PharmacoVigilance SIG

21st October to 22nd October 2003

THE PRISM FORUM

Pharmacovigilance:

- What is it?
- Why should we care?
- How do we do it?
- The Pharmacovigilance Landscape
- A Pharmacovigilance Roadmap
- References

PhV SIG Delegates

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The Big Myth

It is not. It concerns every person in a company from the CEO downwards. If such a misconception exists in a company, it is crucial it is tackled head-on

- **Responsibility for Pharmacovigilance is confined only to those in the company's Pharmacovigilance department**
- **Those in Pharmacovigilance are anti-product and Pharmacovigilance is negative activity for a product's success**

PhV What is it?

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What is Pharmacovigilance?

- Pharmacovigilance is the name given to the process of detection, assessment and prevention of adverse drug reactions in humans.
- What is the difference between Risk Management & Pharmacovigilance?

Whatever it is – it has to be done in Europe!

"The marketing authorisation holder must ensure that it has an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary."

The Rules Governing Medicinal Products in the European Union,

Volume 9 - Pharmacovigilance

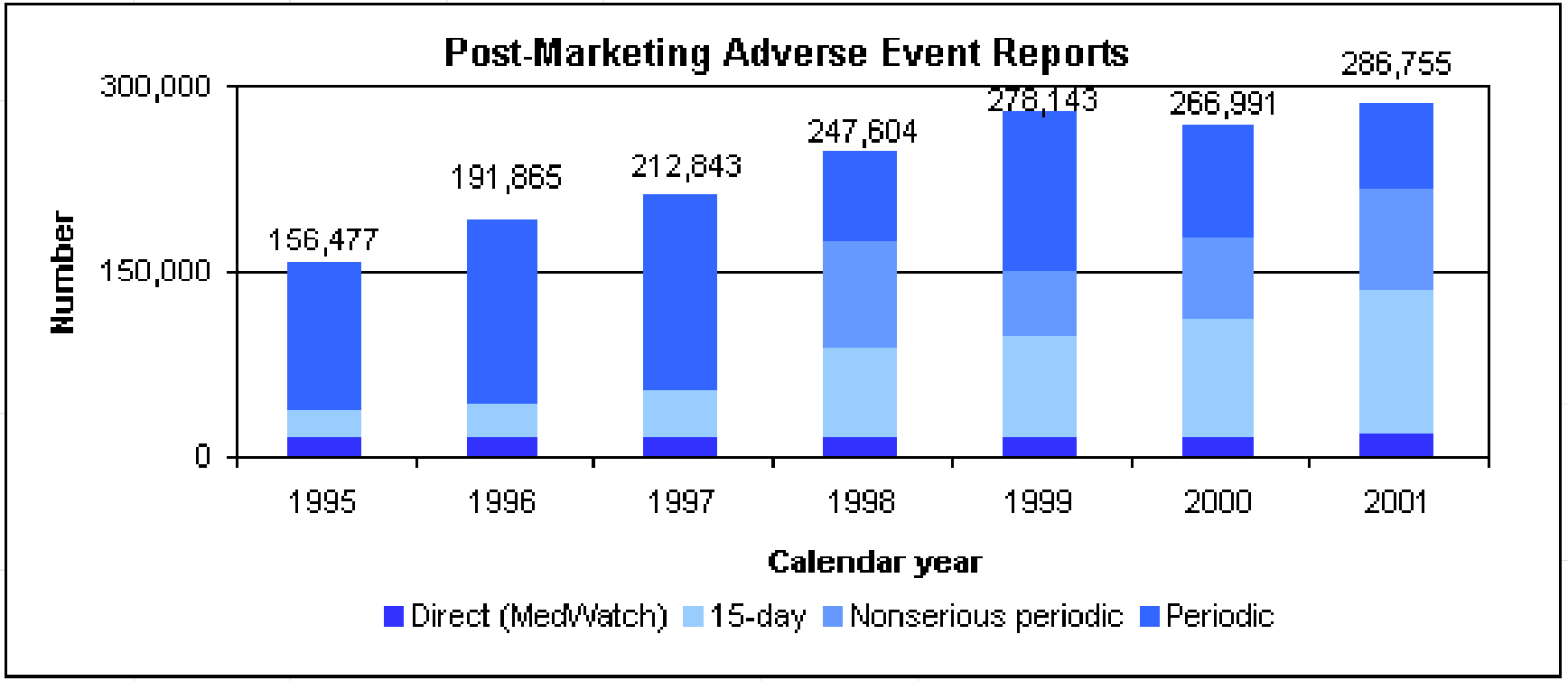
Medicinal Products for Human and Veterinary use, section 1

And in the USA!

- Drug sponsors are required to keep FDA informed regarding any developments that may affect the safety and effectiveness of their products, whether under clinical study or following FDA approval for marketing.
- The authority to require the necessary records and reports is contained in Sections 505(I), (j) and (k) of the Federal Food, Drug, and Cosmetic Act, and the regulations spelling out the kinds of records and reports required are in 21 CFR 310.303, 310.304, 310.305, 312.32, and 314.
- The broad intent of these regulations is to promote the kind of communication needed to ensure safe and effective drugs, and to enable the FDA to take whatever action is needed to accomplish this.
- The basic purpose is health protection through improved drugs.

FDA example – Safety Reports

From The FDA Web Site



* *http://www.fda.gov/cder/reports/rtn/2001/rtn2001-3.htm*

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Suspected Adverse Drug Reactions (SADR)

SADR			
SPONTANEOUS		CLINICAL*	
SERIOUS	UNEXPECTED	SERIOUS	UNEXPECTED
SERIOUS	EXPECTED	SERIOUS	EXPECTED
NON-SERIOUS	UNEXPECTED	NON-SERIOUS	UNEXPECTED
NON-SERIOUS	EXPECTED	NON-SERIOUS	EXPECTED

EXPEDITED REPORTING

PR/PSUR ONLY

* In the clinical space, events can be related and unrelated

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SADRs and their source

- Not Drug related
  - Disease related
  - Treatment-related (Hospitalization etc.)
  - Accidents
  - Suicide Attempts
- User or Physician “Errors”
  - Medication Error (Wrong Fulfillment)
  - Malprescription, Off-label Use
  - Intended Overdose (Non-compliance, Suicide Attempt)
  - Accidential Overdose (Non-compliance, Patient Education)

SADRs and their source

- Drug Titration Problems
  - Slow Metabolism
  - Multi-Drug Regimen (Each Enzyme Substrate is also an Inhibitor)
  - Nutritional Influences (Grapefruit Juice)
  - Gender/Racial Gap
- Drug/Drug Interactions
  - Rare, but usually serious
  - Can happen to established drugs
- Genetic Susceptibility
  - Rare, but usually serious
  - Class related (e.g Rhabdomyolysis for Statins)
  - Drug related (specific metabolites etc.)

PhV Why do we care?

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Public Citizen's Website

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

July 19, 2002

WARNING LETTER
CHI-21-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Miles C. White

[redacted]

Dear Mr. White:

(1) In violation of 21 CFR 314.80(c)(1)(i), your firm did not submit serious and unexpected adverse drug experience reports in several cases to FDA within 15 calendar days of initial receipt of the information. For example, our investigator observed that for the period from January 1, 2000 to October 31, 2001, there were eighteen 15-day alert reports submitted late to FDA. These violative reports include, but are not limited to:

Sec. 314.80 Postmarketing reporting of adverse drug experiences.

(c) Reporting requirements. The applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852. FDA may waive the requirement for the second copy in appropriate instances.

(1)(i) Postmarketing 15-day ``Alert reports``. The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

A Career Limiting Opportunity (CLO)

… and Because Pharmacovigilance is Important

- Pre-marketing phase: experience of a drug's safety and efficacy is limited to its use in clinical trials with limited patient numbers and treatment duration in conditions not necessarily reflecting use in the hospital or in general practice once marketed
- Information on rare but serious adverse drug reactions, chronic toxicity, use in special groups (e.g. pregnant women, children, elderly) and drug interactions may be incomplete or not available
- Certain adverse drug reactions may only be detected after a very large number of people have received the medicine

How do we do it?

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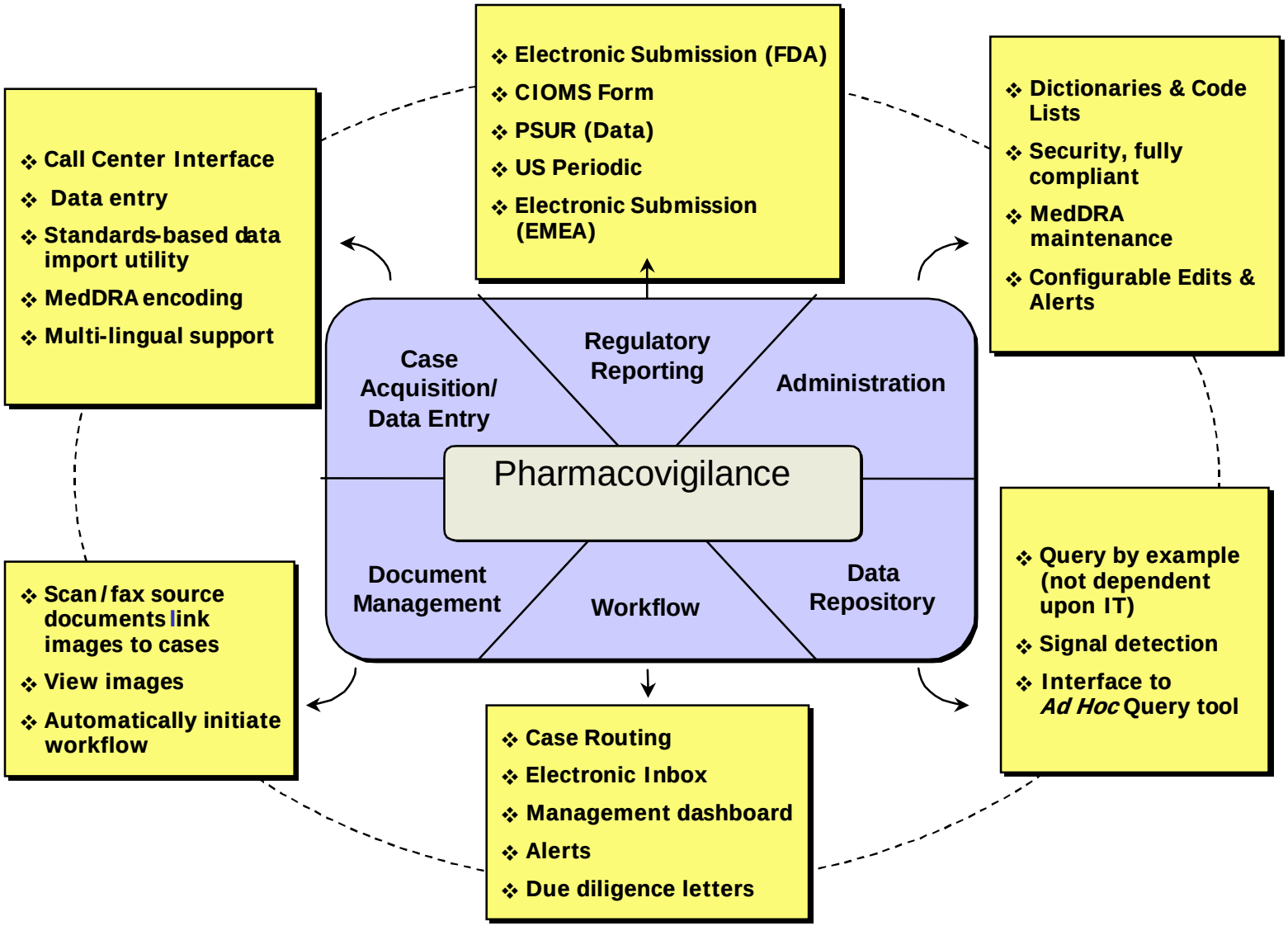
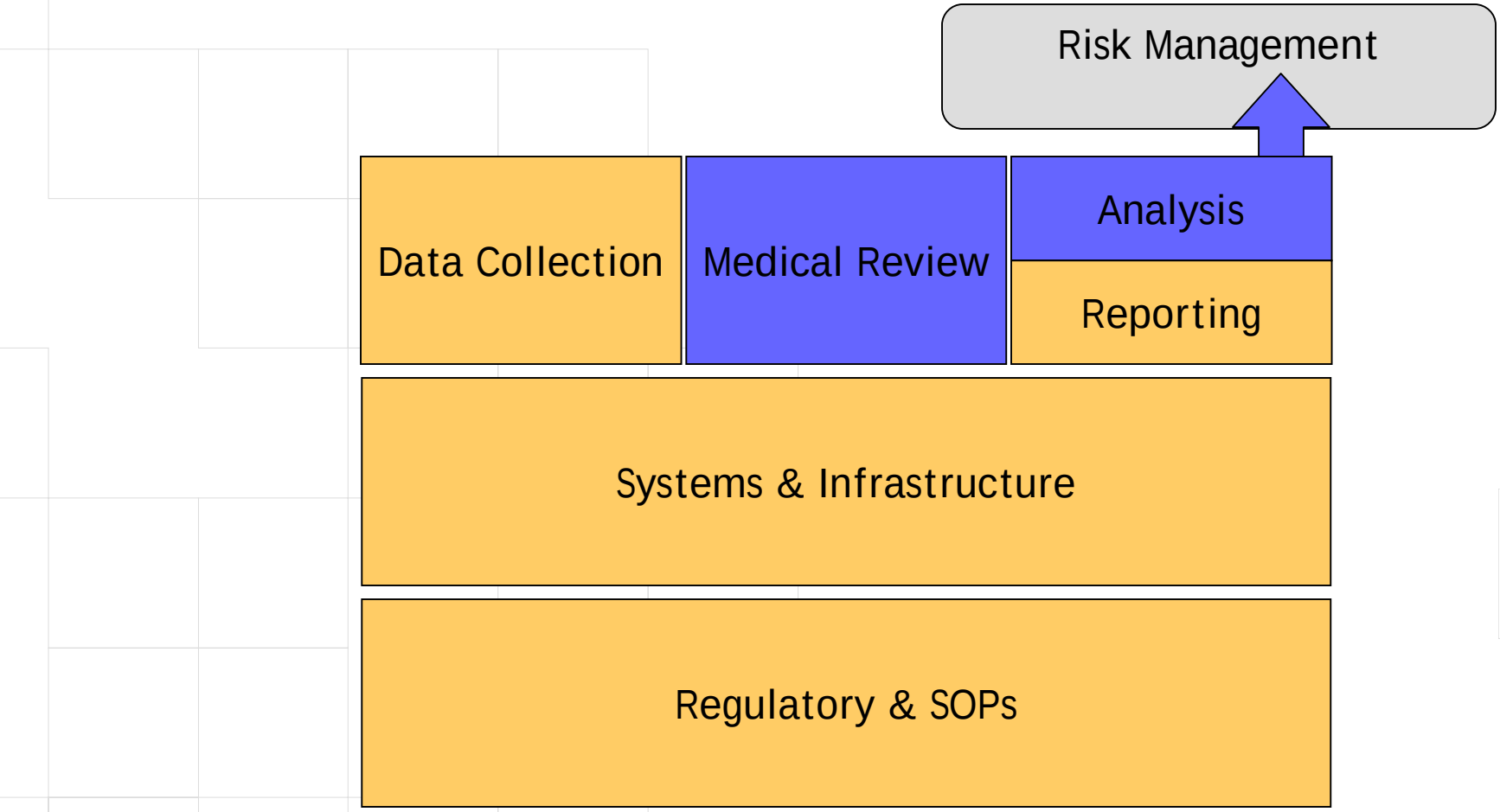
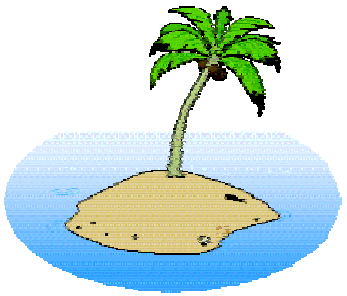
Pharmacovigilance Processes



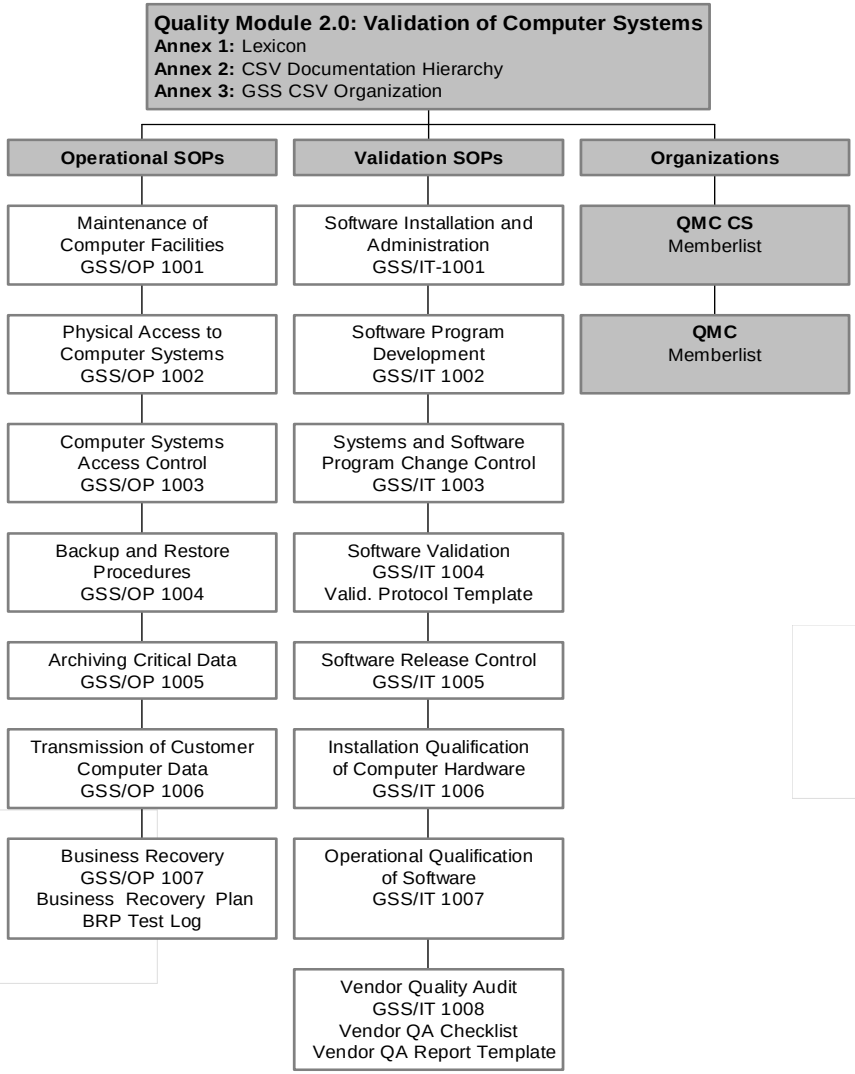
Pharmacovigilance for Management



No Pharmacovigilance Dept. is an Island



Business SOP tied to IT SOPs



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SOP Identification	SOP Title	Final Document Date	Version 1 Effective Date
PVOPS-101	[redacted] Staff Training	12-Sep-02	17-Sep-02
PVOPS-201	Tracking Adverse Event Reports	12-Sep-02	17-Sep-02
PVOPS-301	Processing Clinical Trial Adverse Event Reports	12-Sep-02	17-Sep-02
PVOPS-302	Processing Postmarketing Surveillance Adverse Event Reports	12-Sep-02	17-Sep-02
PVOPS-303	Processing Published Literature Adverse Event Reports	12-Sep-02	17-Sep-02
PVOPS-401	Regulatory Reports	12-Sep-02	17-Sep-02
PVOPS-501	[redacted] Standard Operating Procedures and Working Practices	12-Sep-02	17-Sep-02
PVOPS-502	Project Master Files	12-Sep-02	17-Sep-02
PVOPS-503	Verification and Review	12-Sep-02	17-Sep-02
PVOPS-504	Clinical Quality Assurance Audit	12-Sep-02	17-Sep-02
PVOPS-505	FDA Inspection	12-Sep-02	17-Sep-02
PVOPS-601	Project Management Activities	12-Sep-02	17-Sep-02

Craig's Spreadsheet

1_Final industry survey results (masked).xls

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The Pharmacovigilance “roadmap”

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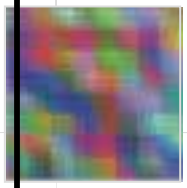
What are the PhV value propositions?

- Maximize risk management
  - Optimize possibility of Marketing Authorization
  - Minimize time to Marketing Authorization
- Minimize Compliance Risk
- Drive down the cost of PhV

	Current	Future (3-5 year)	Transition
Process	• Paper driven • Unclear ownership especially for Risk Management • PhV Processes are high quality but… –Redundant data entry across organisation – clinical SAEs, call centers and partners –Reconciliation overhead • E2B + paper reporting process • EMEA legal demands unrealistic • Spontaneous data is undervalued	• Electronic • Phase II, then submission but with on-going Pharmacovigilance • Pre-approval pure safety trials in clinical • One unique source for where the AEs are stored • E2B reporting process • Electronic patient records, the value of patient safety data will increase	• Emergence of recognized Signal Detection algorithms • Evolution of data exchange standards • Adoption of consistent risk management practices
Regulations	• Increasing global diversity of regulations –Multiplicity of regulations –Uncertainty about regulations –Which GFIs are worth commenting on (FDA have withdrawn 60 this year) • Case reporting focus • EMEA regulations weakly imposed upon nation states • Reactive to regulations	• Proactive partnership with regulators • Risk / benefit management focus • Labeling environment changes • Pharmacogenomics	"The Tome" PDUFA III Co-ordinated input from the industry

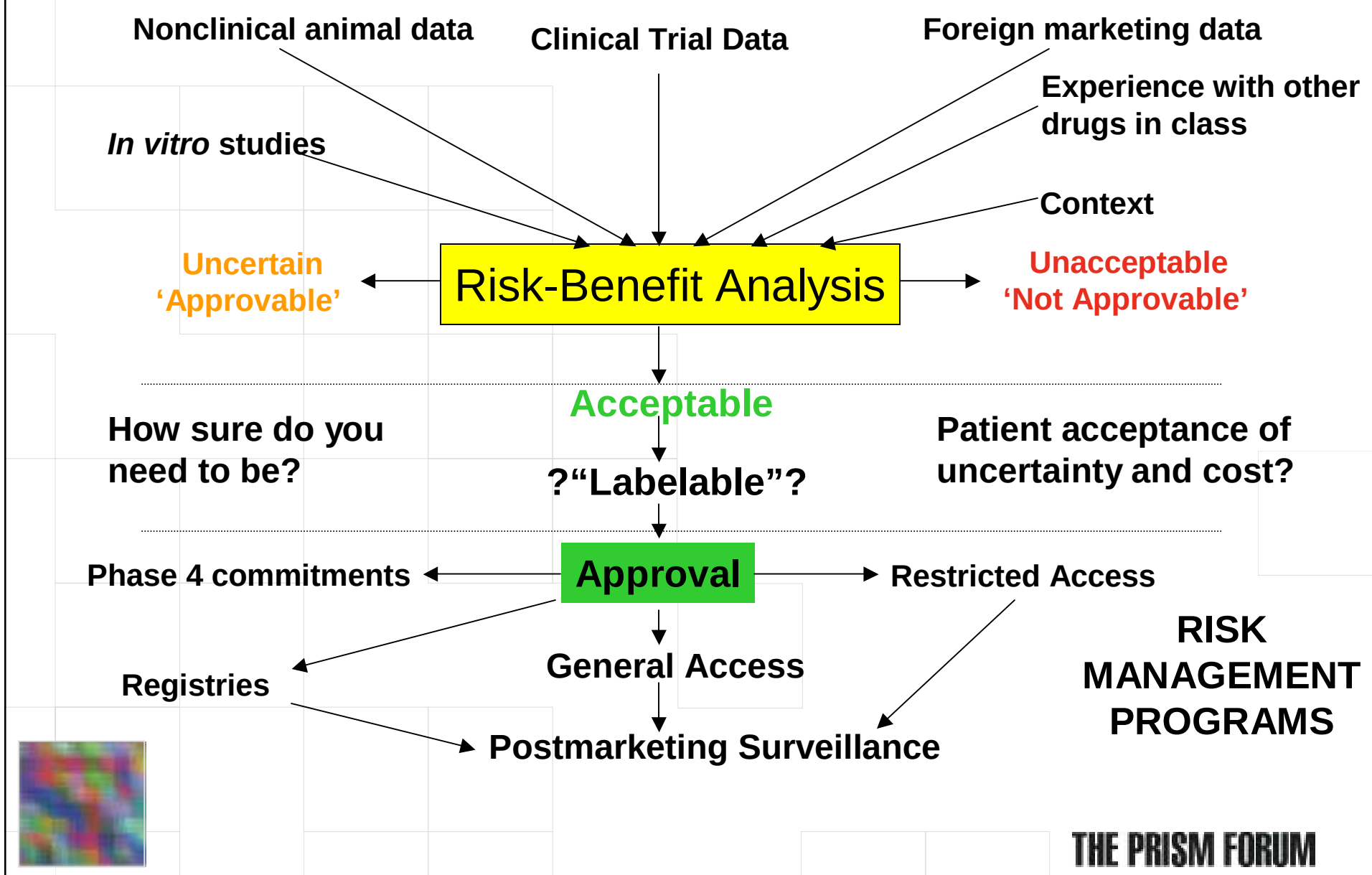
	Current	Future (3-5 year)	Transition
Technology	• Bespoke & O-T-S • Diverse standards e.g. – XML vs SGML – E2B extensions for various countries • Dysfunctional FoI database • Competing dictionaries	• Bespoke & O-T-S • Point-of-Discovery data input componentized, web-based user interface – hyperlinked • Standard electronic patient records and exchange of information • Wireless & handheld (e.g. Sales Reps – NO PATIENTS) • Functional, accurate real-time FoI Database • Sematics and Ontologies – especially for data mining • Greater availability to global epidemiological data base • Trusted Third Party Repository!	More standards required e.g. – HIPPA, – Expanded E2B, – CDISC, HL7m, NCDISC (FMIT) Better dictionaries across product lifecycle
People	• High medical skill, low computer skills • Cost of labour and geographic location • People burden on data collection • Physicians need LAN connection • Safety Physicians are in high demand • Misconception of PhV accountability	• High computer skills • Where they sit won't matter • People burden on data analysis • Physicians want to work from home • Safety Physicians still in high demand • Expectations are for better, faster, cheaper	Major training, development and education



an Innovative Solution?

Risk-Benefit Management: “Tolerable Uncertainty”

(P.Honig, DIA 2003)



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The Genomics Promise

- SNP (Single Nucleotide Polymorphism)
  - Human Genome 3 Gigabases
  - Large Portions are Introns = Not expressed
  - SNP about every 1000 Base
  - Rapid hybridization (18-mers) allow fast analysis
  - Genotypes determine Phenotypes
- Many Adverse Reactions are dependent on Phenotypes
  - Susceptibility probably combination of SNPs
  - AE probably result of interference with major pathway
  - Similar SNP pattern very likely
- Once a pattern is found it is
  - Relatively easy to develop a lab test
  - Possible to determine the interference and develop better drugs

The Genomics Problem

- Finding a statistical relevant sample
  - Established Drugs withdrawn for 80-100 related deaths out of 1.8 Million Patients
  - Usually life-threatening diseases with multiple other causes
  - Filtering out all the non-Phenotype related causes
  - Post-Marketing Surveillance not reliable (3-5% initially)
- Getting Medical Data
  - Clinical Trials Numbers too low (several 1000 patients)
  - Patient Privacy Laws (HIPAA, EU Safe Harbor Act etc.)
  - Lawyers preventing lab tests
- Time Factor
  - Drug is on the Market
  - Large diverse population exposed

Why a SIG on Pharmacovigilance?

Pharmacovigilance Special Interest Group

BMS, Lawrenceville, NJ

21st & 22nd October 2003

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Desired Objectives & Outcomes

- Objectives: Obtain a broader understanding of:
  - Pharmacovigilance
  - IT applied to Pharmacovigilance
- Outcomes:
  - Benchmarking
  - Identify business benefits

- 'Roadmap' for Pharmacovigilance & its IT
- Identify major challenges
- Influence regulators and provide recommendations for the exchange of safety data
- Write a Pharmacovigilance 'White Paper'

References

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Background Reference material for members

- Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Postmarketing Periodic Adverse Drug Experience Reports – June 2003
- Safety Reporting Requirements for Human Drug and Biological Products [Docket No. OON-14843] March 2003
- Guidance for Industry: E2BM Data Elements for Transmission Of Individual Case Safety Reports - April 2002
- FDA Commissioner Dr. Mark McClellan's Statement on FDA's Commitment to MedDRA DIA Annual Meeting ("Ask the Regulators" Session) San Antonio, TX, - 18 June 2003
- ICH web sites – E2A, E2B, W2C, E2D, E2E
- Eudravigilance - *http://www.eudravigilance.org/start.htm*
- Volume 9 – The rules governing medicinal products in the European Union
- PDUFA3 Section viii – risk management programs
- Privacy Laws

Other reference material useful for delegate

- International Society for Pharmacoepidemiology
  - http://www.pharmacoepi.org/resources/goodprac.htm
- Key web sites
  - http://www.emea.eu.int/
  - http://www.eudravigilance.org/
    - EudraVigilance is the European data-processing network and database management system for the exchange, processing and evaluation of Individual Case Safety Reports (ICSRs) related to medicinal products authorised in the European Economic Area (EEA).
  - http://www.cioms.ch/
  - http://www.dataprotection.gov.uk/privacy.htm
  - http://www.mca.gov.uk/ourwork/monitorsafequalmed/currentproblems/cpprevious.htm
    - Current Problems in Pharmacovigilance:
- Key reports
  - "Pharmacovigilance: Effective safety surveillance strategies" by PAREXEL – (JB Publications Ltd.)