#### **PMS and PSUR**



Module 9 Topic 4

# What Is Post-marketing Surveillance (PMS)?

PMS is a surveillance activity under normal practice conditions after a product is marketed, to document its safety and tolerability in the administered population



#### PMS / Also Defined As

"A formal investigation conducted for the purpose of assessing the clinical safety of marketed medicines in clinical practice"



(ABPI Data Sheets Compendium)

### Why PMS?

- A regulatory requirement
- Certain ADRs (VAERs) may not have emerged in prelicensure studies (relatively small numbers)
- No artificial constraints of strict inclusion / exclusion criteria
- Can help in quantifying incidence of known undesirable effects

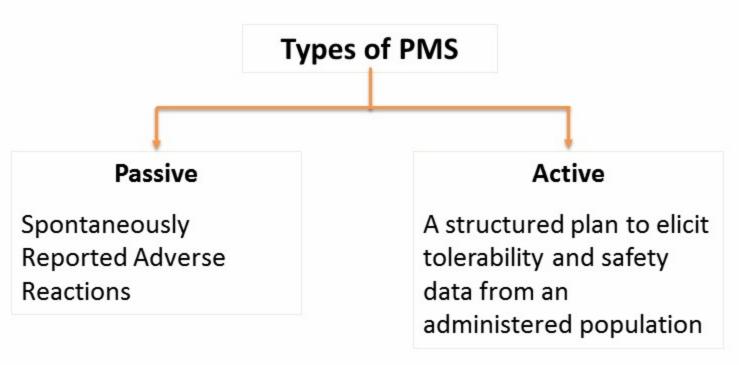


#### Why Trials Are Not Enough

- Limited number of subjects
- Rare undersirable effects may not be elucidated in small study populations
- Strictly controlled selection criteria
- Study population not always representative of normal practice conditions eg. Elderly patients, multiple drug regimens etc.



#### Post-marketing Surveillance





### Passive Surveillance



#### **Yellow Card**

### IN CONFIDENCE – COMMITTEE ON SAFETY OF MEDICINES REPORT ON SUSPECTED ADVERSE DRUG REACTION (For advice on reporting reactions see The Reporting of Adverse Reactions section in this book)

NAME OF PATIENT (To allow for inkage	Family name Forename			Sex	AGE or DATE OF BIRTH	WEIGHT (Kg.)	
with other reports for same patient. Please give record number for hospital patients)							
SUSPECTORUG (Please give brand name if known)	AOUTE	DAILY DOSE	DAT STARTED	STOPPED	INDICATION		
SUSPECTED REACTION			Name	PRTING DOCTOR(6			
DATE OF ONSET OUTCOME (eg fatal recovered)	DATE STOP	PED	Aone	11			
			Tel N	0	Specialty		
SEND TO CSM, FREEPOST, London SW8 OR if you are in one of the following NHS r	egiens:		Signat	ture.	0	ate	
TO CSM WestMidlands, FREEPOST, Birmingham B15 1BR OR CSM Northern, FREEPOST 1085, Newcasde upon Tyne NE1 18R OR CSM Wales, FREEPOST, Cardiff CF4 1ZZ OR CSM Mersey, FREEPOST, Liverpool L3 3AB			report	If you would like information about other reports associated with the suspected drug, please tick box			



### **Yellow Card**

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		Sharing to	
ADDITIONAL NOTES			



# Vaccine Adverse Event Reporting System

VACCINE ADVERSE 24 Hour Toll Free P.O. Box 1100 PATIENT IDENT	For CDC/FDA Use Only VAERS Number Date Received		
Patient Name:  Last Pirst M.I.  Address	Vaccine administered by (Name):  Responsible Physician Facility Name/Address	Form completed by (Name):  Relation	
City State Zip Telephone no. ()  1. State 2. County where administered	City State Zip Telephone no. ()  3. Date of birth 4. Patient age	Telephone no. ()  5. Sex 6. Date form completed	
7. Describe adverse events(s) (symptoms, signs,	mm 6d yy time course) and treatment, if any	Check all appropriate:      Patient died (date mm dd yy )      Life threatening litness     Required emergency room/doctor visit     Required hospitalization (days)     Resulted in protongation of hospitalization     Resulted in permanent disability	
Patient recovered YES NO UNK     Relevant diagnostic tests/laboratory data	NOWN	mm dd yy AM Time PM Time PM	



(contd)

# Vaccine Adverse Event Reporting System

Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
14. Any other vaccinations within 4 week  Vaccine (type) Manufactu  B		Flourie/Site	No. Previous doses	Date given
	☐ Military dinic/hospital ☐ P ☐ Other/unknown ☐ P	Vaccine purchased with:  Private funds   Military funds  Public funds   Other/unknown  hysician-diagnosed allergies, birth de	17. Other medical	
	Trabant days	Only for	children 5 and under	
20. Have you reported No	LI TO DESITE GEOGRAPHICAL		23. No. of brother and sisters	
20. Have you reported No this adverse event previously?	To health department	22. Birth weight lb		ERN DERE SYSTEMS
this adverse event previously?	ctor To menufacturer		oz.	
this adverse event previously?	ctor To menufecturer	b	oz.	zation project
this adverse event previously?	ctor To manufacturer ation (check all applicable, specify) Type Dose no.	Only for reports submitted by	oz. manufacturenfimmuni	zation project



(contd)

# Spontaneously Reported Adverse Reaction

- Reporting of serious or unexpected ADRs are a regulatory requirement for new drugs (upto 2 years after registration)
- Most reputed companies have in-house reporting systems
- A National Pharmacovigilance Advisory Committee is currently being set up



# National Pharmacovigilance Advisory Committee

Chairperson: DGHS

Secretary : DCGI

Committee : Experts from ICMR,

AIMS, NII, JIPMER

and others



### Active (Structured) Surveillance



#### Regulatory Clause in India

"Post marketing surveillance study shall be conducted during the initial period of two years of marketing of the new drug formulation, after getting the protocol and the names of the investigators duly approved by the Licensing Authority"



(Standard Statement in all DCGI permissions under rule 122 A and B)

### PMS/Reporting Results to the DCGI

Although submission of post-marketing surveillance reports is a statutory requirement after granting marketing approval for new drugs in India for the last 5 years, none of the pharmaceutical companies has ever compiled with this condition, it is learnt"

(Pharmabiz, 6th Jan 2005)



### India Today

- PvPI has been set up
- Compulsory for all companies to have a PV team, maintain a PV Master File, employ a PvOI, and report all ADEs/ADRs in a timely fashion
- PSURs and Risk management plans also mandatory



#### Some Features of PMS

- Provides additional assurance about the safety of a new drug
- The drug is prescribed as per the "best clinical judgment" of the doctor
- No constraints from sponsor on selection criteria, co-administration of other drugs, contraindications etc
- Can uncover previously unexpected, undesirable effects



#### Criticisms of PMS

- Patients earlier had to buy the vaccine/drug
- Considered as a pseudo-scientific excuse to increase sales
- Payment to doctors considered as an inducement to prescribe the drug
- Was considered by many as unethical



# The UK Quintapartite\* Guidelines For PMS

- Must be ethical and scientifically valid
- Should represent real use
- Separate prescribing decision from study entry
- Must not be promotional in nature
- Should encourage liason between sponsor and regulator
- Should have the results published
  - \*1) The British Medical Association,
  - 2) The Association of British Pharmaceutical Industry,
  - 3) The Medicines Control Agency,
  - 4) The Committee on Safety of Medicines,
  - 5) The Royal College of General Practitioners



#### Active or Structured PMS Designs

- Mini, multicentre, open, non-comparative studies under normal practice conditions
- Large scale, open or comparative phase IV trials in a large study population
- Cohort Studies eg. safety and tolerance in the elderly. Exclusion limited to contraindications in the Package Insert.

(contd)



#### **Active or Structured PMS Designs**

- Case Surveillance Studies i.e. Study of cases reporting with certain features or reactions suspected to be associated with a particular drug and then to ascertain the drug exposure in those cases eg. A case of aplastic anaemia: which drugs given?
- Case Control Studies, ie. Comparision of ADRs in cases with drug exposure for a particular disease vis-à-vis appropriate controls without the disease. Helps to quantify incidence/prevalence



#### PSUR?

 Its a formal, structured update of the worldwide safety experience for a registered medicinal product (per ICH E2C standards), prepared for submission to regulatory authorities at defined times post-authorisation.



### Why?

- Report all the relevant new safety information from appropriate sources;
- Relate these data to patient exposure;
- Summarise the market authorisation status in different countries and any significant variations related to safety;
- Create periodically the opportunity for an overall safety re-evaluation;
- Indicate whether changes should be made to product information in order to optimise the use of the product



### Schedule Y says.....

- The PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant
- For subsequent two years the PSURs need to be submitted annually
- Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health
- PSURs due for a period must be submitted within
   30 calendar days of the last day of the reporting period



#### ICH region says....

- The US regulations require quarterly reports during the first 3 years, then annual reports
- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for two years, annually for the three following years and then every five years, at time of renewal of registration
- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorisation. Systematic information on this cohort, taking into account a precise denominator, must be reported annually



#### **Glossary Of Special Terms**

 Company Core Data Sheet (CCDS) – A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product



### Glossary Of Special Terms (contd)

Company Core Safety Information (CCSI) - All relevant safety information contained in the Company Core Data Sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the medicinal product, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting



#### **Glossary Of Special Terms**

- Data Lock-Point (Data Cut-off Date) The date designated as the cut-off date for data to be included in a PSUR. It is based on the International Birth Date (IBD) and should usually be in sixmonthly increments.
- International Birth Date (IBD) The date of the first marketing authorisation for a new medicinal product granted to any company in any country in the world.



### Glossary Of Special Terms (contd)

- Listed Adverse Drug Reaction An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.
- Spontaneous Report or Spontaneous Notification –
   An unsolicited communication to a company,
   regulatory authority or other organisation that
   describes an adverse drug reaction in a patient
   given one or more medicinal products and which
   does not derive from a study or any organised data
   collection scheme

#### Glossary Of Special Terms

- Unlisted Adverse Drug Reaction
  - An ADR whose nature, severity, specificity or outcome are not consistent with the information included in the CCSI.



## Model For A Periodic Safety Update Report

#### SAMPLE TITLE PAGE

PERIODIC SAFETY UPDATE REPORT FOR: (PRODUCT)

MAH's NAME AND ADDRESS (Corporate headquarters or other company entity responsible for report preparation)

PERIOD COVERED BY THIS REPORT: (dates)

INTERNATIONAL BIRTH DATE: Date (Country of IBD)

DATE OF REPORT

(Other identifying information at the option of MAH, such as report number)



#### Table of contents...

- Introduction
- Worldwide market authorisation status
- Update of regulatory authority or MAH actions taken for safety reasons
- Changes to reference safety information
- Patient exposure
- Presentation of individual case histories
- Studies
- Other information
- Overall safety evaluation
- Conclusion
- APPENDIX: COMPANY CORE DATA SHEET



#### Introduction...

- The MAH should briefly introduce the product so that the report "stands alone" but is also placed in perspective relative to previous reports and circumstances
- Reference should be made not only to product(s) covered by the report but also those excluded
- Exclusions should be explained; for example, they may be covered in a separate report (e.g., for a combination product)



#### World wide marketing authorisation

- Provides cumulative information
- Information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has been made related to the following:
  - dates of market authorisation, and subsequent renewal;
  - any qualifications surrounding the authorisation, such as limits on indications if relevant to safety;
  - treatment indications and special populations covered by the market authorisation, when relevant;
  - lack of approval, including explanation, by regulatory authorities;
  - withdrawal by the company of an application for marketing authorisation if related to safety or efficacy;
  - dates of launch when known;
  - trade name(s)



TABLE 1: EXAMPLE OF PRESENTATION OF WORLDWIDE MARKET AUTHORISATION STATUS

Country	Action-Date	Launch Date	Trade Name(s)	Comments
Sweden	A - 7/90	12/90	Bacteroff	-
	AR - 10/95		17	-
Brazil	A - 10/91	2/92	Bactoff	-
	A - 1/93	3/93	Bactoff-IV	IV dosage form
United Kingdom	AQ - 3/92 A - 4/94	6/92 7/94	Bacgone Bacgone-C (skin infs)	Elderly (> 65) excluded (PK) Topical cream
Japan	LA - 12/92			To be refiled
France	V - 9/92	-		Unrelated to safety
Nigeria	A - 5/93	7/93	Bactoff	-
	A - 9/93	1/94	Bactoff	New indication



<u>Abbreviations for Action</u>: A = authorised; AQ = authorised with qualifications: LA = lack of approval; V = voluntary marketing application withdrawal by company; AR = Authorisation renewal.

# Update of regulatory authority or MAH actions taken for safety reasons

- Section should include details on the following types of actions relating to safety that were taken during the period covered by the report and between data lock-point and report submission:
  - marketing authorisation withdrawal or suspension;
  - failure to obtain a marketing authorisation renewal;
  - restrictions on distribution;
  - clinical trial suspension;
  - dosage modification;
  - changes in target population or indications;
  - formulation changes



# Changes To Reference Safety Information

 Changes to the CCSI, such as new contra-indications, precautions, warnings, ADRs, or interactions, already made during the period covered by the report, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next report and the next period



#### Patient Exposure...

- Where possible, an estimation of accurate patient exposure should cover the same period as the interim safety data
- An explanation and justification should be presented if the number of patients is impossible to estimate or is a meaningless metric



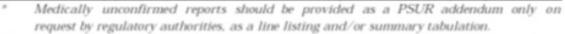
#### Patient Exposure... (contd)

- In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained
- If these or other more precise measures are not available, bulk sales (tonnage) may be used
- The concept of a defined daily dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially paediatric vs. adult) should be provided



# Presentation of individual case history...

	Source	Type of Case	Only Summary Tabulation	Line Listing and Summary Tabulation	
1.	Direct Reports to MAH				
	<ul> <li>Spontaneous ADR reports*</li> </ul>	S	-	+	
		NS U	-		
		NS L**	+		
	MAH sponsored studies	SA	-		
2.	Literature	S	-	+	
		NS U		+	
3.	Other sources				
	<ul> <li>Regulatory authorities</li> </ul>	S	-	+	
	<ul> <li>Contractual partners</li> </ul>	S	+		
	<ul> <li>Registries</li> </ul>	S	+		



<sup>\*\*</sup> Line listing should be provided as PSUR addendum only on request by regulatory authorities.



 $S = serious; \ L = Listed; \ A = attributable to medicinal product (by investigator or sponsor); \ NS = non-serious; \ U = Unlisted.$ 

#### Studies...

 All completed studies (non-clinical, clinical, epidemiological) yielding safety information with potential impact on product information, studies specifically planned or in progress, and published studies that address safety issues, should be discussed.



#### Overall safety evaluation

- A concise analysis of the data presented, taking into account any late-breaking information and followed by the MAH assessment of the significance of the data collected during the period and from the perspective of cumulative experience should highlight any new information on:
  - A change in characteristics of listed reactions, e.g. severity, outcome, target population
  - Serious unlisted reactions, placing into perspective the cumulative reports
  - Non-Serious unlisted reactions
  - An increased reporting frequency of listed reactions, including comments on whether
  - it is believed the data reflect a meaningful change in ADR occurrence



#### Conclusion

- The conclusion should:
  - indicate which safety data do not remain in accord with the previous cumulative experience, and with the reference safety information (CCSI);
  - specify and justify any action recommended or initiated



### Regulatory actions

- Amendment of pack insert in the precautions, contraindications, warning section
- Withdrawal or suspension of a marketing approval
- Suspension of supply by the MAH
- Significant restrictions on distribution or introduction of other risk minimization measures,
- Significant safety-related changes in labelling documents
- Restrictions on use or population treated,
- Communications to HCPs
- New post-marketing study requirement(s) imposed

