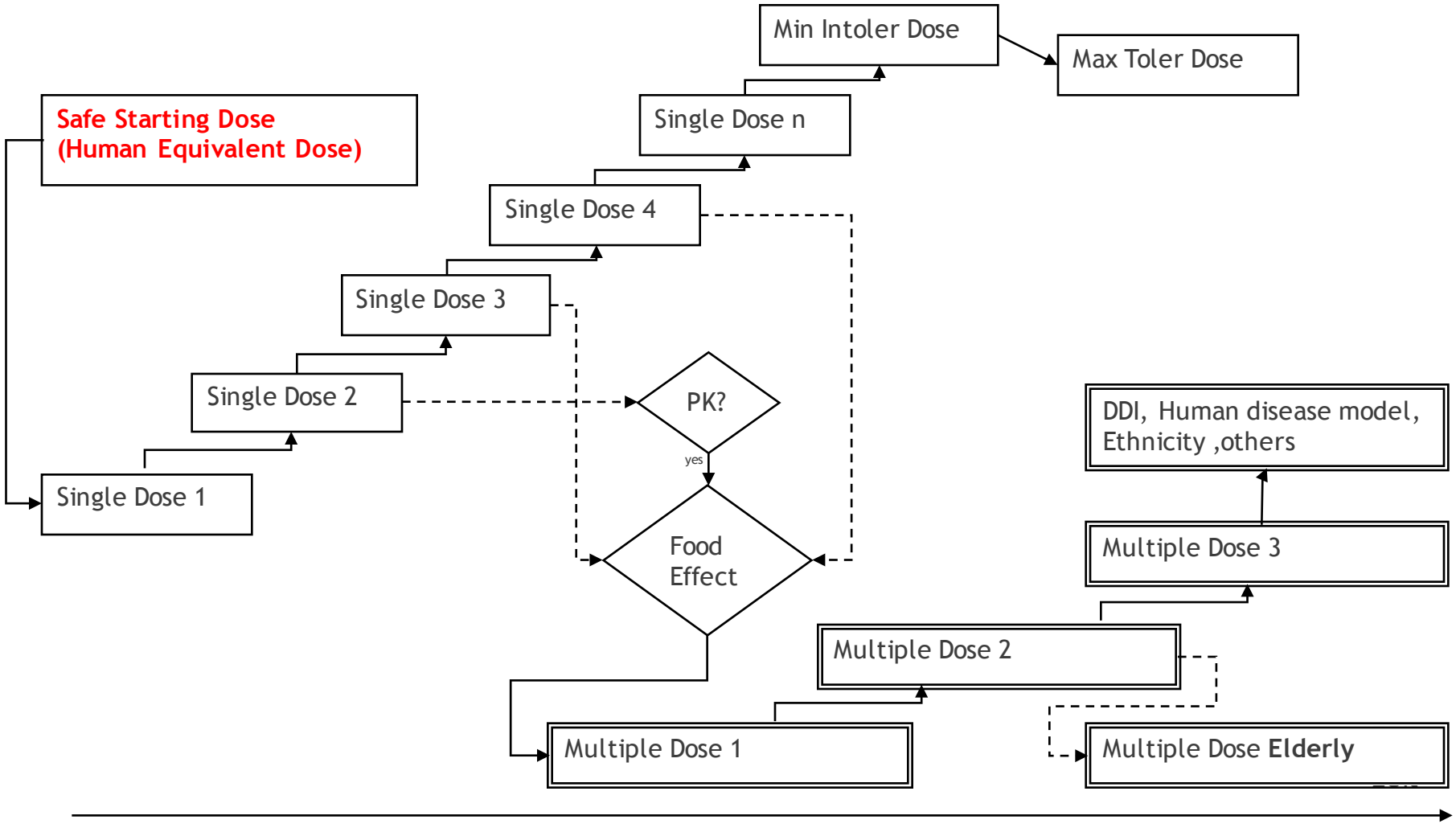
FIRST IN HUMAN COMBINED PROTOCOLS (FLEXIBLE DESIGN)



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RISK MANAGEMENT - REGULATORY ENVIRONMENT

European Medicines Agency

London, 22 March 2007
Doc. Ref.EMEA/CHMP/SWP/28367/2007 Corr.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON REQUIREMENTS FOR FIRST-IN-MAN CLINICAL TRIALS FOR POTENTIAL HIGH-RISK 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

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

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

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

18 November 2013
EMA/269011/2013
Compliance and Inspection

Reflection paper on risk based quality management in clinical trials

Draft Agreed by the Clinical Trial Facilitation Group (CTFG) for release for consultation	31 May 2011
Draft Adopted by the Good Clinical Practice (GCP) Inspectors Working Group for consultation	14 June 20111
Start of public consultation	5 August 2011
End of consultation (deadline for comments)	15 February 2012
Agreed by the Clinical Trial Facilitation Group (CTFG) for publication	13 September 2013
Adopted by GCP Inspectors Working Group	12 September 2013

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 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

ICH harmonisation for better health

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

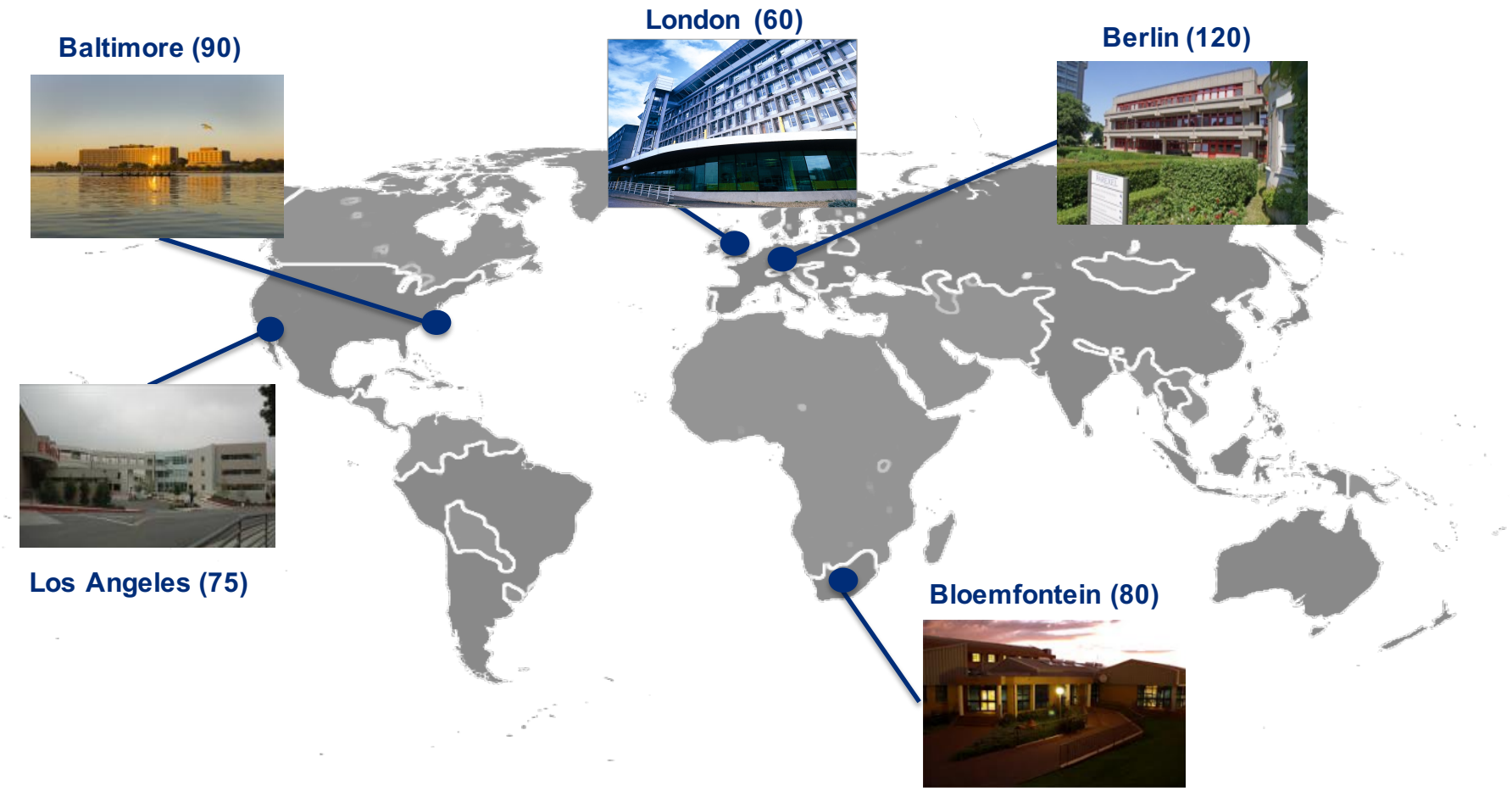
Statement of the Perceived Problem

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 emphasizs 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.

GLOBAL UNITS: GEOGRAPHIC REACH & CAPACITY

5 Early Phase units, 420+ beds hospital based

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



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EARLY CLINICAL - Risk Identification and 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	DB soft lock, conversion	DB hard lock, data transfer	
Biostatistics				generate SAP		interim analysis, TFLs				Analysis, TFLs	
Phamacokinetics				SAP						PK calculation, PK analysis	provide PK section for CSR

EARLY CLINICAL - RISK IDENTIFICATION AND MITIGATION

- Review specific study activities - **identify key areas of potential risks**
- Insure **monitoring and mitigation procedures** in place
- Document above in **Project plan**
- Track studies using relevant **metrics**
- **Identify and Respond to risks** with appropriate corrective actions

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PROJECT RISK IDENTIFICATION AND MITIGATION

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 staggler 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	/ **13** **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		

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KEY RISKS IN CLINICAL PHARMACOLOGY UNIT CONDUCTED CLINICAL STUDIES – SINGLE SITE

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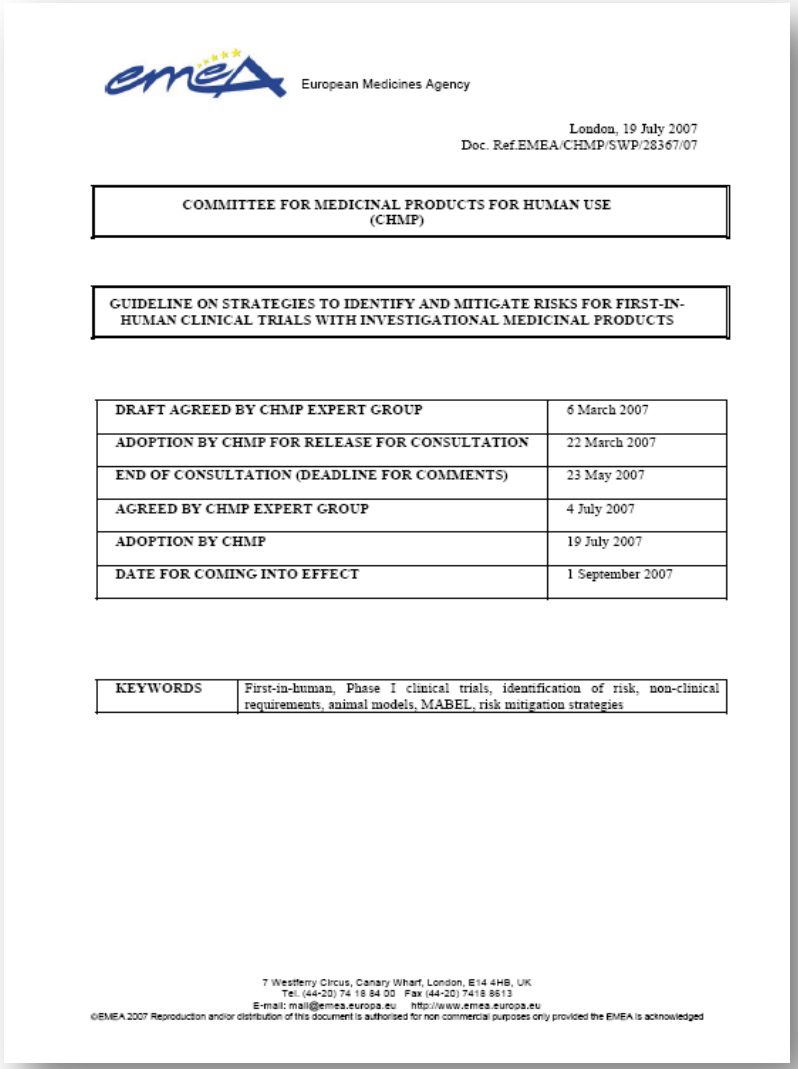
EMA GUIDELINE FIRST IN HUMAN STUDIES



European Medicines Agency

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

PAREXEL EARLY PHASE – SAFETY RISK ASSESSMENT PROCESS

- **SOP-EP.MED-WW-004-01 Identification and Mitigation of Risk in Clinical Trials**
- Applicable for
  - » All PAREXEL First-in-human (FiH) studies, both healthy volunteers and patients, including FiH studies of biosimilars
  - » All Non-FIH studies, where the associated risks appear unclear (on request of the PI)

- Overall objectives of the process:
  - Recommendation on the acceptance of the study
  - Assessment of the risk level of the IMP/study: High Risk – None High Risk, or Not Known
  - Review of the risk mitigation strategy

SAFETY RISK MITIGATION

A structured process developed by PAREXEL Early Phase Medical Affairs and Consulting

- **3 Step approach**
- Step 1 - prepared by senior Clinical Pharmacologist for all studies
- Step 2 - prepared by Principal investigator for in unit studies after study award
- Step 3 - prepared by Principal investigator

- **Overall opinion: High Risk – Not Known – Not High Risk**

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PAREXEL FIH RISK ASSESSMENTS: 2007 - 2015
9 YEAR REVIEW

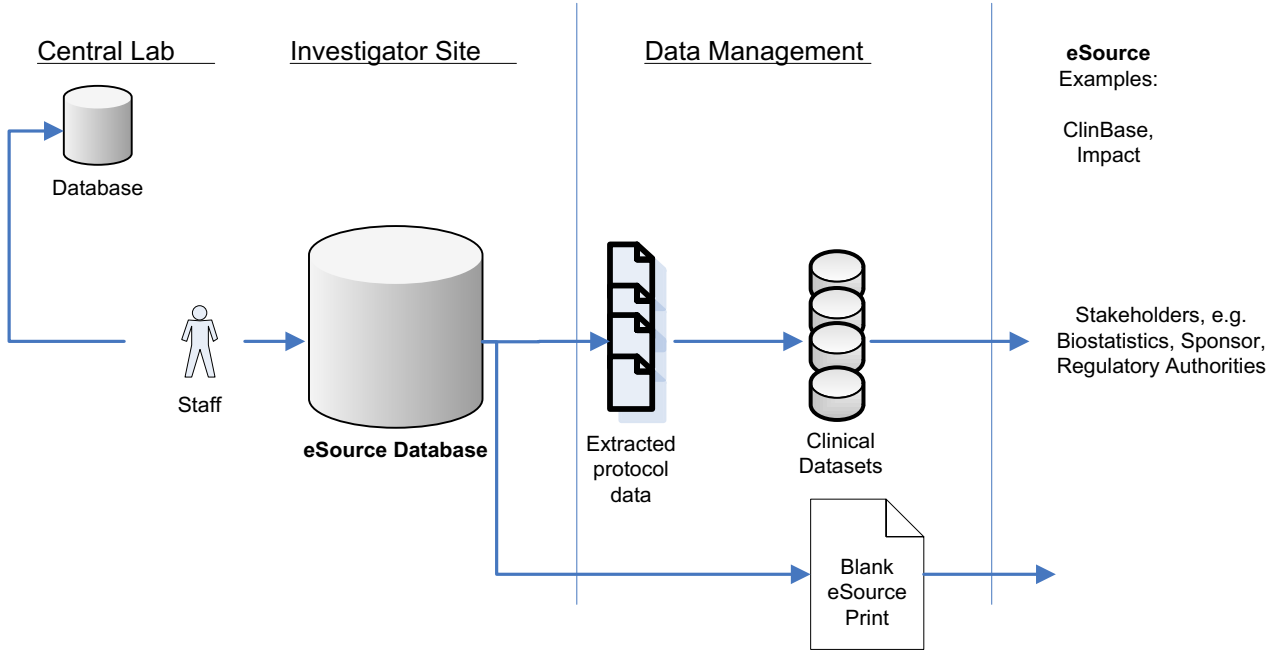
	Biologicals	Non Biologicals		Total
High Risk	15	6		21
Non- High Risk	159	259		418
Not Known	25	26		51
Total	199	291		490

PRACTICAL SAFETY ASPECTS OF FIH STUDY DESIGN AND STAFFING

- Comprehensive knowledge of preclinical information about the compound is essential (PK, PD, toxicology, metabolism etc.)
- Careful starting dose selection based on published Guidelines
- 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
- Sufficient and well trained staff
- Availability of study specific emergency procedures
- Standardized risk assessment to address all of the above should be performed by a qualified person (experienced Clinical Pharmacologist)

ELECTRONIC SOURCE DATA CAPTURE – Essential to Monitor Risks

- eSource Data Flow



- eSource data and „eSource CRF“ are used
- An eSource is the electronic backend of data – rapid data access, safety reviews, data analysis (eg Spotfire), internal and external review (secure web portal)
- eSource database guarantees 21 CFR part 11 system compliance
- Examples of systems for pCRF: ClinBase, Impact

EARLY CLINICAL RISK ASSESSMENT SUMMARY

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THANK YOU

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