



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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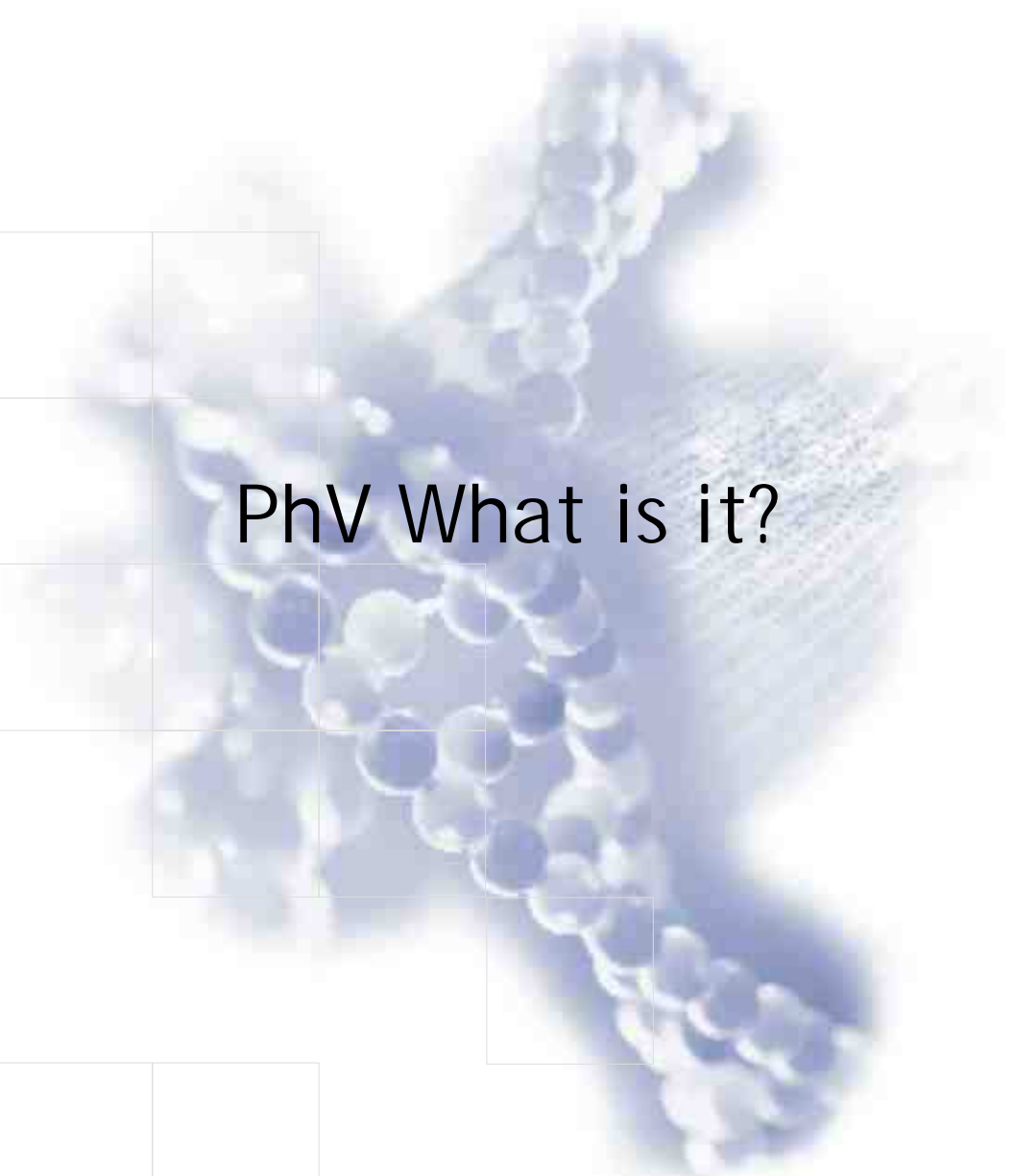


The Big Myths

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*



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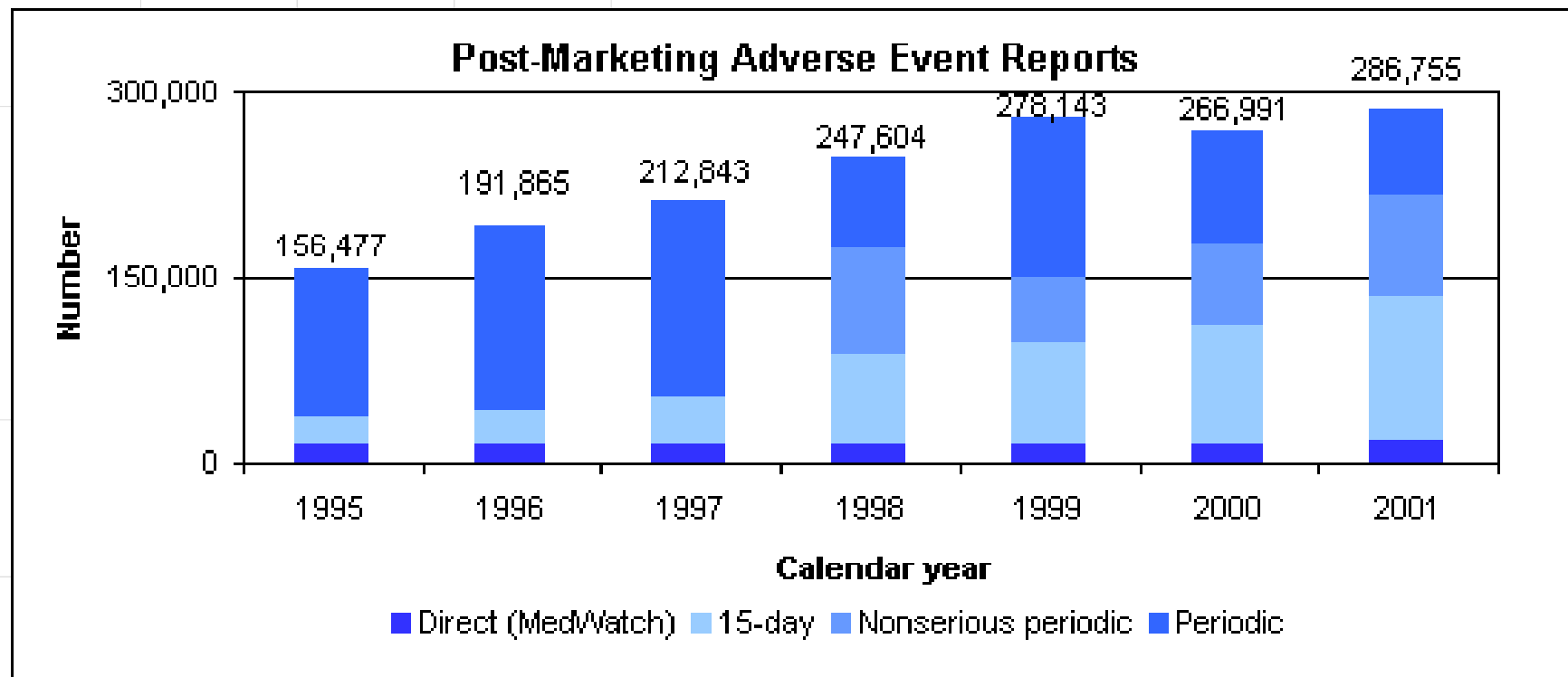
And in the USA!

- 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(l), (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



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)
 - Accidental 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



A DRUG RECALL

RECALLED DRUGS [click here](#)

New! Vigra

Learn More About:

- Vigra
- Vigra Attorney
- Vigra Side Effects
- Contact a Vigra Lawyer

New! Zyprexa

Learn More About:

- Zyprexa Diabetes
- Zyprexa Lactation
- Zyprexa Side Effects
- Information on Zyprexa
- Zyprexa Withdrawal
- Zyprexa Law Suits
- Zyprexa Recall
- Contact a Zyprexa Lawyer

New! Risperdal

Learn More About:

- Risperdal Side Effects
- Risperdal Medication
- Risperdal Stroke
- Risperdal Children
- Risperdal Stroke Lawyer
- Risperdal and Death

- Accolate
- Accutane New!
- Alfa Recombinant
- Androstenedione
- Antifungal
- Ativan
- Avandia
- Bayer
- Celebrex
- Cisapride
- Colchicine
- Cyclosporine
- DES
- Decamethasone
- Dofetilide
- Duract
- Enbrel
- Ephedra
- Fen-Phen
- Fractionate
- Herceptin
- Hismanal
- Lamisil
- Lamictal
- Lofexidine
- Mellin
- Meridia
- Nesiritide
- Norplant
- OxyContin New!
- Pasipar
- PPA
- Progabalin
- Procainamide
- Propulsid
- Prozac
- Ramipril
- Raxar
- Reduct
- Relenza
- Rezum
- Risperdal New!
- Ritalin
- RotaShield
- RU-486
- Seldane
- Serentil
- Simvastatin
- Tasmar
- Thalidomide
- Valium
- Vancoril
- Vigra
- Vioxx
- Vioxx New!
- Vioxx
- Vitamin E
- Welbutin
- Zert
- Zyprexa New!

News, information, and resources about drug recalls.

A study published in the Journal of the American Medical Association found that 20% of all new drugs are found to have serious or life threatening adverse effects unknown or undisclosed at the time of drug approval.

RECENT NEWS

Researchers at Harvard Medical School and Public Citizen, an advocacy organization, performed the study. Will it be first introduced onto the U.S. market, half of a detected, most commonly damaging the heart, causing pregnancy risks.

Over the 25-year study period there were sixteen drug recalls. Half of the drug recalls occurred within two years of their introduction to the market. A 20% probability was estimated that an FDA Black Box warning would be added or there would be an FDA drug recall over 25 years.

From 1998, the FDA is down, U.S. public Citizen, an advocacy organization, performed the study. Will it be first introduced onto the U.S. market, half of a detected, most commonly damaging the heart, causing pregnancy risks.

CLICK HERE TO SPEAK WITH A DRUG RECALL LAWYER

- Accolate
- Accutane New!
- Alfa Recombinant
- Androstenedione
- Antifungal
- Ativan
- Avandia
- Bayer
- Celebrex
- Cisapride
- Colchicine
- Cyclosporine
- DES
- Decamethasone
- Dofetilide
- Duract
- Enbrel
- Ephedra
- Fen-Phen
- Fractionate
- Herceptin
- Hismanal
- Lamisil
- Lamictal
- Lofexidine
- Mellin
- Meridia
- Nesiritide
- Norplant
- OxyContin New!
- Pasipar
- PPA
- Progabalin
- Procainamide
- Propulsid
- Prozac
- Ramipril
- Raxar
- Reduct
- Relenza
- Rezum
- Risperdal New!
- Ritalin
- RotaShield
- RU-486
- Seldane
- Serentil
- Simvastatin
- Tasmar
- Thalidomide
- Valium
- Vancoril
- Vigra
- Vioxx
- Vioxx New!
- Vioxx
- Vitamin E
- Welbutin
- Zert
- Zyprexa New!

significant percent of the population from being exposed to a potential drug recall.

Recent Drug Recall News

BREAKING NEWS!!

September 14, 2003 - High Cost Prescription Drugs No More Effective Research Shows

According to reports, consumers and doctors are receiving too little information about prescription drug effectiveness. Instead, pricey drugs are being pushed, increasing out of pocket costs to an average of \$19 - \$29 from \$13 - \$17 from 2000. According to recent debates over prescription drug benefits for seniors, evidence showed little research is being conducted into comparing the effectiveness of expensive, top-selling drugs. [Read Full Article.](#)

August 18, 2003 - Fraud Fines at a High

The federal government, in fines and settlements, has collected a record amount of money from the healthcare industry. According to the Department of Health and Human Services Office of Inspector General, over the last three fiscal years \$4.21 billion in fines, settlements, and amends as a result of healthcare investigations have been collected, even more than in the prior ten years combined. Companies, including HCA Inc., Abbott Laboratories, AstraZenca PLC, Bayer AG, Guidant Corp., GlaxoSmithKline PLC, Tenet Healthcare Corp., and Pfizer Inc. [Click here to read more.](#)

July 31, 2003 - Public Citizen Tells FDA to Create Safer Alternative

According to the consumer advocacy group Public Citizen, patients are not receiving complete information and are sometimes being misled due to the government's allowance for private sectors to provide prescription drug content patient information. New information shows that the private-sector program is not living up to the FDA's initial goals or expectations of Congress.

The Public Citizen survey of the quality of information regarding 23 top selling drugs in 2002 that are required to carry the FDA's strongest warnings, called a black box warning, found that none of the patient drug information leaflets being distributed in a Washington, D.C. pharmacy complied with the 1996 law's guidelines. The 1996 Congress adopted law was that the private sector design and implement the program requiring the distribution of scientifically accurate and useful written information with all new and refill prescriptions, such as adverse drug effects and how the drug should be used. [Click here to read more.](#)

March 31, 2003 - Consumers Not Protected According to New Report

The Public Citizen consumer group issued a press release on March 31, 2003 in response to the new report, saying that in light of the U.S. Department of Health and Human Services' Inspector General's confirmation that the current drug review process in the U.S. does not protect consumers from potentially deadly prescription medications, changes should be implemented. Of the FDA approved drugs since 1996, seven drugs have

ACCUTANE Side Effects

Personal Injury Lawyer Source

Find a personal injury lawyer near you

Best Place to Find a Medical Malpractice Attorney!

[CLICK HERE!](#)

Contact a lawyer about Pharmaceutical recalls and side effects!

- Fen-Phen Lawsuit News
- Avandia Lawyer
- Meridia Lawsuit News
- Lead Poison Lawyer
- A. Baccal Lawyer
- Whore Celebrex Side Effects
- Whore and Celebrex Legal Help
- Bornova Replacement Therapy Side Effects
- Benzene Lawyer
- Thimerosal News
- A. Baccal Newsletter
- Serene Injury Lawyer
- United National Central Policy Lawyer
- Reduct Settlement
- Metabolite Lawyer Attorney
- Meridia PPH Lawyer
- Hesotheloma Abstracts Online
- Oxycontin Abuse News
- A. Baccal Lawyer Source
- PPA News
- Zoloft Side Effects Lawyer

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

July 19, 2002

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

WARNING LETTER
CHI-21-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Miles C. White



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:



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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



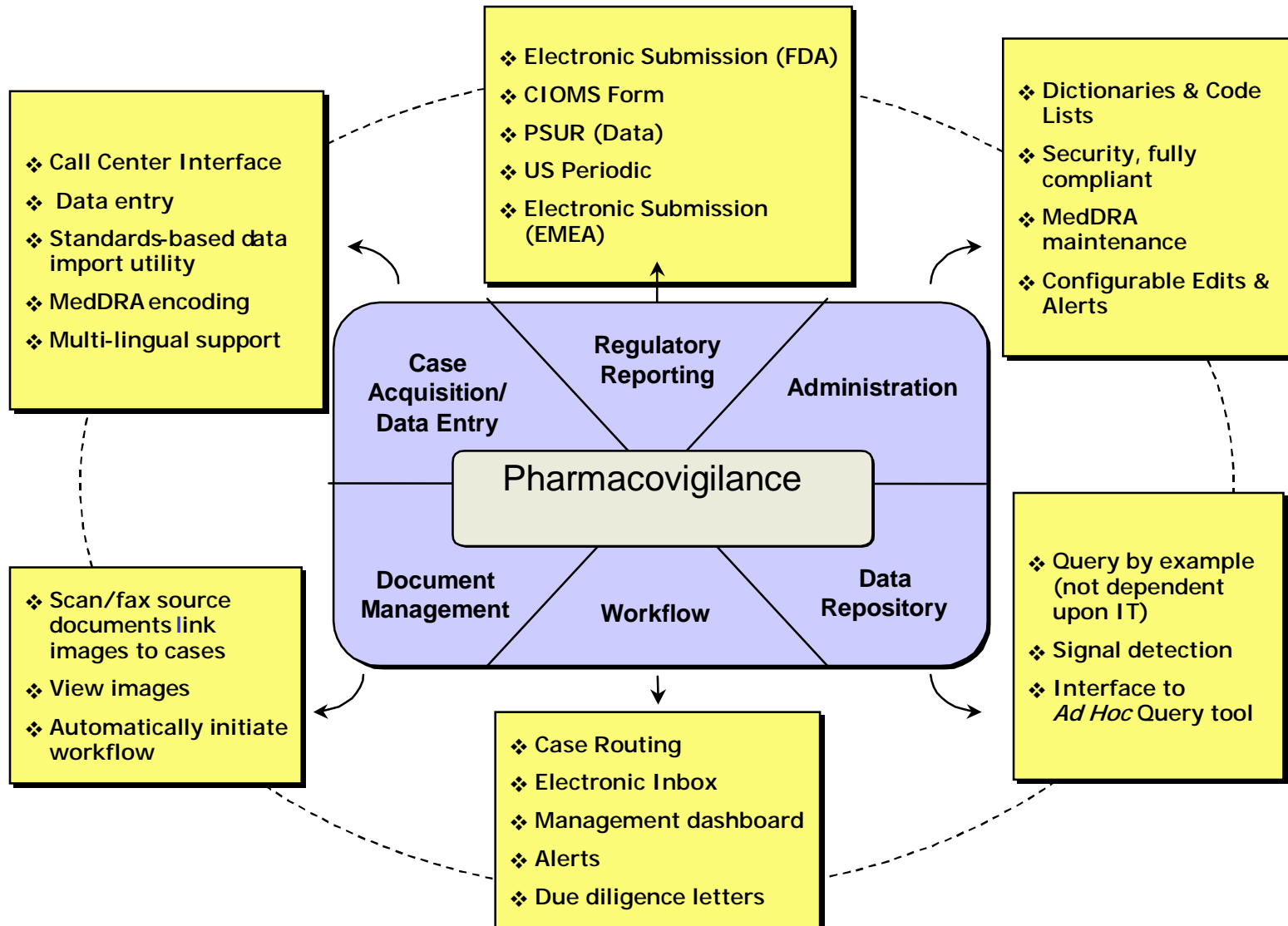


How do we do it?

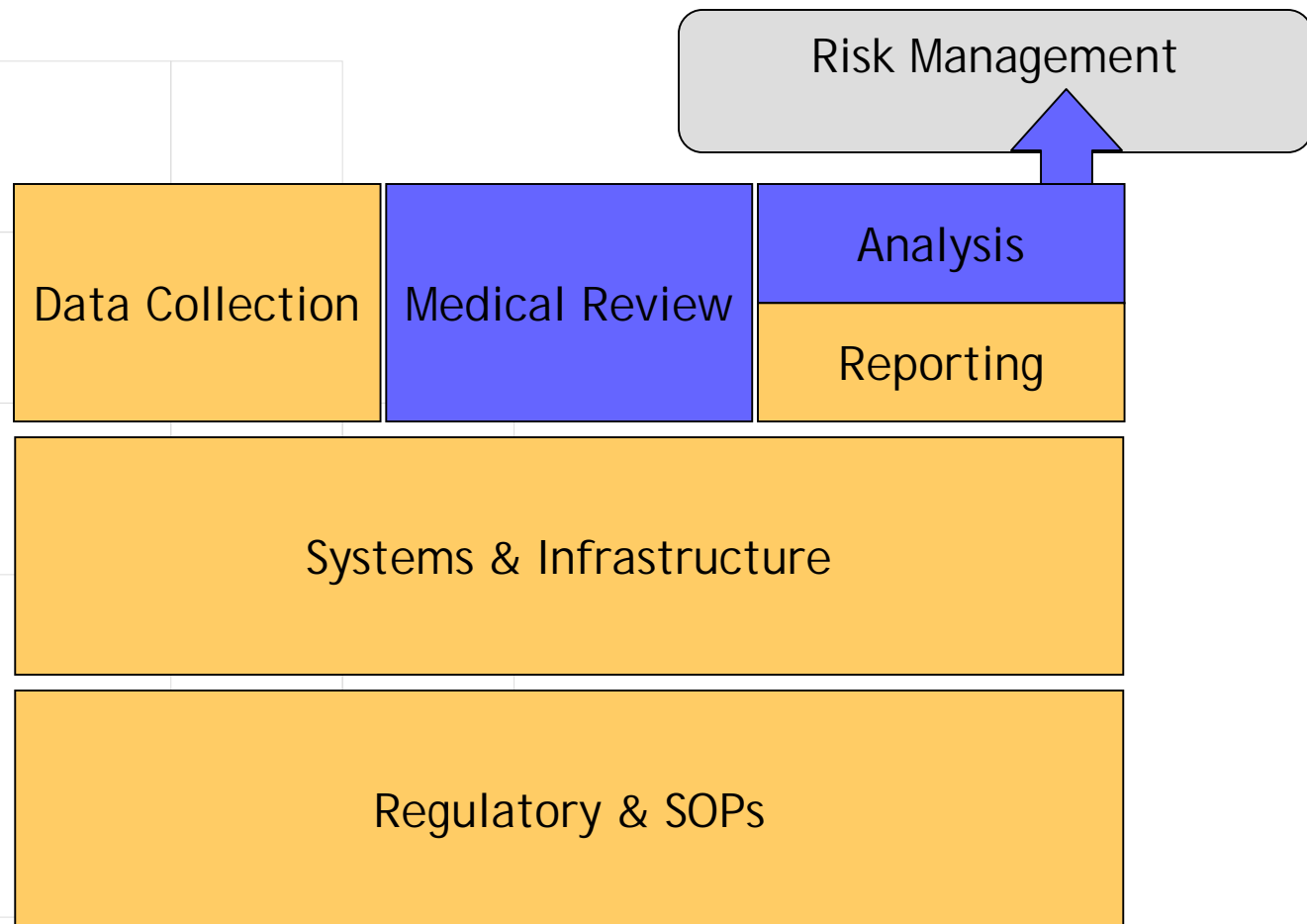


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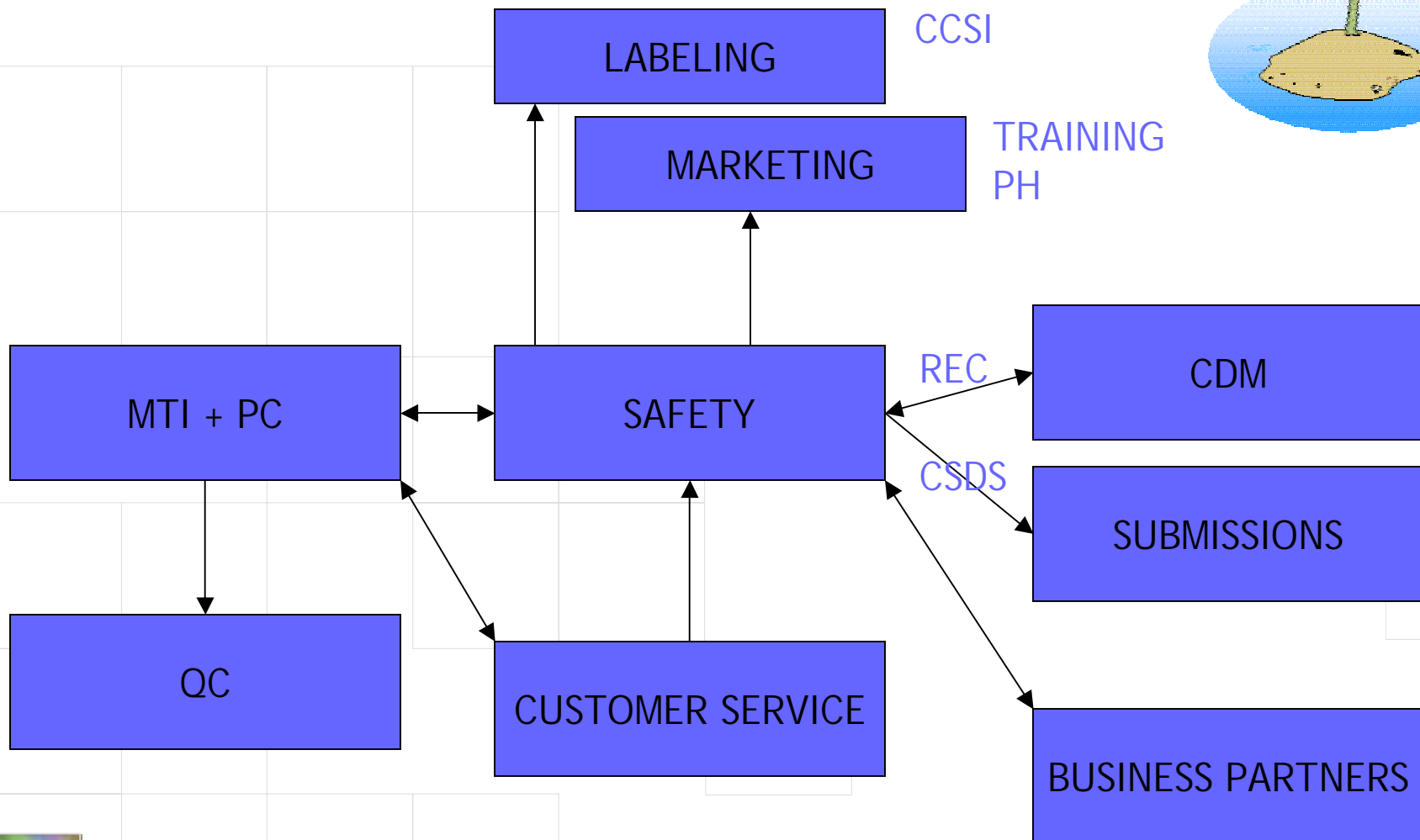
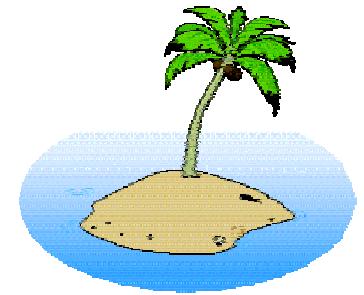
Pharmacovigilance Processes



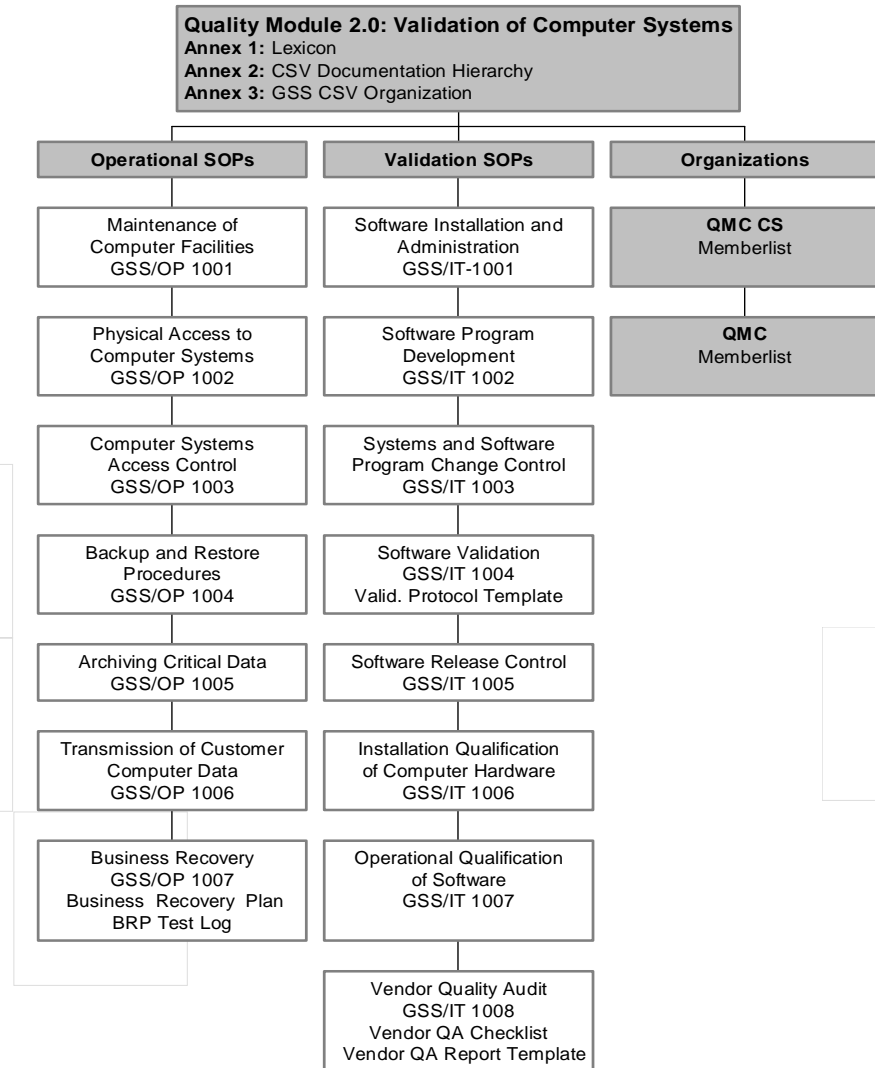
Pharmacovigilance for Management



No Pharmacovigilance Dept. is an Island



Business SOP tied to IT SOPs



SOP Identification	SOP Title	Final Document Date	Version 1 Effective Date
PVOPS-101	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	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	<ul style="list-style-type: none"> Paper driven Unclear ownership especially for Risk Management PhV Processes are high quality but... <ul style="list-style-type: none"> -Redundant data entry across organisation - clinical SAEs, call centers and partners -Reconciliation overhead E2B + paper reporting process EMA legal demands unrealistic Spontaneous data is undervalued 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Emergence of recognized Signal Detection algorithms Evolution of data exchange standards Adoption of consistent risk management practices
Regulations	<ul style="list-style-type: none"> Increasing global diversity of regulations <ul style="list-style-type: none"> -Multiplicity of regulations -Uncertainty about regulations -Which GfIs are worth commenting on (FDA have withdrawn 60 this year) Case reporting focus EMA regulations weakly imposed upon nation states Reactive to regulations 	<ul style="list-style-type: none"> Proactive partnership with regulators Risk / benefit management focus Labeling environment changes Pharmacogenomics 	<p>"The Tome"</p> <p>PDUFA III</p> <p>Co-ordinated input from the industry</p>



	Current	Future (3-5 year)	Transition
Technology	<ul style="list-style-type: none"> Bespoke & O-T-S Diverse standards e.g. <ul style="list-style-type: none"> - XML vs SGML - E2B extensions for various countries Dysfunctional Fol database Competing dictionaries 	<ul style="list-style-type: none"> 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 Fol Database Semantics and Ontologies - especially for data mining Greater availability to global epidemiological data base Trusted Third Party Repository! 	<p>More standards required e.g.</p> <ul style="list-style-type: none"> - HIPPA, - Expanded E2B, - CDISC, HL7m, NCDISC (FMIT) <p>Better dictionaries across product lifecycle</p>
People	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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 	<p>Major training, development and education</p> <p>THE PRISM FORUM</p>

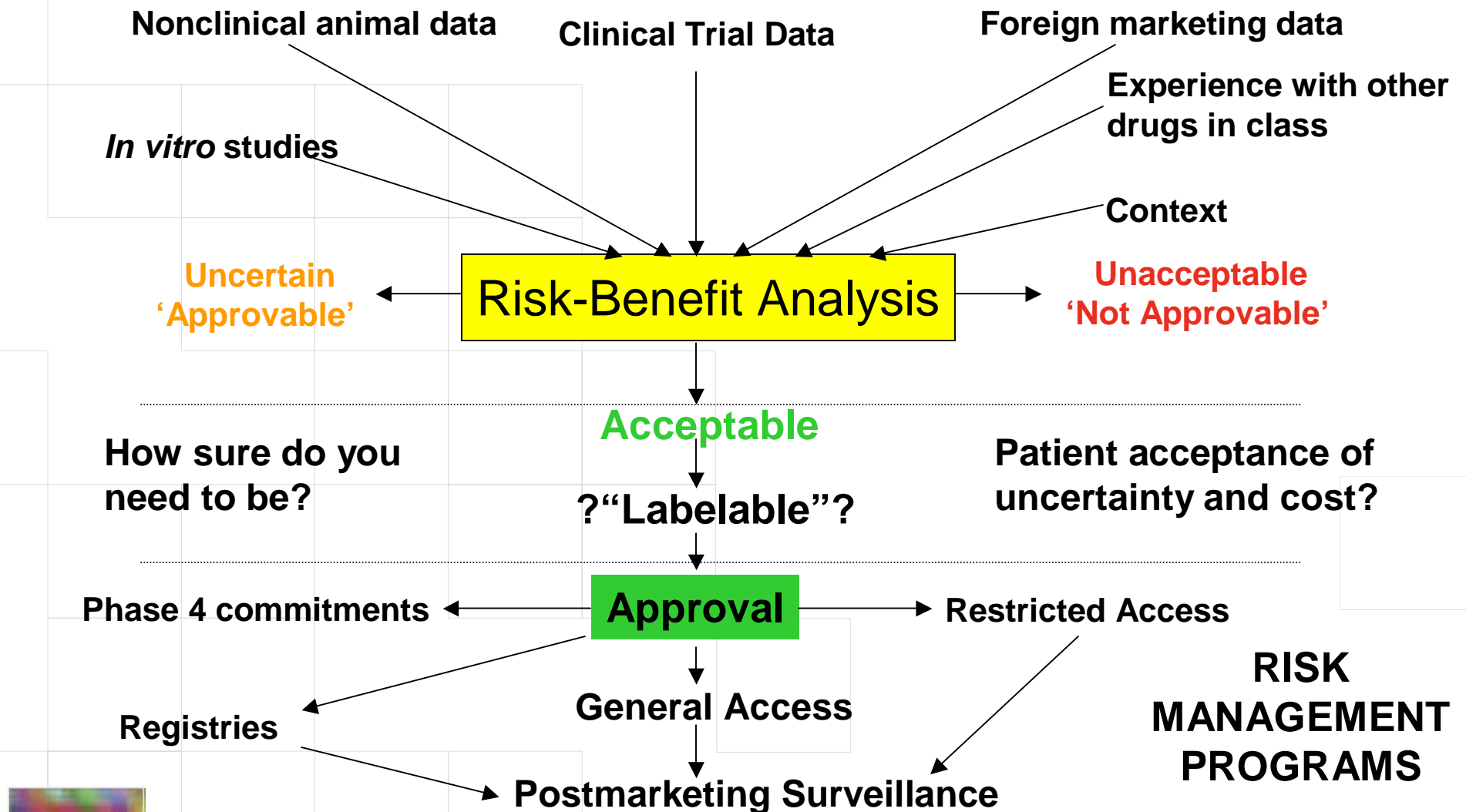
an Innovative Solution?



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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/cppreview.htm>
 - Current Problems in Pharmacovigilance:

➤ Key reports

- “Pharmacovigilance: Effective safety surveillance strategies” by PAREXEL – (JB Publications Ltd.)

