



Rapid Parmacovigilance Implementation in Developing Countries

“Some remedies are worse than the disease”

Pubilius Syrus, Roman writer, 1st century BC.



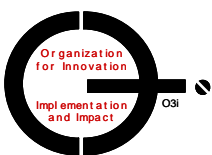
Presentation by


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Advisor to Gates Foundation, WHO, various MoH

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Head, External Affairs

Sept 13, 2007

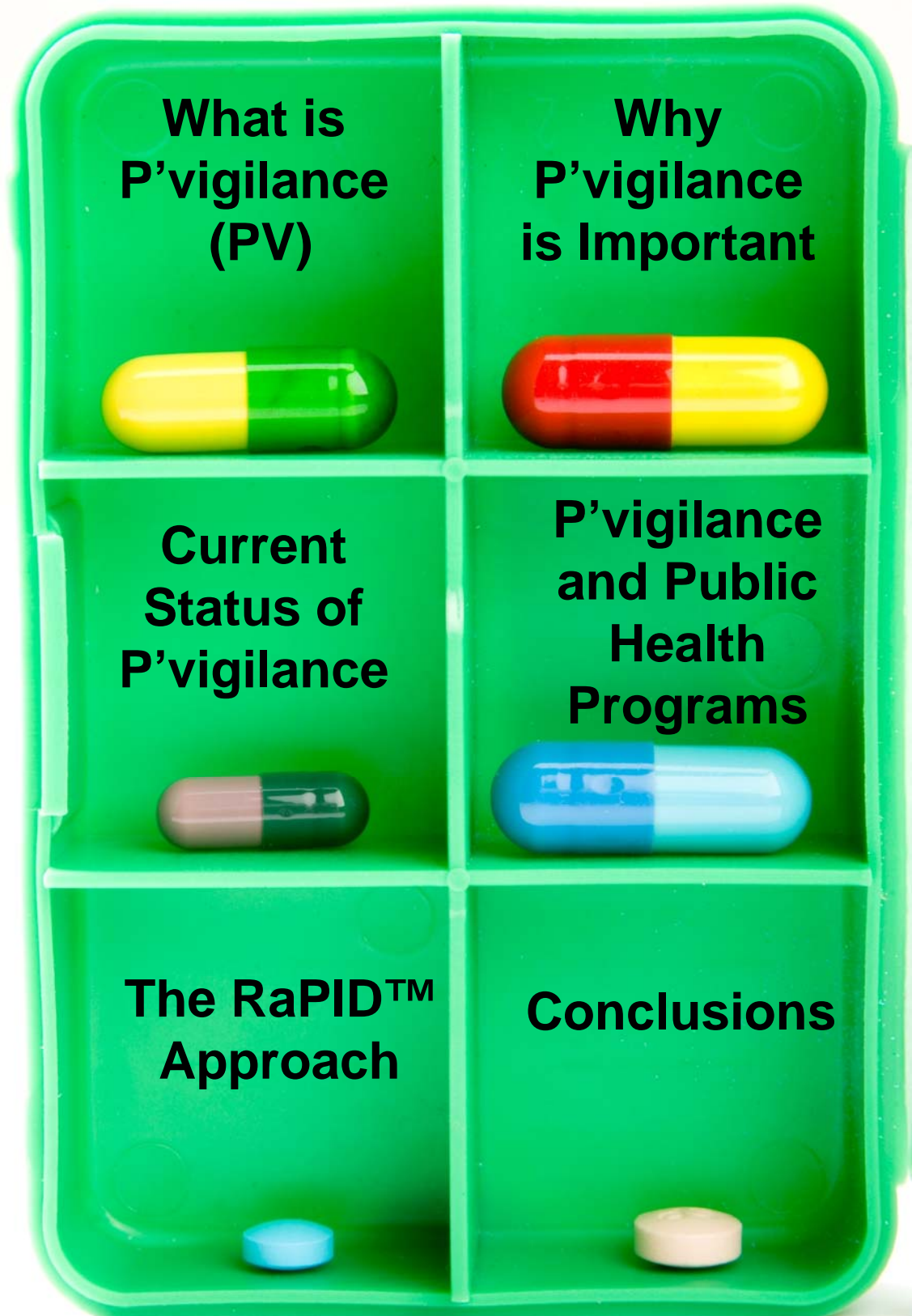
Implementing Drug Safety in 90 days





“Primum non nocere” (First do no harm)
Hippocrates 500BC

Overview of Presentation



Pharmacovigilance

Pharmacovigilance is defined as

“the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems”

The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool, World Health Organization, 2006

November 2, 2007



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Objectives of Pharmacovigilance

- improve patient care and safety
- improve public health and safety
- encourage safe, rational and appropriate use of drugs
- promote understanding, education and clinical training in pharmacovigilance

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page ____ of ____

FDA USE ONLY

Trace unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier: _____
In confidence

2. Age at Time of Event, or Date of Birth: _____

3. Sex: Female Male

4. Weight: _____ lb or _____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. Adverse Event Product Problem (e.g., defective/formulation)
 Product Use Error Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)

Death (m/d/yyyy) Disability or Permanent Damage
 Life-threatening Congenital Anomaly/Birth Defect
 Hospitalization - initial or prolonged Other Serious (Important Medical Events)
 Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (m/d/yyyy) _____ 4. Date of this Report (m/d/yyyy) _____

5. Describe Event, Problem or Product Use Error

6. Relevant Test/Laboratory Data, including Dates

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, renal, pregnancy, smoking and alcohol use, drug/drug problems, etc.)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

Yes No Returned to Manufacturer on: _____ (m/d/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

#1 _____
#2 _____

2. Dose or Amount Frequency Route

#1 _____
#2 _____

3. Dates of Use (if unknown give duration) Route (or description)

#1 _____
#2 _____

4. Diagnosis or Reason

#1 _____
#2 _____

5. Event Recurred After Reintroduction?

#1 Yes No Does Not Apply
#2 Yes No Does Not Apply

6. Expiration Date

#1 _____
#2 _____

7. NDC # or Unique ID

#1 _____
#2 _____

E. SUSPECT MEDICAL DEVICE

1. Brand Name _____

2. Common Device Name _____

3. Manufacturer Name, City and State _____

4. Model # _____ Lot # _____
Catalog # _____ Expiration Date (m/d/yyyy) _____
Serial # _____ Other # _____

5. Operator of Device
 Health Professional
 Lay User/Patient
 Other

6. If Implanted, Give Date (m/d/yyyy) _____ 7. If Explanted, Give Date (m/d/yyyy) _____

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
 Yes No

9. If Yes to Item 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (include treatment of event)

G. REPORTER (See confidentiality section on back)

1. Name and Address _____

Phone # _____ E-mail _____

2. Health Professional? Yes No 3. Occupation _____

4. Who Reported to:
 Manufacturer
 User/Facility
 Distributor/Reporter

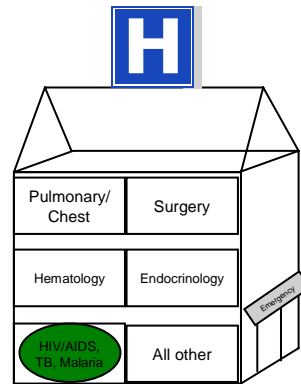
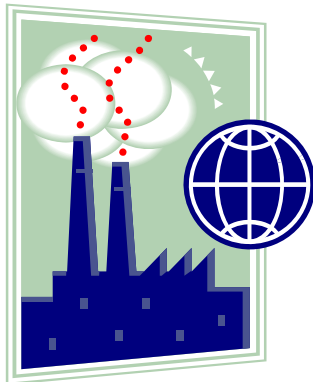
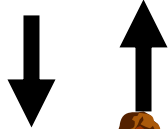
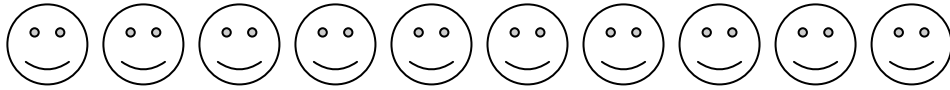
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:

Sample Adverse Drug Reaction Report (ADR Report)

PLEASE USE BLACK INK

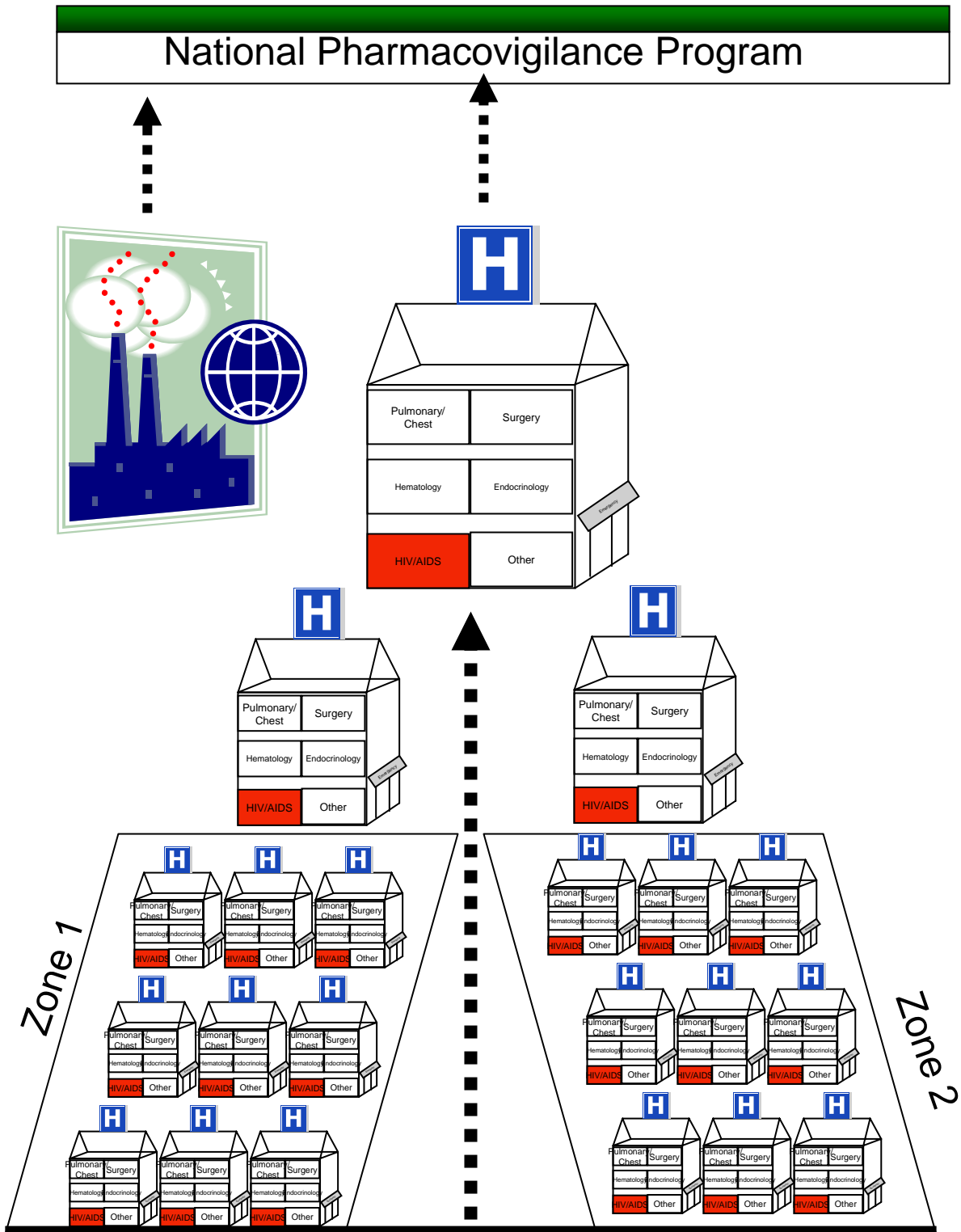


Pharmacovigilance Reporting Process (movement of information)



RaPID's Focus

Illustrative Representation of National Pharmacovigilance Programs



November 2, 2007

Illustrative Representation of National Pharmacovigilance Programs

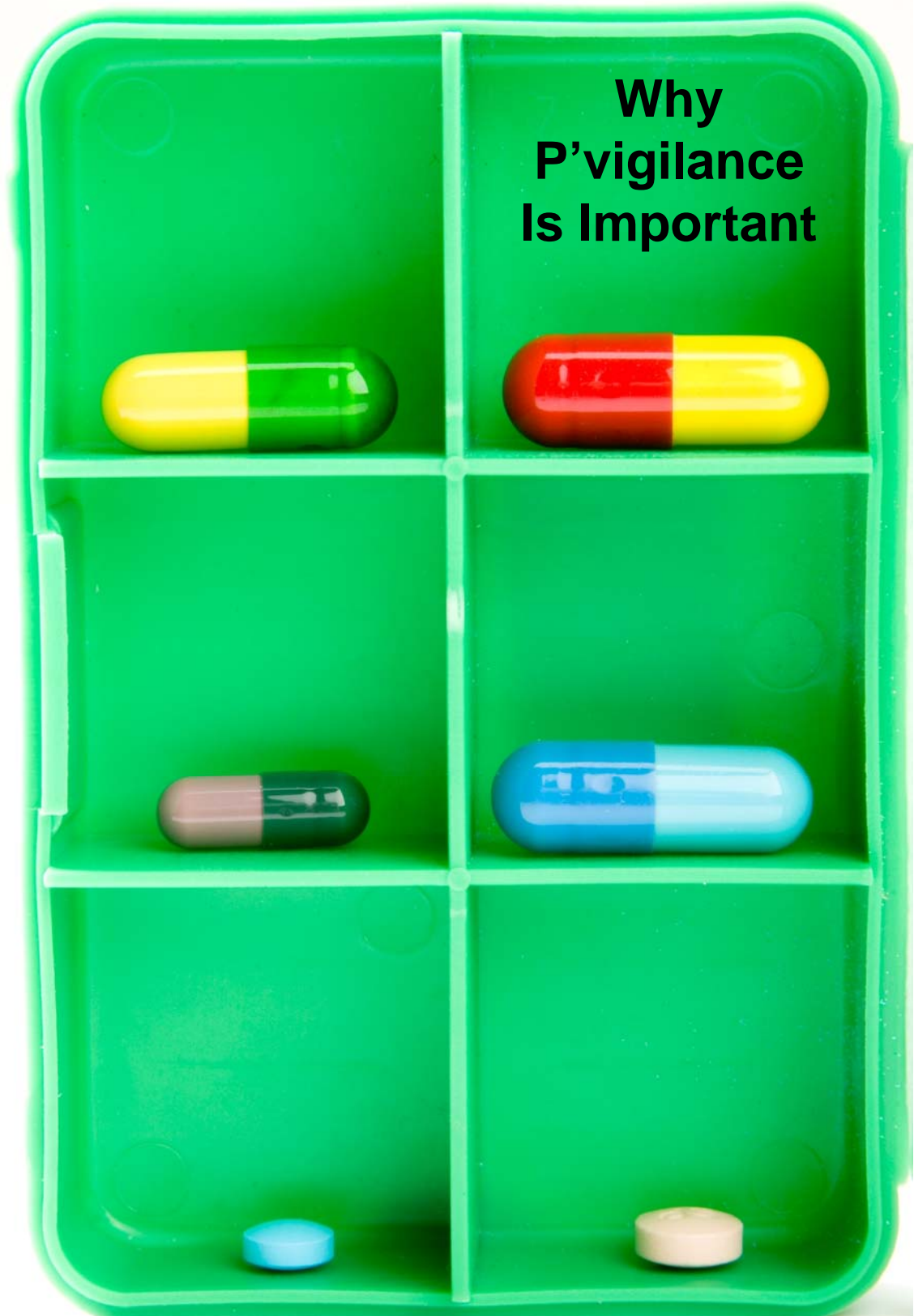
Policy Recommendations and
Fine tuning of Public Health Programs



**Department of
Pharmacovigilance**

National Pharmacovigilance Program

Overview of Presentation



Impact of ADRs in USA

- 1.2 million hospitalized patients in 2004¹
- Cost of drug-related morbidity and mortality >\$177.4 billion²
- ADRs are the 4th - 6th leading cause of death³

1 Exilhauser, Owen AHRQ 2007

2 Ref. Ernst & Grizzle J Am Pharm Assoc. 41: 192(2001)

3 Lazarou et al JAMA 1998;279: 1200 - 1205

Examples of Product Recalls and Product Safety Concerns

- Even developed countries with stringent regulatory authorities, have withdrawn several drugs from the market in the past few years
- Experience/data shows 4% to 5% of drugs on the market are withdrawn and about 20% receive 'black box' warnings (safety concerns not previously identified)

Drug	Year	Examples of Serious and Unexpected Adverse Events Leading to Withdrawal of Drug
Thalidomide	1965	Phocomelia
Practolol	1975	Sclerosing peritonitis
Clioquinol	1970	Subacute neuropathy
Benoxaprofen	1982	Nephrotoxicity, oncholysis, cholestatic jaundice
Terfenadine	1997	Torsade de pointes
Rofecoxib	2004	Cardiovascular effects

Importance of pharmacovigilance

- Complete safety data (especially for unexpected and serious adverse events) can only be captured through pharmacovigilance
- It cannot be captured through clinical trials which are conducted in an “artificial environment.”
 - In clinical trials
 - patients are not taking any other medications
 - do not have concomitant infections
 - are taking the drug short-term (during the duration of the trials only) and
 - are not part of vulnerable groups (e.g., children, pregnant women, elderly, etc.)

Safety concerns with Anti-Retrovirals

Product	Potential ADRs and Risks
Abacavir	Hypersensitivity, potentially fatal, up to 5%
Didanosine	<ul style="list-style-type: none"> • Pancreatitis – often fatal, very difficult to manage • Neuropathy
Indinavir Ritonavir Saquinavir	<ul style="list-style-type: none"> • Lipodystrophy--disfiguring change of fat distribution identifies HIV+ patients on ARV treatment • Leads to discontinuation • Severe skin reactions – potentially fatal

Safety of ARVs in pediatrics is largely a 'black box'

PROMOTING SAFETY OF MEDICINES FOR CHILDREN

Adverse effects associated with antiretroviral medicines have been reported to occur in up to 30% of HIV-infected children on antiretroviral therapy. [Examples of ADR's included]: hepatotoxicity, raised serum amylase without symptomatic pancreatitis, zidovudine-(AZT-) induced anaemia, nevirapine- (NVP-) induced rash, didanosine- (ddI-) induced pain in the abdomen, stavudine- (d4T-) induced angioedema.

Most of the adverse effects are reversible by modifying the dosage or omitting the offending medicine.

Importance and URGENCY of pharmacovigilance

We are accelerating the use of new drugs in new environments, which are mostly devoid of pharmacovigilance activities

- Faster scale up of public health programs due to availability of new funding from major donors such as the Global Fund, World Bank, PEPFAR, UNITAID, etc
- New drugs are reaching developing countries in greater numbers and more quickly because of new funding from several donors, including the Bill and Melinda Gates Foundation

Overview of Presentation

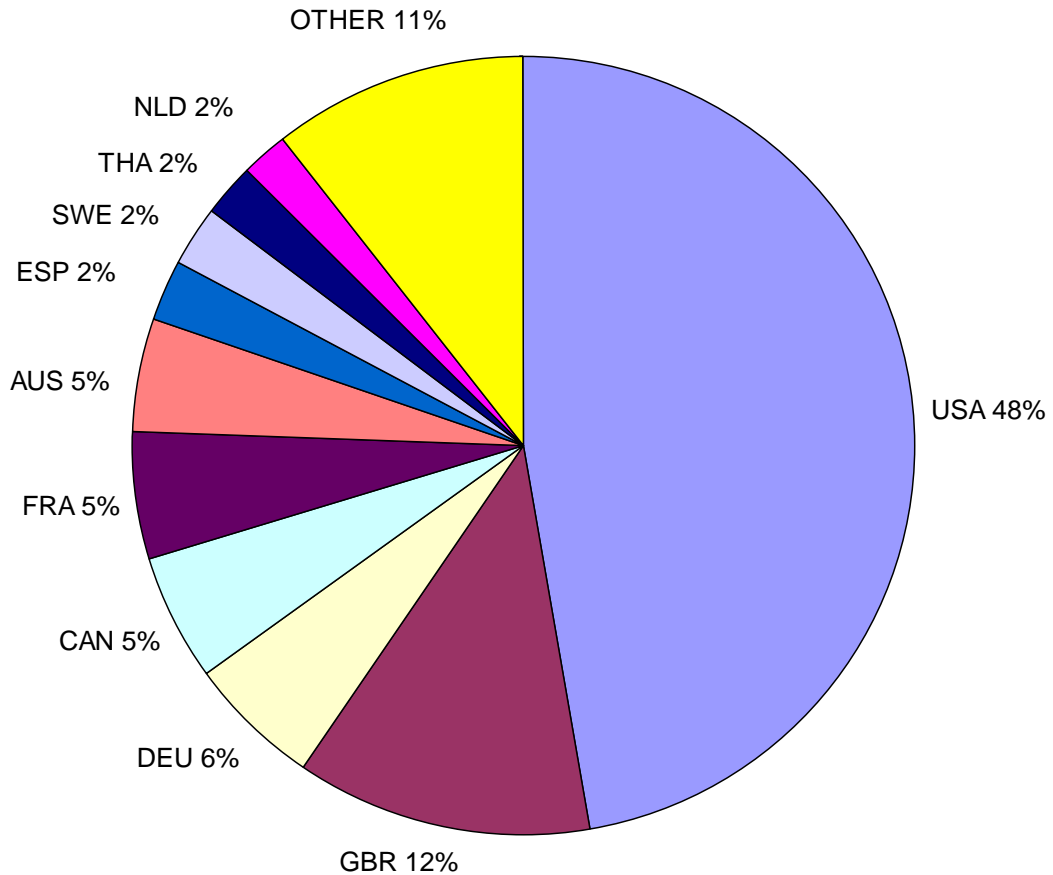


Current Status of Pharmacovigilance

**IN MOST DEVELOPING
COUNTRIES, THERE IS
PRACTICALLY NO CULTURE OF
PHARMACOVIGILANCE
AND DRUG SAFETY.**

**AS A RESULT, THERE IS ALMOST
NO EVIDENCE ON THE SAFETY OF
DRUGS IN PUBLIC HEALTH
PROGRAMS.**

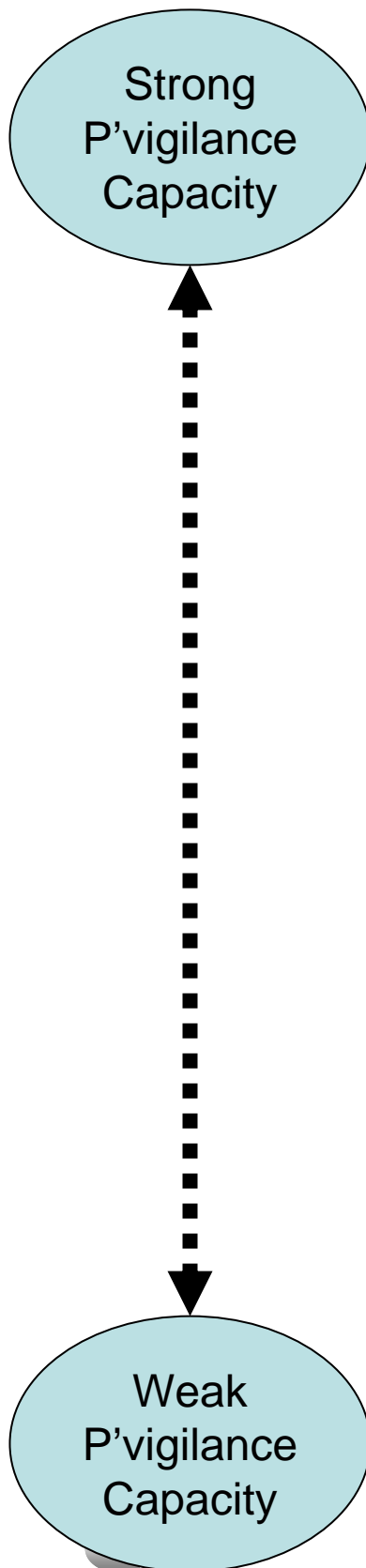
Top Ten Contributors to WHO Database



Globally, only about 500,000 to 600,000 adverse event occurrences are captured annually—developing countries account for less than 5% of all ADR data

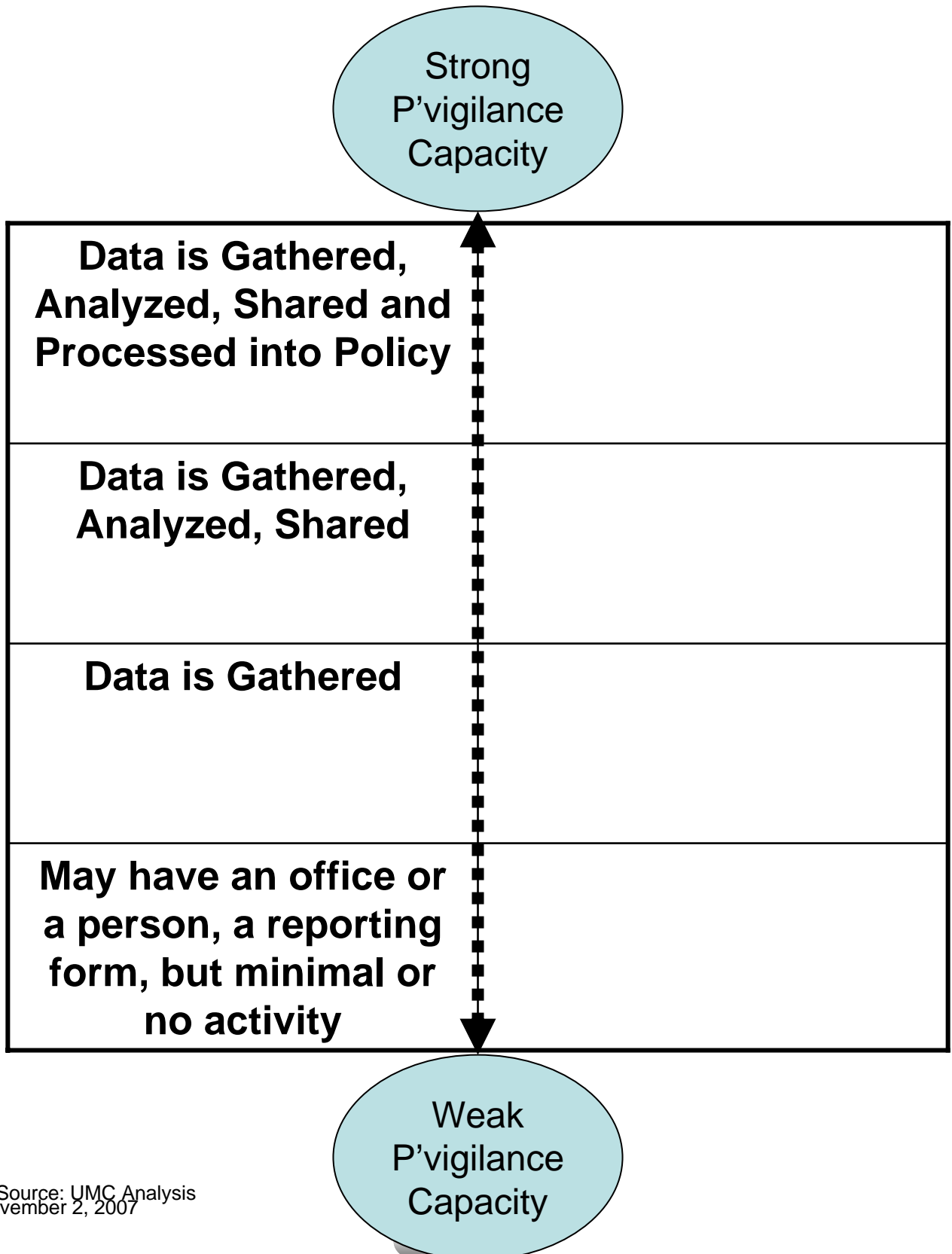
Only developing country represented is Thailand which started pharmacovigilance in 1983

Current Status of PV in Africa



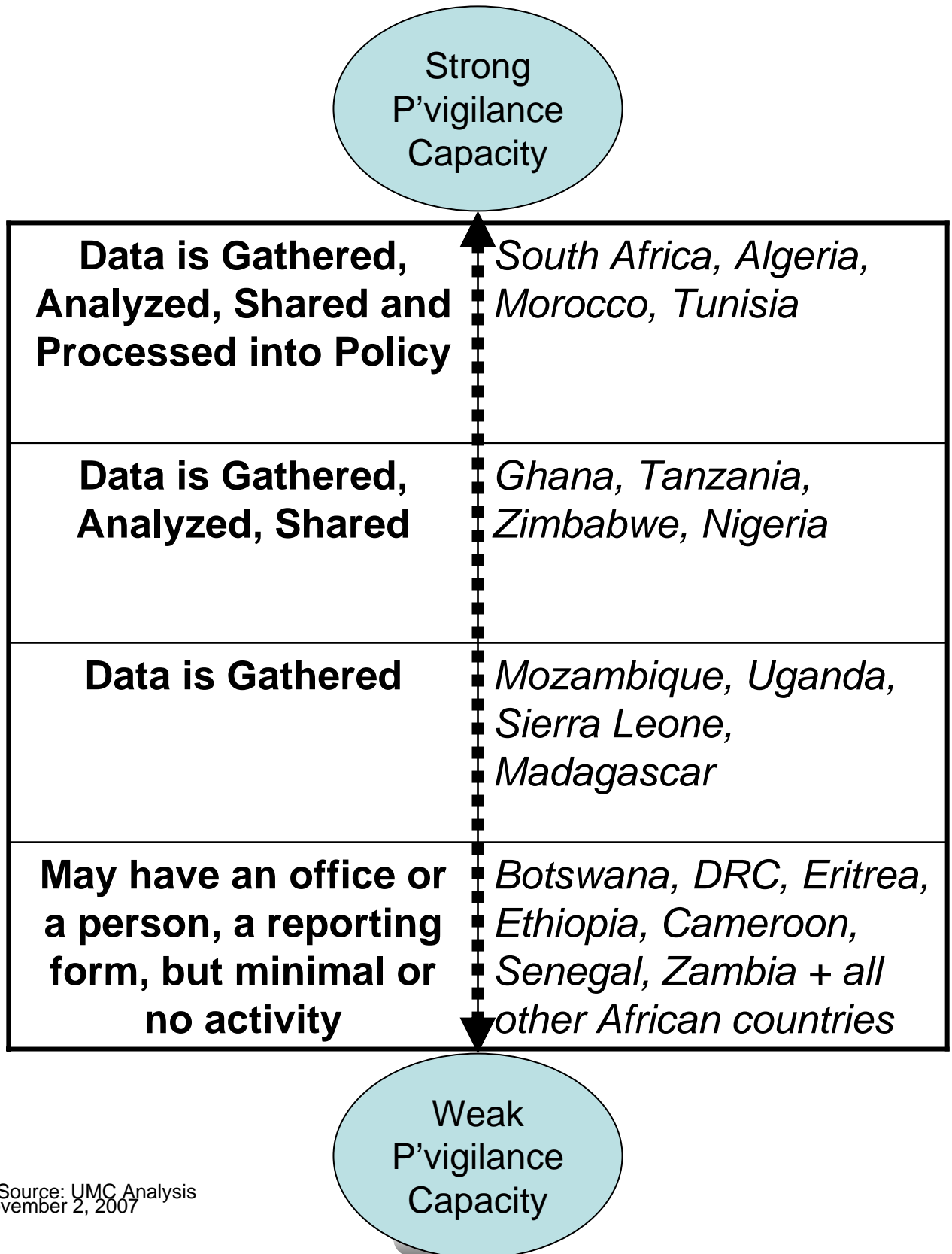
Source: UMC Analysis
November 2, 2007

Current Status of PV in Africa



Source: UMC Analysis
November 2, 2007

Current Status of PV in Africa



Source: UMC Analysis
November 2, 2007

Summary of Key Points-- Pharmacovigilance in PHP

- It has to be done—there are significant risks and deaths associated with it
- It must be established urgently (in existing and new treatment programs)
- How do we do this? What is the RaPID Approach

*“All things are a poison and none is without poison;
it is the dose that determines it is a poison.”*

Paracelsus "father" of toxicology (1500AD)



**The RaPID™
Approach**

RaPID Overview

Current situation in country

RaPID's Approach

Mission

Principles

Process

Activities

Mission

- To conduct pharmacovigilance on behalf of public health programs

and

- To strengthen national pharmacovigilance capacity in developing countries

Guiding Principles

- Establish **complementarity** with National Programs
- Strengthen **local capacity**
- Focus on the **big three killers** (AIDS, TB, Malaria)
- Focus on the **most vulnerable populations**
- **Implement quickly using a ‘RaPID™ Force’**—in months, not years
- **Leverage IT** to connect global specialists
- Use the findings to **formulate policies for patient safety**
- **Ensure sustainability**

RaPID Overview

Current situation in country

RaPID's Approach

Mission

Principles

→ *Process*

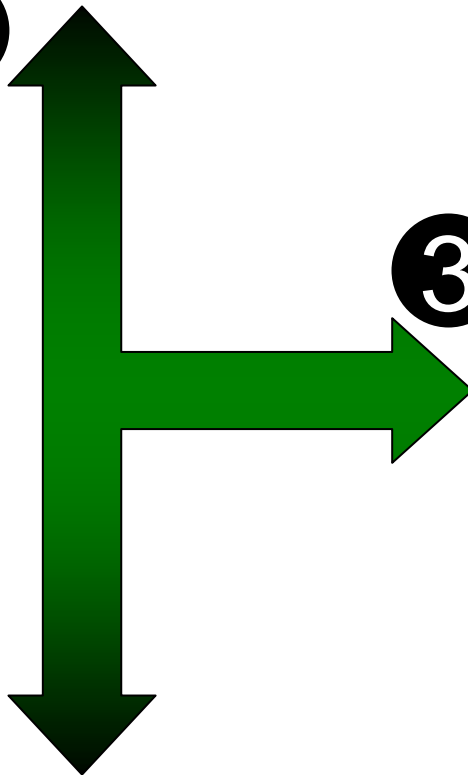
Activities

3 Key Activities of the RaPID™ Program



Data Analysis

2



3



Data Sharing

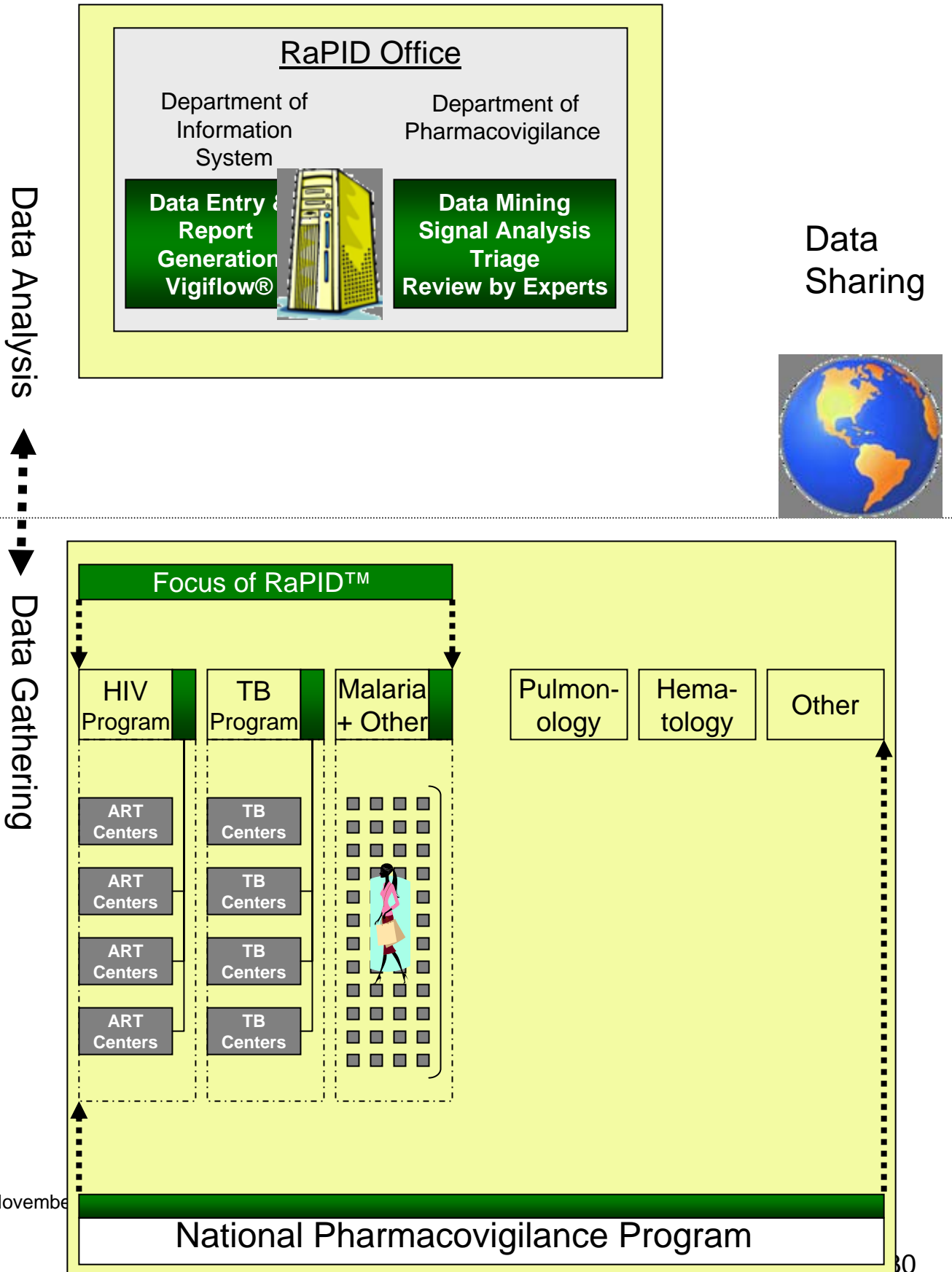
1

Data Gathering

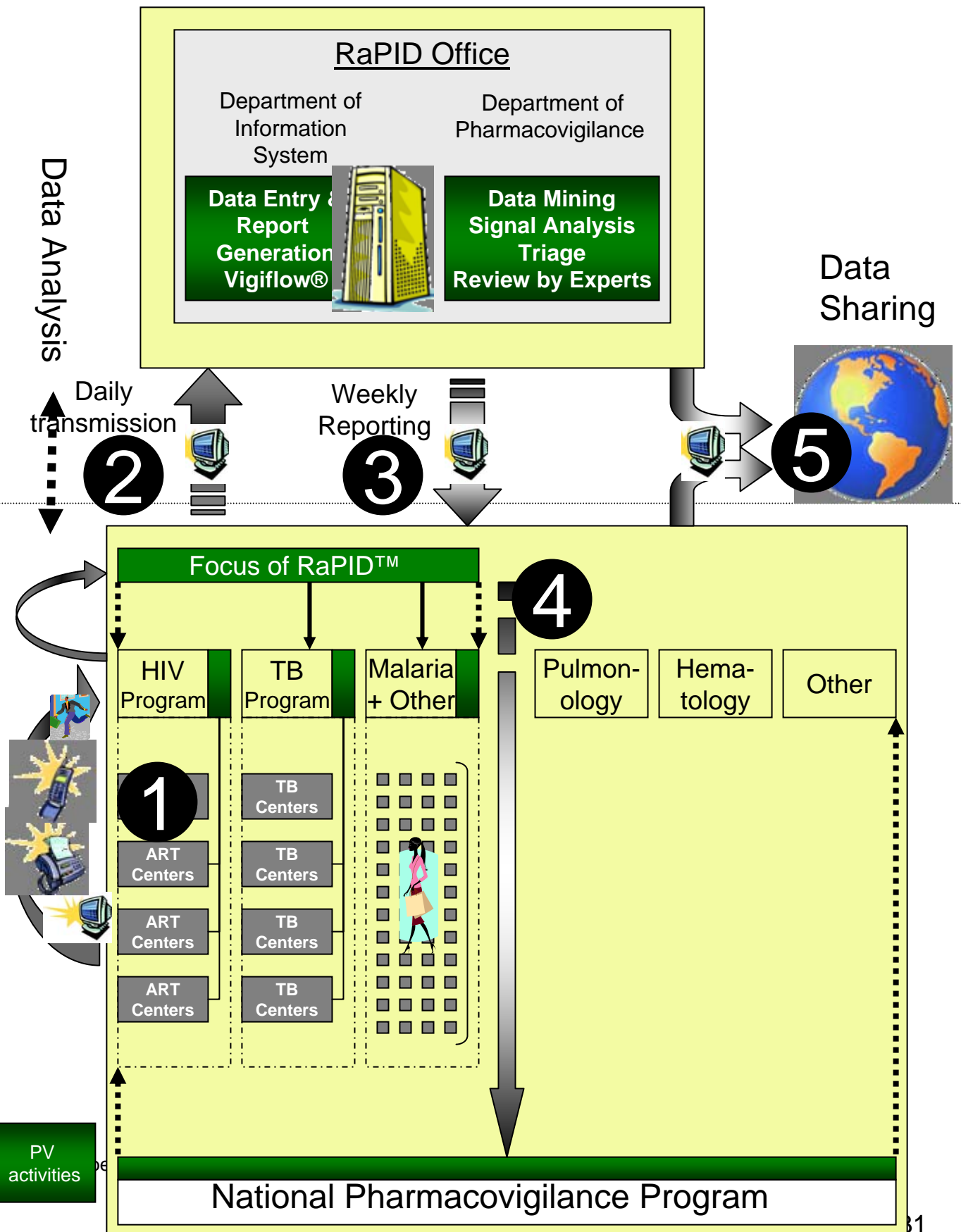


+ In-country partners

Overall Architecture of RaPID™ Program



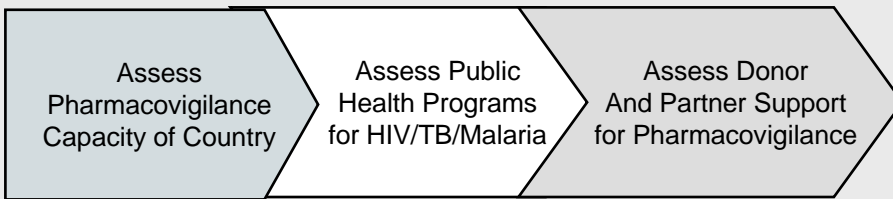
RaPID™ Process Flow



Key activities and roles of partners

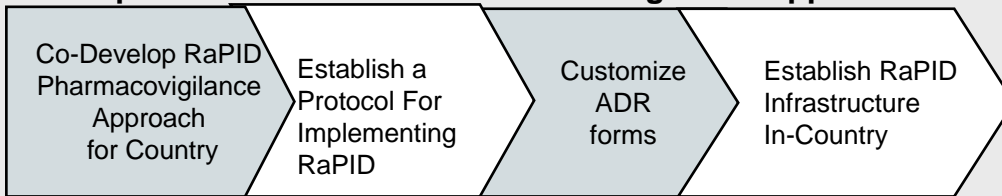
Analyze Pharmacovigilance Capacity In-Country

Implementing Org



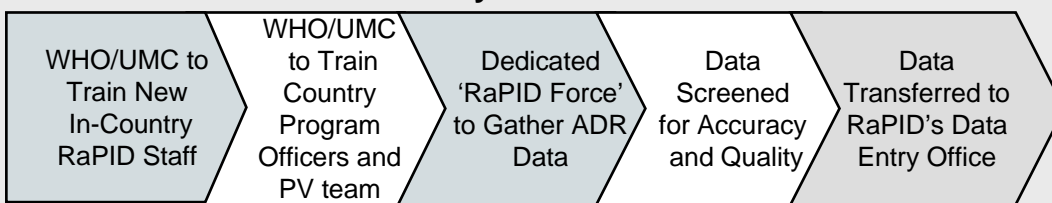
In-country PV Dept, WHO, RaPID team

Develop a Customized RaPID Pharmacovigilance Approach for Program



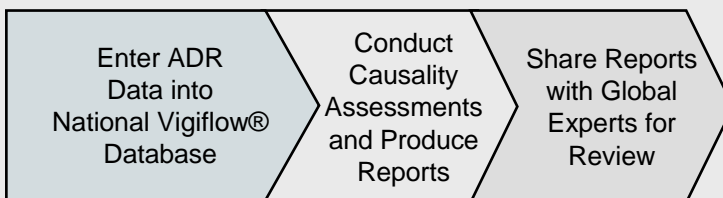
In-country PV Dept, WHO, RaPID team

Gather Data and Ensure Quality



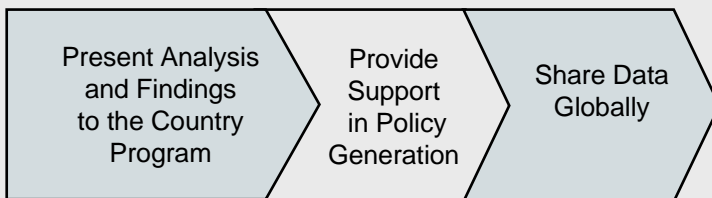
UMC, WHO, Swissmedic, In-country PV Dept, RaPID team

Analyze Data



RaPID Data entry team, In-country PV Dept, UMC, WHO

Provide Support for Policy Change



In-country PV Dept, WHO, UMC, Swissmedic, RaPID team

www.rapidpharmacovigilance.org



Implementing



Upload
ADR
Report

RAPID PHARMACOVIGILANCE IMPLEMENTATION IN DEVELOPING COUNTRIES

HOME | MISSION | CURRENT SITUATION | OUR APPROACH | PARTNERS | TEAM | PUBLICATIONS | CONTACT US



November 2, 2007



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Current Consortia Partners



Uppsala Monitoring Centre (UMC)

An independent centre of scientific excellence, the Uppsala Monitoring Centre is responsible for the collection of data about adverse drug reactions from WHO member states from around the world, and the generation of signals of drugs which might possibly have problematic side-effects. Currently 82 countries are actively contributing to the database.



INDIAN INSTITUTE OF HEALTH MANAGEMENT RESEARCH, JAIPUR

Indian Institute of Health Management Research (IIHMR)

Established in 1984 in Jaipur, IIHMR is the first of its kind of institution in India, with attention solely focused on health systems management. The Institute undertakes training, research and consultancy in health management and has collaboration with international organizations such as UNFPA, UNICEF, WHO, World Bank, ODA, DANIDA, KFW & GTZ, NORAD, CARE and USAID. International collaborations have been established with University of North Carolina, USA to offer masters programs to candidates from South-Asia.



Ecumenical Pharmaceutical Network (EPN)

The Ecumenical Pharmaceutical Network (EPN) is an independent, apolitical non-profit Christian organization that works with its 80 pan-African members to provide health services in 31 countries. EPN's ultimate beneficiaries are in line with the 'Health for All' ideal; however there is a specific emphasis on the poor and the marginalized. The members include Christian Health Associations (CHAs) and Drug Supply Organizations (DSOs).

Swissmedic will collaborate with RaPID on a project basis with a focus on Vigiflow®

November 21, 2007



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Discussions

WHO

MEDICINES STRATEGY

COUNTRIES AT THE CORE

2004-2007



November 2, 2007



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Complementarity to current WHO Medicines Strategy

Quality and safety: assuring the quality and safety of medicines by strengthening and implementation of regulatory and quality assurance standards, with a focus on

- Assuring the quality, safety, and efficacy of priority medicines, especially for HIV/AIDS, TB, and malaria, by establishing standards and training tools.
- Support to national drug regulatory authorities through assessment, information exchange, and capacity building.
- Support to ensure that countries are able to carry out post-marketing safety monitoring of new medicines such as ARVs and antimalarials which are scheduled for use among populations on a wide scale.

Achieving WHO Expected Outcomes

Excerpt from WHO Medicines Strategy:

Meeting the challenges 2004- 2007

Over the next four years WHO
will:

Promote pharmacovigilance
through activities and Annual
Meetings of the National
Centres participating in the
International Drug Monitoring
Programme.

**Collaborate with existing
pharmacovigilance centres
for capacity building** in
countries currently not included
in the Programme.

Maintain normative activities,
including the annual meetings
of the Advisory Committee on
the Safety of Medicinal
Products and the production of
guidelines in the Safety of
Medicines series.

**Increase efforts to provide
training** in pharmacovigilance.

**The RaPID approach
is a way to
accelerate the
implementation of
pharmacovigilance
capacity in country.**

**It is, in effect,
helping to
operationalize
WHO's vision and
strategy**

Enter a new report

From the top menu, choose **report handling** → **new report** you will then be given the choice between entering a **standard case** or a **parent child case** (if your report concerns two persons).

The left hand menu while entering a new report is shown below.

contacts
give feedback
user guide

0.	report info
1.	patient
2.	tests and procedures
3.	medical history
4.	reactions
5.	drugs
6.	assessment
7.	overview
8.	save
9.	print report

The first page shown is the **report info** page. Enter known data in the fields given on this and the following pages. The order of work is shown in the left hand menu. To move to the next page as shown in the menu, either click in the menu or click on **next** at the bottom of the page.

The page **overview** shows the entered data and there it will also be seen if any mandatory fields are missing, or if errors have been found in the entered data.

Do not forget to save the report regularly. While saving it is also possible to add or edit the **report comments** and to generate a **report Id** (unless the report already has an Id).

When a report has been opened for editing, it will be seen as *checked out* for all other users on the **list reports** page. To make the report available for everyone again the user has to *check in* the report. To do this choose **report handling** → **list reports** in the top menu, find the report in the list and click on the link *check in* next to the report.

List of reports page



- report handling
- search and statistics
- exit
- new report
- send report
- list reports

To display the reports that are to be assessed, click on list reports.

- contacts
- give feedback
- user guide

List of reports

After specifying your search criteria, press the refine button to see all reports to be assessed.

(dd mm cory) (dd mm cory)

report id from to 2006-00023

regional centre

sort by Receive date

include reports under regional assessment yes no

Regional Centres cannot search on List of reports page.

This code (year - five digits) is the report Id.

To view a report in the list, click on the view icon.

To commit a complete report, click on the commit icon. (Not for Regional Centre.)

To add comments to a report, click on the comment icon and edit.

To open a report in the list, click on the edit icon.

To set a report as a duplicate, click on the duplicate icon. (Not for Regional Centre.)

To print several reports in the list, check the boxes and click the print selected reports button.

To print a report in the list, click on the print icon.

Click on the link check in when you have finished editing a report, to make it available to others.

Reports with suggested ADRs and/or drugs from the UMC											
Header	Receive date										
<input type="checkbox"/> 2006-00005 test	27 01 2006 (158)										
Reports under central assessment											
Header	Receive date	Created by	Checked out by								
<input type="checkbox"/> 2006-00007 Uncodedtest-drug	25 01 2006 (157)	ncoster									
<input type="checkbox"/> 2006-00006 testUncodedDrug	25 01 2006 (157)	ncoster									
<input type="checkbox"/> 2006-00013 Test uncoded 2006-01-27	27 01 2006 (155)	ncoster									
<input type="checkbox"/> 2006-00009 Test-Title change NC 2006-01-27	27 01 2006 (155)	ncoster									
<input type="checkbox"/> 2006-00011 Test - send to NC	27 01 2006 (155)	ncoster									
<input type="checkbox"/> 2006-00017 date check after reassess	29 01 2006 (153)	ncoster	ncoster								
<input type="checkbox"/> 2006-00022 AT (2) test 1-2-3	31 01 2006 (151)	ncoster									
<input type="checkbox"/> 2006-00023 AL audit trail test 1-2-3	31 01 2006 (151)	ncoster									
<input type="checkbox"/> testing 2006-02-01											
<input type="checkbox"/> test 2006-02-08											
Reports under regional assessment											
Header	Change date	Created by	Checked out by								
<input type="checkbox"/> Test-New report	30 06 2005 (98)	rcster	rcster								
<input type="checkbox"/> 2006-00010 Test report [d 2006-01-27	14 02 2006	rcster	rcster								
<input type="checkbox"/> test - new report		rcster	rcster								
<input type="checkbox"/> 2006-00012 Test-Report Id (no delete) 2		rcster	rcster								
<input type="checkbox"/> Empty report		rcster2									
<input type="checkbox"/> 2006-00004 TestRC2		rcster	rcster								
<input type="checkbox"/> 2006-00016 Test-IF+rc2		rcster									

To delete a report in the list, click on the trash icon. You can only delete reports you have created yourself and only reports without a report Id.

Report info page

the UPPSALA MONITORING CENTRE

report handling search and statistics exit
new report send report list reports

contacts give feedback user guide

0. report info
1. patient
2. tests and procedures
3. medical history
4. reactions
5. drugs
6. assessment
7. overview
8. save
9. print report

Report information - standard case

date received at regional centre: 00 01 2006 (dd mm ccyy)

date first received at national centre: (dd mm ccyy)

report title:

type of report: spontaneous

serious: yes no [clear](#)

reason for seriousness:

- death
- life-threatening
- hospitalization/prolonged
- disabling
- congenital-anomaly
- other medically important condition

country of occurrence: country of reporter:

Information on sender

sender: pharmaceutical company regional pharmacovigilance center [clear](#)
 other

sender identifier/organization:

person responsible:

Other sender case identifiers:

[add new identifier](#)

Information about the reporter

given name: family name:

institution: street address:

postal code: city:

telephone: fax:

e-mail:

reporter qualification: physician pharmacist [clear](#)
 lawyer other health professional
 consumer or other non health professional

[check entries](#) [next](#)

To give feedback to the UMC at any time during the process, click on the *give feedback* link.

To start entering a report, select *new report* from the top menu.

The top menu contains general functions for handling reports, e.g. listing and sending reports.

To see or download the User Guide, click on the *user guide* link.

The *error* icon will warn you of invalid entries.

To complete a report, go through the steps given in the left hand menu.

The *warning* icon indicates e.g. mandatory fields.

At any time during the process, you can choose to print the report by clicking on the link *print report*.

The *help* icon will give you help with the field it is located next to.

When you are working with a report, after completing a step, click the *check entries* button to refresh your information, generate or remove error messages, etc.

The link *clear* will remove your choice in the field it is located next to.

The *next* button will take you to the next page according to the left hand menu, unless you have an unresolved error message on this page.

Drugs page

MONITORIN CENTRE

report handling
new report

no ID - no header

List of suspected drugs

[delete](#) Acetylsalicylic acid
[delete](#) Paracetamol [move up](#)
[Add new drug](#)

List of concomitant drugs

[delete](#) Minerals [nos](#)
[Add new drug](#)

0. report info
1. patient
2. tests and procedures
3. medical history
4. reactions
5. drugs
6. assessment
7. overview
8. save
9. print report

Suspected drug (Acetylsalicylic acid)

drug name [Acetylsalicylic acid](#) [delete](#)
[enter drug](#) ?

characterization Suspect Interacting [change to concomitant](#)

suspected ingredient [dropdown]
batch number [input]
dose [input] [input] [input] ?
start of administration [input] [input] [input]
(dd mm ccyy)
duration [input] [input] [input] [input] ?
indication [input] code [search term](#)

action taken drug withdrawn dose reduced [clear](#)
 dose increased dose not changed
 unknown not applicable

is the ADR adequately labelled [input] ?

comments [input]

frequency of intake [input] [input] [input] ?
end of administration [input] [input] [input]
(dd mm ccyy)
route of administration [dropdown]

was a rechallenge performed yes no [clear](#)
 unknown

did reaction recur after rechallenge yes no [clear](#)
 effect unknown

If you can switch between suspected drugs that you have entered, to add more information on each drug.

If you click on the link *move up* you can choose to sort the drugs in a specific order.

Here you can switch between concomitant drugs that you have entered, to add more information on each drug.

If you click on the link *delete*, you will delete the selected drug and corresponding information from the report.

To add a new concomitant drug, click on the *Add new drug* link here.

To add a new suspected drug, click on the *Add new drug* link here.

If an appropriate drug is not found, suggest a new drug by clicking on the *enter drug* link.

Relatedness of drug to reaction
(* = Yes - if reaction recurred after rechallenge)

	Acetylsalicylic acid	Paracetamol
Dyspepsia	Probable [dropdown] [trash] [add]	
	yes [dropdown] *	
Nausea	Unlikely [dropdown] [trash]	Possible [dropdown] [trash]
	unknown [dropdown] *	
Diarrhoea	No relationship [dropdown] [trash]	Unlikely [dropdown] [trash]
	no [dropdown] *	
Allergic reaction [add]		Unlikely [dropdown] [trash]

This is the causality assessment. It is available on both reactions and drugs page.