

# **Research networks involved in post-market pharmacovigilance in the United States, United Kingdom, France, New Zealand, Australia, Norway and European Union: Lessons for Canada**

Wiktorowicz M.E., Lexchin J., Paterson M., Mintzes B., Metge C., Light D., Morgan S., Holbrook A., Tamblyn R., Zaki E., Moscou K.

## **Acknowledgements**

We would like to thank our co-sponsors: the Canadian Patient Safety Institute and the Canadian Institutes of Health Research for sponsoring the project as well as the national organizations that collaborated to support this initiative: The Canadian Agency for Drugs and Technologies in Health, Statistics Canada, the Canada Health Infoway, the Canadian Institute for Health Information and the Canadian Health Services Research Foundation.

We are also grateful for the contributions of the steering committee members: Noralou Roos, Tony Chin, Joseph Gebran, Cynthia Woodman, Michael Wolfson and Liz Stirling.

## Table of Contents

<b>Main Messages .....</b>	<b>3</b>
<b>Executive Summary .....</b>	<b>5</b>
<b>List of Acronyms.....</b>	<b>8</b>
<b>Introduction .....</b>	<b>9</b>
<b>Current Situation in Canada.....</b>	<b>10</b>
<b>Methods .....</b>	<b>12</b>
<b>Results.....</b>	<b>12</b>
<b>1) Regulators approach to postmarketing surveillance .....</b>	<b>12</b>
a. Improving passive ADR reporting: Links to the healthcare system .....	12
b. Active pharmacovigilance: Prescription Event Monitoring and Database mining .....	14
c. Monitoring completion of industry-sponsored Phase IV studies .....	17
d. Regulators’ access to research networks .....	20
<b>2) Drug Benefit Plans’ approaches to ‘real-world’ safety and effectiveness research ...</b>	<b>25</b>
a. Industry sponsored research .....	25
b. Intramural research.....	27
c. Drug Benefit Plans’ Access to Research Networks .....	29
<b>3) Coordinating Regulators’ and Drug Plans’ commissioned research .....</b>	<b>29</b>
a. Public oversight of research funding.....	29
b. Research networks’ independence and capacity to address safety issues .....	30
c. Pharmaco-surveillance Research Network Funding and Infrastructure.....	30
d. Coordinating regulatory agencies’ and drug benefit plans commissioned research .....	32
<b>Conclusion and Recommendations.....</b>	<b>32</b>
<b>References .....</b>	<b>39</b>
<b>Schematic Figures: International research networks .....</b>	<b>48</b>
Figure 1 International Pharmacovigilance Research Network Framework .....	48
Figure 2 US Health Providers and Health Authorities Network Model .....	49
Figure 3 US Pharmacovigilance Networks’ Policy Environment and Governance .....	50
Figure 4 Centers for Education on Research and Therapeutics (CERTS).....	51
Figure 5 Developing Evidence to Inform Decisions about Effectiveness (DECIDE).....	52
Figure 6 FDA and VA-MedSAFE Health Plan Dyadic Linkage Model .....	53
Figure 7 VA-MedSAFE Channels for Communication and Dissemination of Information .....	54
Figure 8 New Zealand Pharmacovigilance Center at the Otago University Medical School...	55
Figure 9 Vigilance Risk Management of Medicines Division (VRMM) .....	56
Figure 10 MHRA Pharmacovigilance Risk Management .....	57
Figure 11 French Pharmacovigilance Systems .....	58
Figure 12 UK Research Network.....	59

## **Main Messages**

- Safety of prescription drug products is a major issue and is becoming increasingly important.
- A coordinated research effort by research networks, Health Canada and drug plans is key to drug safety. Such an approach will inform Health Canada, particularly as it considers a shift to progressive licensing, and drug plans giving them a better understanding of the public health impact of medicines and helping to ensure optimal use of limited public budgets.
- A proactive strategy incorporates best international practices:
- **Active surveillance** is key to identifying the cause of unexpected ADRs. US FDA and VA have a Memorandum of Understanding to share information from data mining of VA's administrative database, to identify safety issues and offer responsive feedback to the FDA.
- **Coordination of research and information dissemination among regulatory authorities, drug benefit plans and academic research networks** can enhance regulators' capacity to investigate safety and effectiveness issues:
  - US FDA coordinates with VA and the DeCIDE and CERTs research networks.
  - France's regulatory agency coordinates with the Transparency Commission and Regional Pharmacovigilance Centres.
  - NZ's regulatory agency coordinates with the National Pharmacovigilance Centre.
- **Regional Pharmacovigilance Centres** in France offer a link to clinical care that facilitates prospective observational studies as safety issues arise. The integration of Regional Centres within the health care system also offers a framework to conduct 'real world' RCTs.
- **Research networks** make studies possible in areas in which manufactures have a *disincentive* to investigate (e.g. drug class head-to-head product comparisons).

- ***Public oversight of independently conducted postmarketing research*** permits third party review of study protocols, avoids proprietary data conflicts, and allows vetting of industry conclusions to alleviate doubts about the validity of research results.
- ***New drugs with an uncertain safety profile and the potential for large scale use*** should undergo a ‘phased introduction’ by drug plans. An Only in Research (OIR) assessment can limit the use of publicly funded medicines until ‘real-world’ safety and effectiveness of new medicines is determined.
- ***Inadequate funding*** of pharmacosurveillance research network threatens their stability and therefore their ability to retain necessary expertise to address emergent issues.
- ***Risk Management Plans*** introduced in the European Union do not involve a rigorous risk assessment, and risk management study methods have not been standardized, leading RMPs to offer the impression of risk management without evidence as to their effectiveness.

## **Executive Summary**

Our report highlights the role research networks can play in pharmacosurveillance and how the knowledge they produce can be used by drug regulators and drug benefit plans. Examples of how regulators and drug benefit plans can generate pharmacosurveillance research are also included.

### **1) Regulators are adopting innovative approaches to pharmacosurveillance**

#### **a. Improving passive ADR reporting: Linkage to the healthcare system**

- Pharmacovigilance centres in *New Zealand, France and Norway* are connected to healthcare facilities which improves responsiveness to ADR reporting: experts can request additional information of the reporter and offer suggestions in real-time.
- The *US NEISS-CADES* system in hospital emergency departments is more efficient at capturing ADRs than a system of voluntary reporting.

#### **b. Active pharmacovigilance: Data-mining of healthcare data bases**

- ***Prescription Event Monitoring*** used in *NZ*, by the *UK Drug Safety Research Unit*, and for select medicines in *France* provides an early look at the safety profile of selected new drugs by following patients with prescriptions over a period of time.
- ***Data mining***: *US* Veteran Affairs analyzes its database of ADR reports and targets drugs causing the most ADRs for further investigation. *VA MedSafe's* electronic records include outpatient pharmacy and hospital data that allows researchers to link specific drugs with treatments and hospitalizations. *Scotland's Medicine Monitoring Unit* mines its database of linked patient prescriptions, hospitalizations, doctors' visits and death certificates.

#### **c. Monitoring completion of industry-sponsored Phase IV studies:**

- *NZ's* Pharmacovigilance Research Centre conducts commissioned postmarketing studies.
- *France's* Regional Pharmacovigilance Centres support industry-sponsored postmarketing research, but study completion is not enforced.

- US FDA can impose fines on companies that do not complete agreed-to Phase IV studies.
- EMEA's 5-year authorization renewal is *not* conditional on completing postmarketing studies.

**d. National regulators' access to research networks informs their decision-making:**

- *New Zealand's* Medsafe holds meetings with its National Pharmacovigilance Centre members to discuss safety issues and develop its research agenda.
- *UK's* MHRA Pharmacovigilance Expert Advisory Group meets monthly to discuss and offer independent advice on pharmacovigilance. MHRA's Vigilance and Risk Management of Medicines Division engages external research centres to enhance its intelligence.
- US FDA has relationships to research networks through the DEcIDE and CERTs.
- US FDA's Memorandum of Understanding with VA will promote better data sharing.
- *France's* AFSSaPS' relationship with 31 Regional Pharmacovigilance Centres enhances its pharmacovigilance research capacity.
- An EU-wide network of researchers will enable regulators to commission studies on product safety and will expand the methodological approaches to pharmacovigilance.

**2) Coordinating Regulators' and Drug Plans commissioned research**

**a. National commissioning and oversight of post-marketing research** by research networks - *US* DEcIDE, *NZ* Pharmacovigilance Centre, *French* Regional Pharmacovigilance Centres - addresses real world safety, effectiveness, and use of medicines and ensures accountability for: **a) Funding:** funds are allocated to arm's length research centres; **b) Validity:** public oversight helps ensure scientific validity; **c) Independence:** regulators and drug plans commission research that generates publicly accessible rather than proprietary data, including head-to-head drug studies

**b. Research networks require stable funding and infrastructure:**

- Pharmacoepidemiologic research capacity and expertise is limited, requiring stable funding.

- Epidemiologic observational studies call for an infrastructure of linked healthcare data bases.
- Real world clinical trials rely on research centre links to practicing clinicians.
- **Research resource models:** *Italian Medicines Agency:* drug companies contribute 5% of their yearly promotional budgets to a national fund that supports publicly sponsored post-marketing research on real world clinical end-points and pharmacoepidemiology studies.
- *UK CRC* draws on a bank of scientific experts to expand its pharmacovigilance capacity.

**c. Research centers' expertise and database access enables them to identify safety issues:**

- *US FDA* issues 1-2 year task-orders to DEcIDE Centers to address emerging safety issues.
- *New Zealand's* Medsafe commissions research from its National Pharmacovilance Centre.
- *France's* Agency for the Safety of Medicines (AFSSaPS) commissions targeted studies from its Regional Pharmacovigilance Centres to address safety issues regarding new medicines.
- Research Networks' independence to pursue research topics is key to expanding the scope of pharmacovigilance methodological approaches and studies e.g. *US CERTs*

**d. Drug Benefit Plans' access to research networks supports decision-making:**

- *US VA* uses its pharmacovigilance data to determine the drugs on its formulary and whether to impose conditions on their use.
- *UK NHS* includes drugs with a favourable recommendation from NICE in its insurance plan.
- *UK NICE Only-in-Research* designation limits the use of new medicines until enough patient years experience is gathered to determine 'real-world' safety and effectiveness.
- *France's* national drug benefit plan requests drug sponsors to commission studies from the Regional Centres to support decisions on formulary listing and level of reimbursement.

**e. Coordinating regulatory agencies' and drug benefit plans commissioned research**

- A 'Comité de liaison' in *France* enables joint discussions between the regulator, the drug benefit plan and the research network to coordinate concurrent postmarketing studies.

## **List of Acronyms**

ADR =	Adverse Drug Reaction
AFSSaPS =	Agence Francaise de Securité Sanitaire des Produits de Santé
AHRQ =	Agency for Healthcare Research and Quality
DEcIDE =	Developing Evidence to Inform Decisions about Effectiveness
CERTs =	Centers for Education and Research on Therapeutics
CHM =	Commission on Human Medicines
DOH =	Department of Health
DSRU =	Drug Safety Research Unit
EAG =	Expert Advisory Group
EMA =	European Medicines Agency
FDA =	Food and Drug Administration
GATC =	Genotype-specific Approaches to Therapy
GPRD =	General Practice Research Database
HAS =	Haute Autorité de Santé
IMMP =	Intensive Medicines Monitoring Programme
MAH =	Marketing Authorization Holder
MARC =	Medicines Adverse Reactions Committee
Medsafe =	Medicines and Medical Devices Safety Authority
MEMO =	Medicines Monitoring Unit
MHRA =	Medicine and Healthcare products Regulatory Authority
MOU =	Memorandum of Understanding
MS =	Multiple Sclerosis
NEISS-CADES =	National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance
NHS =	National Health Service
NICE =	National Institute for Health and Clinical Excellence
NIHR =	National Institute of Health Research
NOC/c =	Notice of Compliance with conditions
NoMA =	Norwegian Medicines Agency
NPSA =	National Patient Safety Agency
NZ =	New Zealand
OIR=	Only in Research
PBAC =	Pharmaceutical Benefits Advisory Committee
PEM =	Prescription Event Monitoring
PHI=	Public Health Impact
PASS =	Post-authorization Safety Study
RCT =	randomized controlled trial
RMP=	Risk Management Plan
UK =	United Kingdom
UKCRC =	United Kingdom Clinical Research Collaboration
US =	United States
VA =	Veteran Affairs
VAMedSAFE =	VA Center for Medication Safety
VRMM =	Vigilance and Risk Management of Medicines

## **Introduction**

Although pharmaceuticals are assessed for pre-market safety and efficacy, their evaluation involves a risk-benefit analysis recognized as incomplete given the much larger postmarketing experience to follow.<sup>1-4</sup> The market for a product once it has been approved most often includes patient and disease groups never assessed in pre-market clinical trials.<sup>5</sup> Canada's lack of systematic prospective monitoring of drugs once they are marketed means that adverse drug reactions (ADRs) are often not uncovered until years after a drug is on the market. The result is that drugs with unacceptable harm/benefit ratios remain on the market for prolonged periods of time<sup>6</sup> and Canadians are left exposed to these unanticipated risks. It seems counterintuitive that just as a new drug enters the market and its use increases exponentially, its effects and patterns of use are no longer systematically monitored.

As Food and Drug Administration (FDA) representatives note, "...the immense biological subtlety of human pharmaceuticals often cannot practically or adequately be detected in formal clinical studies."<sup>7</sup> ADRs are between the 4th and 6th leading cause of death in the US, contributing to more than 100,000 deaths and 1.5 million hospitalizations yearly.<sup>8,9</sup> Experts advise a risk assessment plan be in place for each new medicine to monitor its safety and effectiveness based on how it is used, particularly in groups not tested and for off-label uses.<sup>10</sup> The European Medicines Agency (EMA) requires a risk management plan for new drugs.<sup>11, 12</sup> Although the EMA system has not been in place for long enough for effectiveness to be evaluated, in principle the requirement for systematic planning of post-approval safety studies as a precondition of market approval is sound, as long as it is not introduced as a trade-off for lower pre-market safety and effectiveness standards.

Developing a pharmacovigilance system and carrying out the research is a complex process. Questions remain as to the type of evidence needed to inform regulatory and

reimbursement decisions, and the respective roles of observational studies and randomized controlled trials. These decisions are often complicated because determining the cause of adverse events is usually based on observational studies not randomized controlled trials (RCTs).<sup>13, 14</sup> How best to fund, oversee, conduct and disseminate the research are other important issues to address.

In this report we highlight the role research networks can play in pharmacosurveillance<sup>1</sup> and how the knowledge they produce can be used by drug regulators and drug benefit plans (Figure 1). Examples of how information can be generated by regulators and benefit plans is also included. Our findings are organized around themes that highlight the organization, capacity and funding of research networks in the 7 jurisdictions assessed and give examples of best practices. We conclude by offering recommendations based on best practices to guide the establishment of a Canadian pharmacosurveillance research network.

### **Current Situation in Canada**

Most information available to the Canadian regulator and public drug plans about postmarketing drug safety comes from voluntary ADR reports. In 2006, Health Canada received over 10,500 reports of domestic suspected ADRs. These reports are submitted to one of 7 regional centres or directly to Ottawa. Health Canada also received over 250,000 reports of foreign ADRs.<sup>15</sup> Domestic reports are publicly accessible on a searchable web site. (<http://cpe0013211b4c6d-cm0014e88ee7a4.cpe.net.cable.rogers.com/CADRMP/LocaleAction.do?lang=en>). Health Canada has recently issued a draft guidance document about triggers for issuance of risk communication documents (available at: <http://dsp.psd.pwgsc.gc.ca/collection/2007/hc-sc/H164->

---

<sup>1</sup> The World Health Organization (WHO) defines pharmacosurveillance and pharmacovigilance as “terms used to refer to the monitoring of drug safety, for example, by means of spontaneous adverse-effect reporting systems, case-control and cohort studies.” The terms will be used interchangeably in this report.

[48-2007E.pdf](#)) but it is unclear what methodology and information it uses in making its decisions.

The Marketed Health Products Directorate has about one-fifth the budget allocation and personnel compared to the Therapeutic Products Directorate<sup>16</sup> and cannot routinely evaluate all ADR reports for causation because of resource constraints.<sup>17</sup> If a drug is approved with a Notice of Compliance with conditions (NOC/c) then heightened postmarketing safety monitoring may be imposed, but a NOC/c cannot be issued if there are unresolved safety issues.<sup>18</sup>

The province of Alberta recently initiated a program to monitor biologic agents used in the treatment of rheumatologic diseases.<sup>19</sup> The program consists of a partnership between academic and community rheumatologists, government and industry where patients' access to therapy is conditional on participation in a pharmacovigilance study that assesses effectiveness, safety, and cost-benefit. The program is funded by industry but administered by government.

In a 2005 review, Carleton et al.<sup>20</sup> documented sources of data available to Health Canada and provincial drug plans. The Pharmaceutical Outcomes and Policy Innovations Programme based at the BC Children's and Women's Health Centre, has several projects designed to inform the drug regulatory process. Examples include: (a) Suspected paediatric ADRs reported to the Canadian Adverse Drug Reaction Monitoring Programme; (b) ADR reporting within the Canadian Paediatric Surveillance Program; (c) Genotype-specific Approaches to Therapy (GATC) in Childhood active surveillance network for adverse drug reactions.

GATC has completed three years of study and will continue until December 2008, incorporating more than 1000 serious ADRs and more than 7000 controls.<sup>20</sup> The most innovative aspect is the comparative group of data collected from drug-matched controls. More than 10,000 cases/controls are anticipated by December 2008. Finally, several Canadian academic/research units provide postmarketing surveillance expertise to provincial drug plans on a contract basis or

with year-to-year funding. Some, like the Institute for Clinical Evaluative Sciences in Toronto, the Population Health Research Unit at Dalhousie University, and the Manitoba Centre for Health Policy, have a group of researchers who focus on prescription drug issues within a larger research unit. Some studies are funded by peer reviewed grants and some are funded directly by provincial drug plans. Drug plans are included as supporters or collaborators in the case of some grant-funded studies, but not as investigators.

## **Methods**

Our analysis compares and highlights best practices regarding research networks that support national and international systems of pharmacovigilance to address questions of safety and effectiveness of medicines, with some examples of cost-effectiveness. We examine research networks dealing with pharmacovigilance in the European Union through the EMEA and six countries: the United States (US), the United Kingdom (UK), France, New Zealand (NZ), Australia and Norway. (The order in which the countries are listed reflects their contribution to the information in the report.) Countries were chosen to include jurisdictions with a range of mechanisms and innovations for drug regulation, postmarketing pharmacovigilance and public drug plan reimbursement. Countries with different levels of resources available to monitor drug safety were also included. Our research combined literature and government document review with qualitative policy analytic methods that involved interviews with international key informants within national drug regulatory agencies and drug benefit evaluation organizations.

## **Results**

### **1) Regulators approach to postmarketing surveillance**

#### **a. Improving passive ADR reporting: Links to the healthcare system**

Passive ADR reporting systems world-wide are generally considered to capture only 1-10 percent of all reactions and that figure may in fact be considerably lower.<sup>21</sup> British data based on

a direct comparison between spontaneous ADR reporting and an observational event monitoring system for a group of more than 44,000 patients suggests that under-reporting may be as high as 98 percent.<sup>22</sup> One French study estimated that as few as 1 in 24,000 reactions in general were reported to the Regional Pharmacovigilance Centres. Even for serious and unlabelled reactions the estimate was 1 in 4600.<sup>23</sup> Moore and colleagues note that while the US FDA received an average of 82 reports about ADRs related to digoxin annually, greater than 200,000 hospitalizations were due to ADRs secondary to digoxin over seven years, uncovered through data-mining of hospital records.<sup>24</sup> ADR reporting can be invaluable as a method of first detecting potential problems with medications<sup>25</sup> but in order for it to function optimally it needs to capture a far greater percentage of events.

In 2003, the US Centers for Disease Control and Prevention, in collaboration with the Consumer Product Safety Commission and the FDA, created the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project.<sup>26</sup> The NEISS-CADES project reviews emergency department charts in the 64 cooperating hospitals looking for keywords and diagnoses that would indicate ADRs (Figure 2). Researchers from outside the network have used the data, for example, in a study documenting adverse events associated with stimulant medications used for attention deficit hyperactivity disorder.<sup>27</sup> This system is more efficient at capturing ADRs than a system of voluntary reporting.

In France, reports are made to Regional Pharmacovigilance Centres which means their experts can request additional information from the reporter and offer suggestions in real-time to address the problem, or make suggestions for subsequent actions to clarify the causal link, such as product 'challenge, de- and re-challenge'. The level of ADR under-reporting in France appears to be similar to that of other countries (<5% of ADRs reported) despite a system of mandatory reporting for health professionals.<sup>28-31</sup>

In the UK, public and regulatory agencies along with the Drug Safety Research Unit (an independent research charity), independently collect ADR reports. Although confusion may exist in the public's eye between data the National Patient Safety Agency (NPSA) collects and Medicine and Healthcare products Regulatory Authority's (MHRA's) Yellow Card scheme, and general practitioners tend to see the yellow card and the green form sent by the Drug Safety Research Unit (DSRU) as the same, triple agency reporting may increase the reporting rate (UK Key Informants 1, 3). Cooperation exists between agencies whereby NPSA transmits to MHRA consumer ADR reports that correspond with MHRA reporting criteria.

New Zealand has the highest reporting rate of ADRs of all member countries in the World Health Organization International Drug Monitoring program both in terms of reports per 1000 doctors and reports per million population.<sup>32, 33</sup> However, as it is estimated that only 5 - 10 percent of all reactions are reported, there is still room for improvement. New Zealand's higher reporting rate is due to several factors: staff in the Centre for Adverse Reactions Monitoring are committed to providing feedback to individuals filing reports; outreach strategies, such as presentations on a monthly basis to health care providers are used to promote the Centre's services and activities; education about ADR reporting is integrated into medical curricula; ADRs experienced by individuals are recorded with their National Health Index (NHI) number; previous ADRs are thus available to hospitals and increasingly general practitioners, through linkage with the NHI number, so that healthcare professionals are sensitized to look for future ADRs in these individuals (NZ Key Informant 1).

**b. Active pharmacovigilance: Prescription Event Monitoring and Database mining**

Many drug safety withdrawals are made solely on the basis of spontaneous ADR reports. In France for example, spontaneous case reports were the sole evidence supporting the removal of more than half (12 of the 21) of the drugs withdrawn from the market between 1998 and 2004,

while spontaneous reports combined with case-control or cohort studies (with comparison group) provided the needed evidence for one quarter of the withdrawals (4 of 21).<sup>34</sup> For many products, the signals generated by spontaneous reports thus had to be confirmed by methods that allowed hypothesis testing through pharmacoepidemiological studies. Research suggests that published case reports are, in fact, seldom subjected to formal confirmatory investigation.<sup>35</sup> Active pharmacosurveillance methods are thus an important adjunct to evaluation of passively reported ADRs, and methods for such studies include Prescription Event Monitoring (PEM) and interrogation of ADR databases and healthcare databases.

PEM is a system whereby all prescriptions issued for particular drugs over a specified period of time are collected and the patients issued these prescriptions are tracked to look for any untoward events. The Intensive Medicines Monitoring Programme (IMMP) based at the University of Otago in NZ undertakes prospective observational cohort studies of selected new drugs. The cohorts are established from prescription data received from hospital and community pharmacies. Questionnaires are sent to the prescribers at regular intervals following receipt of the pharmacy printouts requesting information on any adverse events that have occurred since the most recent prescription.<sup>33</sup> While the IMMP obtains spontaneous adverse event reports filed by doctors, it does not undertake computer searching of clinical records at this time.

The UK's DRSU also conducts PEM. An electronic copy of targeted prescriptions, written by general practitioners and submitted to the Prescription Pricing Authority for claims reimbursement, is transmitted to the DRSU. The DRSU requests prescribers of target medicines to voluntarily complete a 'green card form' questionnaire for each patient detailing any adverse drug event(s), including deaths, following the prescription of newly marketed drugs.<sup>36, 37</sup> The DSRU which is funded by drug companies is the only agency in the UK that is approved by the ethics board to collect National Health Service (NHS) prescription data. Drug companies or

MHRA can ask the DSRU to conduct a PEM study, but the DSRU decides which studies it will undertake as it may not have the interest or capacity to conduct an MHRA recommended PEM study.

There are however wide differences in the reporting rates for PEM programs. For example, in one review of NZ doctors participating in the IMMP, 80 percent of the questionnaires sent to doctors were returned.<sup>38, 39</sup> Conversely, a UK study of PEM for 58 newly marketed drugs found an average of 58.2% (range 39.6 to 74.1%) forms were returned by doctors to the DSRU.<sup>40</sup> This figure of 60% has remained stable in more recent research.<sup>41</sup> A review of a UK PEM carried out by the DSRU revealed an inverse reporting relationship, whereby the more patients prescribed a targeted medicine by one physician and consequently the more green forms the physician was sent, the fewer were returned.<sup>41</sup>

France also undertakes prospective monitoring of particular drugs through one or more of its 31 Regional Pharmacovigilance Centres. As one example, the National Pharmacovigilance Committee of the Agence Francaise de Sécurité Sanitaire des Produits de Santé (AFSSaPS) commissioned a prospective postmarketing observational study to detect rare but severe or unexpected adverse effects associated with the Prevenar® vaccine.<sup>42</sup> Moreover, regular monthly meetings of the Technical Pharmacovigilance Committee, comprised of directors of the Regional Pharmacovigilance Centres, determine whether a potential ADR merits study, in which case it is referred to the National Pharmacovigilance Commission which considers whether to involve the Regional Centres in a follow-up survey.

The Medicines Monitoring Unit (MEMO) is an independent research unit established by the University of Dundee in Scotland that engages in retrospective hypothesis testing case-control and cohort studies using data sets derived from prescriptions, hospitalizations and death certificates. The research is enabled by Tayside Scotland's policy of assigning a unique

identifying number to each patient registering for care by a general practitioner.<sup>43</sup> By data mining all Scottish prescriptions of a selected drug, MEMO is able to conduct prospective Phase IV<sup>2</sup> studies in which patients in primary care are observed for exposure to a particular drug and their health outcomes assessed.<sup>44</sup>

Finally, the US FDA Amendments Act passed in September 2007 calls for the creation of a new database of 25 million patient hospital and insurance records to be scanned for trends in side effects of certain drugs by 2010.<sup>45</sup> In addition, FDA has developed software to help epidemiologists to more efficiently mine spontaneously-reported ADRs. [See: <http://www.fda.gov/cder/Offices/OPaSS/datamining.htm>]

### **c. Monitoring completion of industry-sponsored Phase IV studies**

The US FDA formerly had limited authority to enforce the implementation of postmarketing studies: 91% of postmarketing commitments were based on FDA requests but lacked a statutory or regulatory basis. The FDA only had the legal authority to require postmarketing studies in such cases as: accelerated approval, clinical benefit studies, or pediatric studies.<sup>46, 47</sup> In 2006, 71% of postmarketing study commitments were pending, meaning the study had not been initiated, and did not meet *a priori* criteria for delay.<sup>48</sup> The FDA Amendments Act now gives FDA the ability to fine companies to help ensure postmarketing study completion.

Post-approval studies may be required if other reports and active surveillance are insufficient to answer safety questions. Post-approval clinical trials can be mandated only if post-approval studies are insufficient. Timetables are to be established for completing each study or trial. Failure to meet the timetable raises the specter of fines, unless there is good cause, as determined by FDA.<sup>49</sup>

Conversely, while the UK MHRA can request Phase IV or Safety Assessment Marketed Medicines studies as part of a risk management plan (RMP) it has few legal tools to enforce completion of postmarketing studies agreed to by companies. “The vast majority of regulatory

---

<sup>2</sup> Phase IV is the term used for postmarketing studies.

action is undertaken on a voluntary basis by the Marketing Authorization Holder (MAH)”<sup>3</sup> (UK Key Informant 3). The only action the MHRA can take against MAHs for failure to conduct postmarketing pharmacovigilance studies is to alter the product license, an option exercised only if voluntary compliance fails (UK Key Informant 3).

The EMEA requires companies to submit a RMP as a condition of market authorization. Risk management strategies are also indicated for drugs that pose potential safety issues, have perceived risks and the public health impact is high or a new safety concern arises in the post-authorization period. A post-authorization safety study (PASS) is an example of a risk management strategy. The study is supervised by a designated EMEA monitor(s) in the Member State(s) in which the study will be conducted to ensure compliance.<sup>50</sup> If a Phase IV study is a condition of authorization, EMEA may apply a specific obligation<sup>4</sup> to comply with EMEA terms. EMEA currently has around 145 RMPs in progress. The RMP protocol summary is public, as are the results. There is, however, no legal control for study completion.

In France, the company proposes an RMP and the tools it will develop to minimize risks (usually for drugs approved through the EMEA centralized system). These can include information for patients and physicians and closer follow-up of patients. The Regional Pharmacovigilance Centres coordinate and implement the RMPs. One Centre is designated the ‘rapporteur’ and carries out the RMP studies. Such studies are observational, and not RCTs which limits the conclusions that can be drawn from their results. Concern was also raised that physicians will tire of the extra work filling out forms for the growing number of RMPs and may not participate (France Key Informant 3).

---

<sup>3</sup> The Market Authorization Holder is the company marketing the drug in question.

<sup>4</sup> Specific Obligations data to be submitted in the post-authorization phase are specific to marketing authorizations granted under exceptional circumstances due to limited efficacy and/or safety data available at the time of the opinion of the Committee for Medicinal Products for Human Use, the expert advisory group of the EMEA.

While the EMEA RMP system has been in operation for too brief a period to evaluate its effectiveness, the current RMP process demonstrates several weaknesses. First, the methodologies are developed by companies, on a case-by-case basis, with vetting and eventual approval by the EMEA. These methodologies are often poor, and even for studies carried out in France for example, the decisions are made at a European level, sidelining existing expertise in methodology at the Regional Centres and Technical Pharmacovigilance Committee. One key informant noted that some RMP methodologies are unacceptable and companies have delayed implementing the plans due to lack of interest, which raises questions about their commitment to postmarketing surveillance (France Key Informant 3).

EMEA centrally approved products are subject to a five-year renewal. In theory, should postmarketing studies agreed to by the sponsor and required per “specific obligation” as part of market authorization not be completed within the initial 5-years, renewal could be withheld. In practice, such studies are more often categorized as a “follow-up measure” and not linked to renewal of market authorization. Recent EMEA legislative changes have also shifted the burden of proof to alter a product’s risk benefit ratio from manufactures to regulators. Regulatory authorities must now produce a burden of proof that the drug has a negative benefit ratio in order to *halt* market renewal. Otherwise the risk benefit is assumed to be positive.

We are no longer doing the routine five year renewal. We used to do it in the past, but what has happened with it is that it became more like an administrative procedure. (EU Key Informant 1)

While legislation exists to require manufacturers to develop a risk management strategy there is currently no legal requirement for companies to complete the data collection specified in RMPs;<sup>51</sup> nor is submission of an EU-RMP mandatory for all drugs. It is the responsibility of the company to discuss with the EMEA the need for an EU-RMP. If the company believes it is unnecessary, they submit a justification to EMEA. Risk minimization activities are not prescribed either.

They may be developed with advisement of national authorities however consultation is voluntary.<sup>50, 52</sup> The RMPs have not been in place for sufficient time to observe whether market renewal might be withheld should a sponsor not complete studies agreed to as part of a “follow-up measure” or a “specific obligation.”

In NZ all postmarketing studies are commissioned by contract through the National Pharmacovigilance Centre located at the University of Otago. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe), informs the sponsor of its decision to commission a study. Although Medsafe has no legal mandate to request studies from drug sponsors it oversees study completion through its contracted research centre. In Australia, the situation is similar to that in Canada; the Therapeutic Goods Authority (TGA) has no legal tools to enforce study completion agreed to as part of a sponsor’s risk management plan. TGA provides only guidelines on sponsor’s risk management plans. Sponsors are advised to follow these guidelines but they are non-obligatory.

#### **d. Regulators’ access to research networks**

Regulators’ access to research networks has the capacity to inform their regulatory decisions through assessments of ‘real-world’ use of medicines in larger and more diverse populations than typical Phase III RCTs allow. Several nations are adopting assessment approaches that incorporate academic expertise and observational studies including those that draw on healthcare data bases to generate and test hypothesis regarding marketed products. Regulatory agencies in Australia, France, NZ, UK and US (Figure 3) and the EMEA have relationships with research networks or plan to develop them.

The FDA, EMEA and MHRA<sup>53-55</sup> are committed to strengthening their relationship with research networks; France and NZ already have administrative arrangements with a research network. These latter two include a regulatory framework that enables them to commission

research and establish closer links to academic research groups to enhance the regulator's capacity to investigate drug safety and effectiveness issues. EMEA is working with the European Commission's Directorate General for Research to establish a network of researchers and research centers to conduct commissioned studies referred to as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP), a network of pharmacoepidemiology centres, medical care centres, Automated Healthcare Databases and electronic Registries to assist in identifying, characterizing and assessing risks related to medicines to enable more proactive pharmacovigilance. More than 60 centres have been included in EMEA's inventory. EMEA is also exploring mechanisms to fund studies on product safety and methodological approaches to pharmacovigilance.<sup>56</sup>

The Italian Medicines Agency has developed a model in which drug companies contribute 5 percent of their yearly promotional budgets to a national fund that supports publicly sponsored postmarketing research on real world clinical end-points and pharmacoepidemiology studies.<sup>57</sup>

The US FDA has a framework to commission independent research through the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) network, the Centers for Education & Research on Therapeutics (CERTs) network, and contracts with other research centres.<sup>58</sup> The CERTs model involves investigator-initiated projects that are funded for 5-year periods on a peer-review research grant basis in response to Requests for Applications. CERTs, created in 1999, are based in 12 universities. The CERTs proposals address the request for applications announced by the Agency for Healthcare Research and Quality (AHRQ) or the FDA. CERTs research studies span a wide range of areas; those most relevant to the FDA are based on observational pharmcoepidemiological population-based research (Figure 4).

AHRQ created the DEcIDE network based in academic institutions that are service providers to healthcare plans in 2005. DEcIDE projects are AHRQ or FDA task-order initiated

projects that specify research questions and designs with a turn around time of 1-2 years. The main purpose of the DEcIDE network is to expeditiously develop valid scientific evidence about the comparative clinical effectiveness, safety, and appropriateness of health care items and services (Figure 5).<sup>53</sup>

FDA has also established a Memorandum of Understanding (MOU) with the Veteran's Affairs to promote better data sharing between the FDA and the VA. Through the MOU, the VA should be able to access the clinical trials data submitted to the FDA although there is some uncertainty about this (US Key Informant 7) (Figures 6, 7).

New Zealand's Medsafe has the capacity that allows it to commission independent research, including postmarketing studies, from the National Pharmacovigilance Research Centre based at the University of Otago. Medsafe's expert Medicines Adverse Reactions Committee (MARC) recommends specific medicines to be monitored through the IMMP run by the University of Otago, which are discussed with members of the Pharmacovigilance Centre (Figure 8). (NZ Key Informant 1) MARC thus creates an organizational process for the regulator to consult with experts and commission studies from a university-based Pharmacovigilance Research Centre.

The UK MHRA was restructured (March 2006) to include a new Licensing Division, Information Processing Unit (in the Information Management Division) and a new Vigilance and Risk Management of Medicines (VRMM) Division to support greater research engagement and access to intelligence to aid risk/benefit and decision making.<sup>59</sup> MHRA's reorganization also established therapeutic category teams to facilitate communication across divisions (Figures 9, 10), which were prompted by the need to comply with EU regulations for MAHs to submit risk management plans. "With reorganization you know exactly who is responsible for what and who to talk to." (UK Key Informant 3)

The MHRA also formed a series of independent advisory bodies made up of professionals, lay and patient representatives to provide advice to the Minister on issues related to the regulation of medicines; these bodies include the Commission on Human Medicines<sup>5</sup> and the Independent Scientific Advisory Committee<sup>6</sup>. These advisory bodies in turn can form expert advisory groups (EAGs) to address specific problems, such as the Pharmacovigilance Expert Advisory Group, the Clinical Trials Expert Advisory Group, and the Paediatric Medicines Expert Advisory Group.

The VRMM Pharmacovigilance Risk Management Section engages in epidemiological research and produces reports and for its EAGs. Alternatively, the VRMM's Pharmacovigilance Signal Management staff (see Figure 9) provides raw ADR data and works with external researchers in interpreting the information to guide their applications to use the GPRD to conduct independent research. The resulting reports and research findings are submitted to the Pharmacovigilance EAG,<sup>54, 59</sup> which meets monthly to discuss and give independent advice on pharmacovigilance issues including assessments of the risks and benefits of medicines. "The EAG recommendations following discussion of the assessment report produced by the MHRA are then taken into consideration in the decision making process by the Commission on Human Medicines and its EAGs, which are independent expert advisors. The Agency does not necessarily have to act on the advice it receives from its independent advisors, although in reality that advice is generally taken forward." (UK Key Informant 4).

---

<sup>5</sup> The Commission on Human Medicines (CHM) is a committee of the UK's [Medicines and Healthcare products Regulatory Agency](#). It was formed in October 2005 by the amalgamation of the [Medicines Commission](#) and the [Committee on Safety of Medicines](#). The CHM's responsibilities include advising the UK government ministers on matters relating to human medicinal products, giving advice in relation to the safety, quality and efficacy of human medicinal products, and promoting the collection and investigation of information relating to adverse reactions for human [medicines](#).

<sup>6</sup> The role of the Independent Scientific Advisory Committee is to review the scientific merit of proposals for research using data from the MHRA General Practice Research Database (GPRD) and Yellow Card Scheme database.

Certain drugs that are believed to present particular risks are monitored through *patient* and *disease* registries in the UK. Clozapine is an example of a drug monitored through a *patient registry*, where use is restricted to a specific patient sub-population and the registry functions to monitor that criteria for use have been met. *Patient registries* are managed by the MAH. Serious unexpected adverse reactions due to use of the drug must be reported in a suspected unexpected serious adverse reaction report submitted according to MHRA and EMEA guidelines and timeframes. The Biologics Registry and National Cancer Registry are examples of *disease specific registries*, which are not managed by drug companies. They may be run by professional organizations, e.g., the British Society for Rheumatology (Biologics Register), the Department of Health (National Cancer Registry), physicians or academia. Hospitals may be involved in the administration of a registry. Their primary function is more pharmacosurveillance, to monitor risk-benefit throughout the life-cycle of the drug. They provide on-going, long-term data to better understand the disease, the drug, and to identify rare side effects.

In France, AFSSaPS is associated with the network of Regional Pharmacovigilance Centres. The Regional Centres collect and analyze spontaneous ADR reports, and oversee observational studies. The Technical Pharmacovigilance Committee comprised of regional centre directors discusses on-going studies and methodological issues. Individual Centres are designated as ‘Rapporteurs’ to conduct a pharmacovigilance survey in response to ADR signals. The Regional Centres also have direct links to specialist clinicians which facilitates the implementation of prospective observational studies. The National Pharmacovigilance Commission, comprised of healthcare authority representatives, pharmacologists, physicians, pharmacists and an industry representative, reviews the study results and recommends measures to the AFSSaPS to prevent or reduce ADRs including: changing a product’s approved use, disseminating information to physicians, reconsidering a drug’s risk/benefit ratio or its

withdrawal (Figure 11).<sup>60</sup> Although France does not have linked administrative population healthcare databases, a new project will prospectively follow a 500,000 population sample for 20 years, linking ADR survey results to electronic health care records such as hospitalizations and dispensed prescriptions.

## **2) Drug Benefit Plans' approaches to 'real-world' safety and effectiveness research**

Prescription reimbursement falls under the auspices of different authorities in each country. In Australia, France, Norway and the UK the national authority is required to fund medicines for the entire population; thus they are vested in trying to create mechanisms to ensure equitable access to safe, effective and affordable medicines. Drug benefit plans in several countries therefore conduct intramural postmarketing research, or commission technology appraisals of medicines to determine which drugs should be publicly funded.

### **a. Industry sponsored research**

Technology appraisals that are conducted by the Norwegian Medicines Agency (NoMA) Department of Pharmacoeconomics, Australia's Pharmaceutical Benefits Advisory Committee (PBAC) and UK's National Institute for Health and Clinical Excellence (NICE) involve assessment of safety, effectiveness and cost-effectiveness of new and current therapies, based on studies submitted by pharmaceutical manufacturers. If, upon the conclusion of its assessment, the NoMA Department of Pharmacoeconomics concludes that one drug within a class has increased side effects and is not as effective as alternatives within a class, that drug will not be reimbursed under the Blue Prescription Scheme (Norway Key Informant 1) or reimbursement might be limited or restricted to prescription by authorized specialists only. The PBAC operates in a similar manner.

NICE's technology appraisal process may result in one of three recommendations: 1) routine use by the NHS in all or specific sub-group populations; 2) not recommended for use

because evidence of clinical effectiveness or cost-effectiveness is lacking; or 3) use Only in Research (OIR) because existing evidence is not robust enough to make a recommendation.<sup>61</sup> NICE may additionally recommend that a technology be used only if a registry to collect outcomes data is established.<sup>62, 63</sup> The OIR designation limits the use of new medicines until enough patient years experience is gathered to determine ‘real-world’ safety and effectiveness.

In France, postmarketing studies may be commissioned by the section of the Haute Autorité de Santé (HAS) which oversees the Public Health Impact (PHI) Post-Formulary Listing Studies (Impact de Santé publique études post-inscription et bases de données) on behalf of the Commission de la Transparence, responsible for determining the medicines listed on the national formulary. The studies carried out at the request of the Commission de la Transparence are observational drug utilization studies, including descriptions of the populations taking the medicines, how they are used, and what benefits occur as a result of medicine use. These are national formulary ‘post-listing’ studies, conducted to inform the reimbursement decision.

The Commission de la Transparence has introduced an initiative in which new drugs that have the potential to be used on a large scale undergo a ‘phased introduction’ in which pharmaceutical companies are asked to conduct a post-listing study of the “public health impact” of a drug that includes end-points of concern related to ‘real-world’ use. A formal agreement between France’s Health Product Economic Committee and the Association of Drug Enterprises, the organization representing pharmaceutical companies, in May 2003 led to a framework in which the specific aspects of PHI studies - including the study design and timelines - are required before reimbursement is granted by the Commission de la Transparence. PHI studies are large-scale epidemiologic evaluations that measure changes in disease-related morbidity and mortality at the population level, a risk assessment evaluation, and the implications for the use of other drugs.<sup>64</sup>

The 'Comité Économique' of the French Health Ministry signs an agreement with the company that includes: the reimbursement price, volume of sales, and any requirement for a post-listing study, which becomes part of the legal agreement between the Health Ministry and the company concerning conditions of sale. All products are reviewed every 5 years, prior to which the company must submit the study results, along with annual reports. If the results indicate the product is less effective than anticipated in terms of expected public health impact, the drug would get a lower therapeutic rating (Amélioration du service médical rendu), which may lead to a price reduction. In 2004, the Commission de la Transparence required 27 studies; in 2005, 28 studies were required, in 2006, 16 studies and in 2007 (to August) 20 studies were required. The Regional Pharmacovigilance Centres often oversee the 'post-listing' studies and therefore address the research needs of both the national regulator and drug benefit plan.

Postmarketing studies may thus be used to determine listing of medicines on the national drug benefit formulary as with PHI studies commissioned on behalf of the Commission de la Transparence in France. While the Commission de la Transparence has the autonomy and the authority to set criteria for postmarketing research conducted by pharmaceutical manufacturers, prescription benefit plans in Australia, Norway and UK have considerably less authority. They may require that a postmarketing study be carried out but cannot dictate the study criteria.

#### **b. Intramural research**

Technology assessments and technology appraisals may be conducted by an agency external to the drug benefit plan as with the UK Department of Health (DOH) agreement with NICE, or they may be conducted intramurally.

Of the drug benefit plans studied, only the UK DOH and the US Veterans Affairs (VA) Center for Medication Safety (VAMedSAFE) conduct intramural pharmacovigilance studies. The VAMedSAFE conducts both pharmacoepidemiologic and pharmacoeconomic studies.

A strength of the VA's system is that it has a robust electronic medical record with pharmacy data, including all outpatient prescriptions, that has been collected since the late 1990s. This data can be used to track utilization patterns and is connected to hospital data that includes information such as diagnoses and procedure codes. In the past the VA has made use of its database to identify patients on short-acting nifedipine, used in the treatment of hypertension, in order to switch them to another drug when the literature indicated that this product was not an appropriate choice (US Key Informant 7). The database is also regularly queried for information about ADRs; a list of the 10 drugs with the greatest number of ADRs within a given time period is identified and reviewed monthly or quarterly. VA uses pharmacovigilance research, generated by VAMedSafe and others, in deciding on whether to place a drug on its formulary. VA assesses the overall quality of the evidence, the net benefit (benefit minus harms) and then combines these two measures to grade the recommendation.<sup>65</sup>

In a new pilot project, the VA is building a signal detection program, or active surveillance program (i.e., syndromic surveillance). The VA also reviews drugs that are either in high use in its system, high-risk based on known potential ADRs or that might cause a greater number of ADRs in the VA's population compared to the general population. These drugs are monitored through an integrated database to evaluate ADRs based on diagnostic codes and changes in laboratory values (US Key Informant 8).

The UK DOH offers another example of intramural research with respect to drugs used in the treatment of Multiple Sclerosis (MS). The DOH oversees the MS risk sharing scheme in which a cohort of patients is monitored over time as part of an observational hypothesis-testing study under real-life prescribing conditions. The cost to the NHS of the drugs covered by the MS risk-sharing scheme will be adjusted on a sliding scale if effectiveness outcome indicators differ from the target that the DOH and the MAHs agreed to for the drugs studied.<sup>63</sup>

### **c. Drug Benefit Plans' Access to Research Networks**

Drug Benefit Plans have developed administrative arrangements with researchers and technology assessment agencies to expand their research capacity given their need for evidence to inform decision-making. An example of a publicly funded research network that addresses 'real-world' safety and effectiveness is the UK NICE. NICE's ability to engage in technology appraisal is enhanced through a collaborative relationship with the National Institute for Health Research (NIHR) Health Technology Assessment Programme to provide technology assessments and with the Medical Research Council Biostatistics Unit to conduct meta-analyses to validate submissions by drug manufacturers (Figure 12).<sup>66</sup> NICE sub-contracts with academic institutions to perform Sheffield School of Health and Related Research modeling of cost-effectiveness and clinical effectiveness.<sup>67-69</sup>

### **3) Coordinating Regulators' and Drug Plans' commissioned research**

#### **a. Public oversight of research funding**

Drug benefit plans seek comparative data on medicines in the same class to inform their formulary decisions, but rely mainly on indirect comparisons between placebo-controlled trials because of companies' reluctance to conduct head-to-head studies.<sup>70</sup> As a result, separate studies are carried out, which is inefficient and a missed opportunity scientifically when the same resources could be used to design direct comparative research. If the characteristics of patients enrolled in trials or co-interventions differ between studies, it can be difficult to know whether differences in outcome reflect difference in the effects of the drugs or these other factors.

Drug plans and regulators also require an assessment of safety and effectiveness under real-world conditions. Drug plans find it important to understand how a medicine is used in normal clinical care given the link between adverse effects and adherence. For example, an osteoporosis drug must be taken for at least 1-2 years to prevent fractures. If observational

studies show that most women discontinue the medication within the first year, the product's therapeutic effect will not be achieved and the money spent on the drug will have been wasted. Since conditions of use can also affect a product's safety, regulators and drug plans would benefit from data derived from such observational studies.

**b. Research networks' independence and capacity to address safety issues**

There are two conflicting pulls on research networks – they must have the ability to independently pursue research topics and at the same time they also need to be able to respond to urgent safety issues. The former means that the members of the network should be able to design studies that meet the standards of peer-review and be assured of stable funding while the research is ongoing. The latter means that regulators and drug reimbursement schemes should be able to call on the networks to do directed research into unanticipated safety problems and report in a timely fashion. Different countries have addressed this issue in different ways. In the US this dual function has been addressed by developing relationships with the CERT and DEcIDE networks, and other academic research centres (see Section 1.d). The French Regional Pharmacovigilance Centres undertake both functions, as the national regulator, AFSSaPS, commissions targeted studies from the Regional Centres to address new safety issues.<sup>71</sup>

**c. Pharmaco-surveillance Research Network Funding and Infrastructure**

Postmarketing pharmacovigilance requires adequate research infrastructure and stable funding. Current funding models include public, private or public-private partnerships. Research networks include the UK NIHR; US CERTs,<sup>7</sup> DEcIDE; NZ's National Pharmacovigilance Centre; and France's Regional Pharmacovigilance Centres.<sup>60</sup>

---

<sup>7</sup> CERTs combine both public and public-private funding. CERTs projects may be publicly funded by the AHRQ and the FDA or funded through a combination of public and private funds, the latter coming from organizations such as pharmaceutical companies and Health Maintenance Organizations that act as partners to the CERTs.

Public oversight of research networks means decisions concerning the allocation of research funds prioritize safety concerns and are independent from commercial considerations. One example of how to achieve this goal is the example from Italy referred to in section 1.d.<sup>57</sup> An alternate source of private funds for pharmacovigilance research in the UK is private foundations such as the British Heart Foundation and the Wellcome Trust. The UK Clinical Research Collaboration (UKCRC) is a broad-based partnership of independent organizations and regulatory authorities which is jointly funded by public and private partners.

Several research networks have stable although in some cases limited funding: the UKCRC, France's Regional Pharmacovigilance Centres, NZ's National Pharmacovigilance Centre, and the US CERTs and DEcIDE. UKCRC partners have contributed more than £134 million since its inception to build a UK-wide infrastructure for clinical research and experimental medicine.<sup>67</sup> UKCRC Clinical Trials Unit and Research Design Services also has expertise in research design, methodology, data collection, and analysis.<sup>68</sup> CERTs and DEcIDE network centres possess expertise and infrastructure comprised of academic and clinical centres with access to the electronic databases of large healthcare providers.

In contrast, funding for other research networks is often inadequate, limiting infrastructure and capacity to conduct pharmacoepidemiologic research. Research networks have thus entered into various administrative arrangements to expand their capacity to conduct research in a limited resource environment. Scotland's MEMO collaborates with the University of Dundee's Biostatistical and Information Technology group and works with other disciplines in clinical, laboratory or social sciences.<sup>72</sup>

External experts are used regardless of whether the agency is under-resourced or sufficiently resourced. The UKCRC and Wellcome Trust have entered into a collaborative partnership to review the potential to use the 50 million electronic patient records the NHS has in

its database. The UKCRC has proposed that the UK healthcare datasets be linked in a National Pharmacovigilance Data Centre to concentrate expertise and oversee all aspects of pharmacovigilance.<sup>69</sup> EMEA and UKCRC have also created, or are in the process of creating, resource banks of scientific experts to expand their capacity for pharmacovigilance and pharmacovigilance.

#### **d. Coordinating regulatory agencies' and drug benefit plans commissioned research**

Pharmaceutical benefit schemes fall along a continuum with regards to their relationship to regulatory agencies and research networks. At one extreme is the Blue Prescription Scheme (Norway) that is managed by the regulatory agency (NoMA) but has limited relationships with research networks. The Commission de la Transparence provides the best example of tri-agency cooperation for pharmacovigilance.

In France, the formation of the 'Comité de liaison' is a new initiative designed to increase collaboration between the regulatory agency, the network of Regional Pharmacovigilance Centres and the Commission de la Transparence on postmarketing and post-listing studies; reducing duplication and maximizing benefit. Oversight of the postmarketing and post-listing studies by the manufacturer remains a limitation for the reasons described in Section 2a.

### **Conclusion and Recommendations**

Drug safety was the 4<sup>th</sup> to 6<sup>th</sup> leading cause of death in the U.S. in the 1990s;<sup>8</sup> a problem whose severity has since heightened given the increase in reported deaths and serious injuries associated with Vioxx®, Avandia®, SSRIs and other medicines for which warnings or withdrawals were issued. From 1998 through 2005, reported serious adverse drug events in the US increased 2.6-fold from 34,966 to 89,842 and fatal adverse events increased 2.7-fold. Reported serious events increased 4 times faster than the total number of outpatient prescriptions during the period.<sup>73</sup> . Drug benefit plans must decide which medicines to list in the absence of a

complete understanding of the effectiveness, safety and cost-effectiveness of therapies. Given competing demands on their limited budgets, difficult choices are being made. Our comparative analysis highlights the approaches national regulators and drug benefit plans are using to better inform their decisions on the safety, effectiveness and cost-effectiveness of medicines by incorporating more adequate postmarketing research. As Health Canada contemplates shifting to progressive licensing in the regulatory context, a phased regulatory approach will be reliant on active pharmacosurveillance research to inform its decisions concerning the safety and effectiveness of medicines under ‘real-world’ conditions across a wider population and lengthier time intervals than RCTs allow.

While premarket RCTs demonstrate short-term efficacy, their controlled context prevents them from identifying safety issues: the small size and short duration of RCTs does not allow them to detect late-onset or less frequent ADRs. As patients with co-morbid diseases are usually excluded, and surrogate end-points of efficacy are often used, pre-market RCTs do not offer the complete understanding of medicines sought. Pre-market RCTs are however essential to establish efficacy and an initial assessment of safety before wide-spread population exposure, making them necessary but insufficient.

Active pharmacosurveillance methods - such as PEM and interrogation of ADR and healthcare databases - must be more widely supported as adjuncts to passive ADR reports to ensure data generated from administrative database mining supplements passive ADR reporting. For example, while the US FDA received an average of 82 reports about ADRs related to digoxin annually, greater than 200,000 hospitalizations were due to ADRs secondary to digoxin over seven years. This ‘order of magnitude’ increase in ADRs was uncovered through post-market data-mining of hospital records<sup>24</sup> and emphasizes the important of active pharmacosurveillance approaches. The US FDA-VA, FDA-DEcIDE and Scotland’s MEMO enabled by Tayside’s

electronic health records,<sup>72</sup> offer examples of collaborative regulator-health care plan arrangements for sharing the findings of healthcare data-mining research.

Phase IV RCTs offer another important means to better establish a product's risks and benefits given that medicines can receive market approval on the basis of surrogate endpoints, without establishing their long-term effect on patient morbidity and longevity. Postmarketing RCTs are particularly helpful when considering safety and effectiveness from a public health perspective. The research challenge can be exemplified by two products made by the same company to treat age-related macular degeneration (AMD). The most common treatment (bevacizumab) is being used off-label for AMD, as it has not been proven safe and effective in a clinical trial. The same company also markets a newly developed drug for AMD (ranibizumab) but will not undertake a head-to-head comparison. As ranibizumab's cost of \$1950 per injection is 50 times that of bevacizumab, and treatment may be required every 4 to 6 weeks, their relative effectiveness and safety is important to establish. The US National Institutes of Health is overseeing a \$16.2 million Phase IV trial to compare the two treatments.

ADRs of drugs often only become evident during prolonged exposure and can lead to the withdrawal of medications, for example, Vioxx® (used for arthritis and pain control) and Baycol® (used for high cholesterol) or, in the case of Zyprexa® (an antipsychotic), patient lawsuits. The inability to recognize the severity of ADRs in the pre-market trials for these products argues for Phase IV RCTs that are lengthier in duration than pre-market ones. Observational studies with larger populations that are followed for a lengthier time offer another approach to generate and test hypotheses.<sup>74</sup>

Relying on industry to oversee postmarketing studies however poses serious limitations. Our assessment of the EMEA RMPs for example, reveals a lack of transparency and systematic planning concerning study protocols which are developed on a case-by-case basis and often do

not entail rigorous scientific methods. RMPs should instead be informed by a process of risk assessment that precedes risk management, where the magnitude of harm is modeled by incorporating all pre-market data generated and expected population exposure levels. An example of this approach is the Canadian study estimating the net health impacts of tamoxifen administration on high-risk Canadian women with no prior history of breast cancer.<sup>75</sup>

Unless Health Canada applies a more systematic, rigorous approach to post-marketing studies than the EMEA - a framework in which standards for research methods are defined similar to the pre-market Phase I, Phase II and Phase III trials, and conditions regarding blinded assessments are determined - alternate methods to the current RMPs should be used to assess postmarketing safety and effectiveness. These methods could include studies developed and conducted by arm's length centres of pharmacoepidemiologic research excellence. EMEA RMPs are thus of limited value even though they lend the impression of systematic surveillance.

Reliance on drug company studies is also imprudent given conflicts of interest, even when the above safe-guards are incorporated. When industry agrees to conduct individual postmarketing studies with narrow aims, comparative head-to-head studies may not take place and postmarketing research is uncoordinated. There is also concern that physicians may tire of participating in the growing number of uncoordinated studies. While safe-guards are included in industry sponsored postmarketing studies, such as the use of a scientific committee to oversee the protocol and study design in France for example, key informants indicated the system would be improved if academics or the HAS carried out the study.

Conflict of interest is also avoided when compliance with study protocols is monitored by an independent third party and industry suggestions are vetted independently, as with the UK DOH MS risk sharing scheme.<sup>63</sup> Key informants preferred a system in which academics or a publicly sponsored research networks carry out the studies (NZ Key Informant 2, France Key

Informant 4). Industry could still fund the research, as is the case in Italy.<sup>57</sup> It would also allow studies of an entire drug class that individual companies are reluctant to perform (France Key Informant 4).

Pharmaceutical companies have for example been shown to report their research selectively, by either publishing only studies with positive results, or by publishing those with negative results in a way that conveys a positive outcome. For example, based on the published literature for 12 antidepressant agents, Turner et al.<sup>76</sup> reported it would appear that 94 percent of the trials conducted were positive; by contrast a separate meta-analysis of the entire range of trials submitted to the FDA found only 51 percent were positive. For each of the 12 drugs the effect-size based on published literature was higher than the effect-size based on FDA data, with increases ranging from 11 to 69 percent.; the median effect size for the entire drug class was 32 percent higher in the published literature than in the FDA analysis. These issues further highlight the need for public oversight to ensure postmarketing studies address key research questions, are designed to produce valid results and are accurately reported. Minimizing study duplication is also likely to foster continued cooperation from doctors.

An independent research network creates a framework to allow oversight of study design and ensure validity, creates independence from commercial interests and makes head-to-head comparative drug studies possible. Research results would also be much more likely to be publicly accessible rather than proprietary. From a funding perspective, comparative studies are more efficient than several individual studies whose results can only be compared indirectly. Inadequate funding to support research networks however threatens the continued availability of experts and long term feasibility to plan studies in emergent priority areas (New Zealand Key Informant 2, France Key Informant 1). Several national regulators and drug benefit plans commission postmarketing studies from research centres to address the safety, effectiveness, and

use of medicines: US DEcIDE, NZ National Pharmacovigilance Centre, and France's Regional Pharmacovigilance Centres. The UK MHRA has re-organized to establish a framework to commission and use postmarketing research and is thus taking steps in this direction. EMEA has developed an EU-wide approach to commission international pharmacovigilance research.

Canada is well positioned to realize the potential for a national network of research centres. Provincial public health care plans incorporate electronic health care records and pharmacy dispensing records could be used to conduct observational research, augmenting an activity already underway in Canadian research centres. A commitment and will to cooperate among provincial healthcare systems and Health Canada is however essential to develop the needed infrastructure for pharmacovigilance and public health impact studies. In terms of best practice, several nations offer innovative, responsive models. France's system of Regional Pharmacovigilance Centres not only provide a framework for ADR reporting, assessment and consultation, it also creates regional bases with pharmacoepidemiologic expertise integrated within the health care system. Regional Centres' links to physicians offer them a framework to oversee observational studies, with which industrial sponsors cooperate.<sup>60</sup> The French Regional Centre model also holds the potential to extend research to Phase IV RCTs. Canada would be wise to create centres of pharmacoepidemiologic research excellence linked to academic clinical centres to make a range of study types possible, including 'real-world' clinical trials.

New Zealand offers an alternate independent research model – in which its university-based National Pharmacovigilance Centre – is responsible for overseeing postmarketing studies. Meetings between NZ Medsafe's regulatory staff and Centre experts allow a forum for drugs to be evaluated to be discussed, including methodologic and operational issues. Alternatively, the US FDA's relationships with the DEcIDE and CERTs networks, and the VA suggest

arrangements based on regulator task orders and MOUs offer another means to enhance the FDA's expertise and access to a variety post-market research evidence.

While resources are important, they are not necessarily a limiting factor, as countries with modest resources, such as NZ and Italy, have developed models to fund postmarketing research with public oversight. Moreover, the EMEA has endorsed a plan to coordinate publicly sponsored postmarketing research across Europe. While national approaches are emerging, international coordination holds the potential to extend global resources to address this policy challenge. In order to be a global participant in such international cooperation, it is in Canada's interest to explore the models of research networks emerging internationally and to develop an approach that optimizes its innovative research capacity to address public health concerns.

## **References**

1. Carne X, Arnaiz JA. Methodological and political issues in clinical pharmacology research by the year 2000. *European Journal of Clinical Pharmacology* 2000;55:81-5.
2. Ray WA, Stein CM. Reform of drug regulation. *New England Journal of Medicine* 2006;354:194-201.
3. Wiktorowicz ME. Shifting priorities at the Health Protection Branch: challenges to the regulatory process. *Canadian Public Administration* 2000;43:1-22.
4. Wiktorowicz ME. Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain and France. *Journal of Health Politics, Policy and Law* 2003;28:615-58.
5. Auleley GR, Deligne C, Hanston C, Blum-Boisgard C. Selection cyclooxygenase-2 inhibitors. A population-based analysis of use in France over a three-year period and comparison with randomised clinical trials. *La Presse médicale* 2005;34:703-10.
6. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. Safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA* 1999;281:1728-34.
7. Friedman MA, Woodcock J, Lumpkin M, Shuren J, Hass A, Thompson L. Reply to Lurie et al. Safety of FDA-approved drugs. *JAMA* 1999;282:2297-8.
8. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-1205.
9. van der Hooft C, Sturkenboom CJF, van Grootheest K, Kingma HJ, Stricker B. Adverse drug reaction related hospitalizations. *Drug Safety* 2006;29:161-8.

10. Centers for Education and Research on Therapeutics Risk Assessment Workshop. Risk assessment of drugs, biologics and therapeutic devices: present and future issues. *Pharmacoepidemiology and Drug Safety* 2003;12:653-62.
11. European Medicines Agency. Pharmacovigilance planning: planning of pharmacovigilance activities (CPMP/ICH/5716/03) London: EMEA;2004. (Accessed February 19, 2008, at <http://www.emea.eu.int/pdfs/human/ich/571603en.pdf>.)
12. European Parliament and the Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. *Official Journal L-311* 2004:67-128.
13. Abenheim L. Lessons from the withdrawal of rofecoxib, France has policy for overall assessment of public health impact of new drugs *BMJ* 2004;329:1342.
14. Laupacis A, Paterson JM, Mamdani M, Rostom A, Anderson GM. Gaps in the evaluation and monitoring of new pharmaceuticals: proposal for a different approach. *CMAJ* 2003;169:1167-70.
15. Lo J. Adverse reaction reporting - 2006. *Canadian Adverse Reaction Newsletter* 2006;17(2):3-4.
16. Progestic International Inc. Final report for the financial models project. Ottawa: Health Canada; 2004.
17. Lexchin J. New directions in drug approval. *CMAJ* 2004;171:229-30.
18. Lexchin J. Notice of compliance with conditions: a policy in limbo. *Healthcare Policy* 2007;2:114-22.
19. Barr SG, Martin L, Chung C, Maksymowych WP. Mandatory pharmacovigilance - a Canadian model for access to therapy and research. *Clinical and Experimental Rheumatology* 2004;22:S39-43.

20. Carleton B, Foerster V, Warren L, Smith MA. Post-marketing pharmacovigilance in Canada: a background paper prepared for the working conference on strengthening the evaluation of real world drug safety and effectiveness.: Health Canada; 2005 August 31.
21. Hazell L, Shakir SAW. Under reporting of adverse drug reactions: a systematic review. *Drug Safety* 2006;29:385-96.
22. Fletcher A. Spontaneous adverse drug reaction reporting vs event monitoring: a comparison. *Journal of the Royal Society of Medicine* 1991;84:341-4.
23. Moride Y, Haramburu F, Requejo A, Bégaud B. Under-reporting of adverse drug reactions in general practice. *British Journal of Clinical Pharmacology* 1997;43:177-81.
24. Moore T, Psaty B, Furberg C. Time to act on drug safety. *JAMA* 1998;279:1571-3.
25. Rossi AC, Knapp DE, Anello C, et al. Discovery of adverse drug reactions: a comparison of selected phase IV studies with spontaneous reporting methods. *JAMA* 1983;249:2226-8.
26. Centers for Disease Control and Prevention. Assessing the national electronic injury surveillance system - cooperative adverse drug event surveillance project - six sites, United States, January 1 - June 15, 2004. *Morbidity and Mortality Weekly Report (MMWR)* 2005; 54:380-3.
27. Cohen AL, Jhung MA, Budnitz DS. Stimulant medications and attention deficit-hyperactivity disorder. *New England Journal of Medicine* 2006;354:2294-5.
28. Afsscaps: Agence française de sécurité sanitaire des produits santé. Bonnes pratiques de pharmacovigilance. Le ministre des solidarités de la santé et de la famille, 2005. (Accessed February 19, 2008, at <http://agmed.sante.gouv.fr/pdf/5/5010.pdf>.)
29. Alvarez-Requejo A, Carcajal A, Bégaud B, Moride Y, Vega T, Arias LH. Under-reporting of adverse drug reactions: estimate based on a spontaneous reporting scheme and a sentinel system. *European Journal of Clinical Pharmacology* 1998;54:483-8.

30. Smith CC, Bennett PM, Pearce HM, Reynolds DJ, Aronson JK, Grahame-Smith DG. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. *British Journal of Clinical Pharmacology* 1996;42:423-429.
31. Sweis D, Wong IC. A survey on factors that could affect adverse drug reaction reporting according to hospital pharmacists in Great Britain. *Drug Safety* 2000;23:165-72.
32. Centre for Adverse Reactions Monitoring. Guide to adverse reaction reporting. n.d. (Accessed February 19, 2008, at <http://carm.otago.ac.nz/pdfs/Guide%20to%20adverse%20reacation%20reporting.PDF>.)
33. Medsafe: New Zealand Medicines and Medical Devices Safety Authority. New Zealand Regulatory Guidelines for Medicines. Volume 1: Guidance notes for applicants for consent to distribute new and changed medicines and related products. Ministry of Health, 2001. (Accessed February 19, 2008, at <http://www.medsafe.govt.nz/regulatory/Guideline/medicines.asp>.)
34. Olivier P, Montasruc J-L. The nature of the scientific evidence leading to drug withdrawals for pharmacovigilance reasons in France. *Pharmacoepidemiology and Drug Safety* 2006;15:808-812.
35. Loke YK, Price D, Derry S, Aronson JK. Case reports of suspected adverse drug reactions - systematic literature survey of follow-up. *BMJ* 2006;332:335-9.
36. Heeley E, Wilton LV, Shakir SAW. Automated signal generation in prescription-event monitoring. *Drug Safety* 2002;25:423-32.
37. Paterson M. Overview of novel drug plan and drug regulatory pharmacovigilance initiatives in the United States, United Kingdom, and select other jurisdictions: a background paper prepared for the working conference on strengthening the evaluation of real world drug safety and effectiveness, September 13-15, 2005. Toronto: Institute for Clinical Evaluative Sciences; 2005.

38. Coulter MD. The New Zealand Intensive Medicines Monitoring Programme. *Pharmacoepidemiology and Drug Safety* 1998;7:79-90.
39. Coulter MD. The New Zealand intensive medicines monitoring programme in proactive safety surveillance. *Pharmacoepidemiology and Drug Safety* 2000;9:273-80.
40. Mann RD. Prescription-event monitoring - recent progress and future horizons. *British Journal of Clinical Pharmacology* 1998;46:195-201.
41. Key C, Layton B, Shakir SAW. Results of a postal survey of the reasons for non-response by doctors in a prescription event monitoring study of drug safety. *Pharmacoepidemiology and Drug Safety* 2002;11:143-8.
42. Bensouda-Grimaldi L, Jonville-Vera AP, Autret-Leca E. Post licensure safety surveillance for Prevenar(R). *Archives de pédiatrie: organe officiel de la Société française de pédiatrie* 2007;14:870-4.
43. Medicine Monitoring Unit. Tayside population-based dataset. 2004. (Accessed February 13, 2007, at [http://www.dundee.ac.uk/memo/Data/Tayside/tayside\\_data.php](http://www.dundee.ac.uk/memo/Data/Tayside/tayside_data.php).)
44. Medicine Monitoring Unit. Research capabilities. 2004. (Accessed February 13, 2007, at [http://www.dundee.ac.uk/memo/ResearchCapabilities/research\\_capabilities\\_pharma\\_vigil.php](http://www.dundee.ac.uk/memo/ResearchCapabilities/research_capabilities_pharma_vigil.php).)
45. Mandavilli, A. Rx for the FDA: faced with controversies over drug warnings and recalls, the drug agency tries to revamp itself. *Discover: science, technology, and the future*, 2007. (Accessed December 18, 2007, at <http://discovermagazine.com/2008/jan/rx-for-the-fda>.)
46. Institute of Medicine. *The future of drug safety: promoting and protecting the health of the public*. Washington D.C.: Institute of Medicine; 2006.
47. U.S. Food and Drug Administration. *Guidance for industry: reports on the status of postmarketing study commitments - implementation of Section 130 of the Food and Drug*

Administration Modernization Act of 1997. Rockville, MD: Department of Health and Human Services, 2006. (Accessed January 8, 2008, at <http://www.fda.gov/CDER/guidance/5569fnl.htm>.)

48. Health and Human Services. Report on the performance of drug and biologics firms in conducting postmarketing commitment studies; availability. Federal Register 2007:71(42):5069-70.

49. FDALegislativeWatch.com. FDA bill passes; Congress adds \$225 million to industry user fee burden. 2007. (Accessed January 8, 2008, at <http://www.fdalegislativewatch.com/2007/09/fda-bill-passes.html>.)

50. Guidelines on pharmacovigilance for medicinal products for human use: volume 9A of the rules governing medicinal products in the European Union. 2006. (Accessed January 8, 2008, at [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9A\\_2007-01.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9A_2007-01.pdf).)

51. European Medicines Agency. Annual report of the European Medicines Agency 2006. 2007. (Accessed February 10, 2008, at [http://www.emea.europa.eu/pdfs/general/direct/emeaar/EMEA\\_Annual\\_Report\\_2006\\_full.pdf](http://www.emea.europa.eu/pdfs/general/direct/emeaar/EMEA_Annual_Report_2006_full.pdf).)

52. Committee for Medicinal Products for Human Use (CHMP). Guideline on risk management systems for medicinal products for human use. EMEA, 2005. (Accessed February 10, 2008, at <http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf>.)

53. Agency for Healthcare Research & Quality. Overview of the DEcIDE research network. 2005. (Accessed January 9, 2008, at <http://www.google.com/search?q=%22Overview%20of%20the%20DEcIDE%20Research%20Network%22>.)

54. Medicines and Healthcare products Regulatory Agency. Annual report and accounts 2005/06. The Stationery Office, 2006. (Accessed January 8, 2008, at <http://www.mhra.gov.uk/Publications/Corporate/AnnualReports/CON2025135>.)

55. Medicines and Healthcare products Regulatory Agency. Business plan for 2006/07. 2006.

(Accessed January 8, 2008, at

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodeId=974.](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=974.))

56. European Commission, Enterprise and Industry. Strategy to better protect public health by strengthening and rationalising EU pharmacovigilance. 2007. (Accessed January 8, 2008, at

[http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance\\_acs/index.htm.](http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm.))

57. Agenzia Italiana del Farmaco. Independent research on drugs: funded by the Italian Medicines Agency. Rome: AIFA; 2007.

58. Staffa J. Contracts expand rapid evaluation of newly marketed drugs. CDER News along the pike. 2006(September 15):8-9.

59. Medicines and Healthcare products Regulatory Agency. Guide to the new structure: licensing (LD), vigilance risk management of medicines (VRMM) and information management division (IMD). March 2006. (Accessed January 8, 2008, at

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2023467&ssTargetNodeId=387.](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023467&ssTargetNodeId=387.))

60. Moore N, Kreft-Jais C, Dhanani A. Spontaneous reporting – France In: Mann RD, Andrews EB, eds. Pharmacovigilance. Chichester: Wiley 2007:217-27.

61. Chalkidou K, Hoy A, Littlejohns P. Making a decision to wait for more evidence: when the National Institute for Health and Clinical Excellence recommends a technology only in the context of research. *Journal of the Royal Society of Medicine* 2007;100:453-60.

62. Chalmers I. Addressing uncertainties about the effects of treatments offered to NHS patients: whose responsibility? *Journal of the Royal Society of Medicine* 2007;100:440-1.

63. Department of Health. Drug treatments for multiple sclerosis (beta-interferons and glatiramer acetate): risk-sharing scheme (HSC 2002/004) briefing note November 2006. 2006.

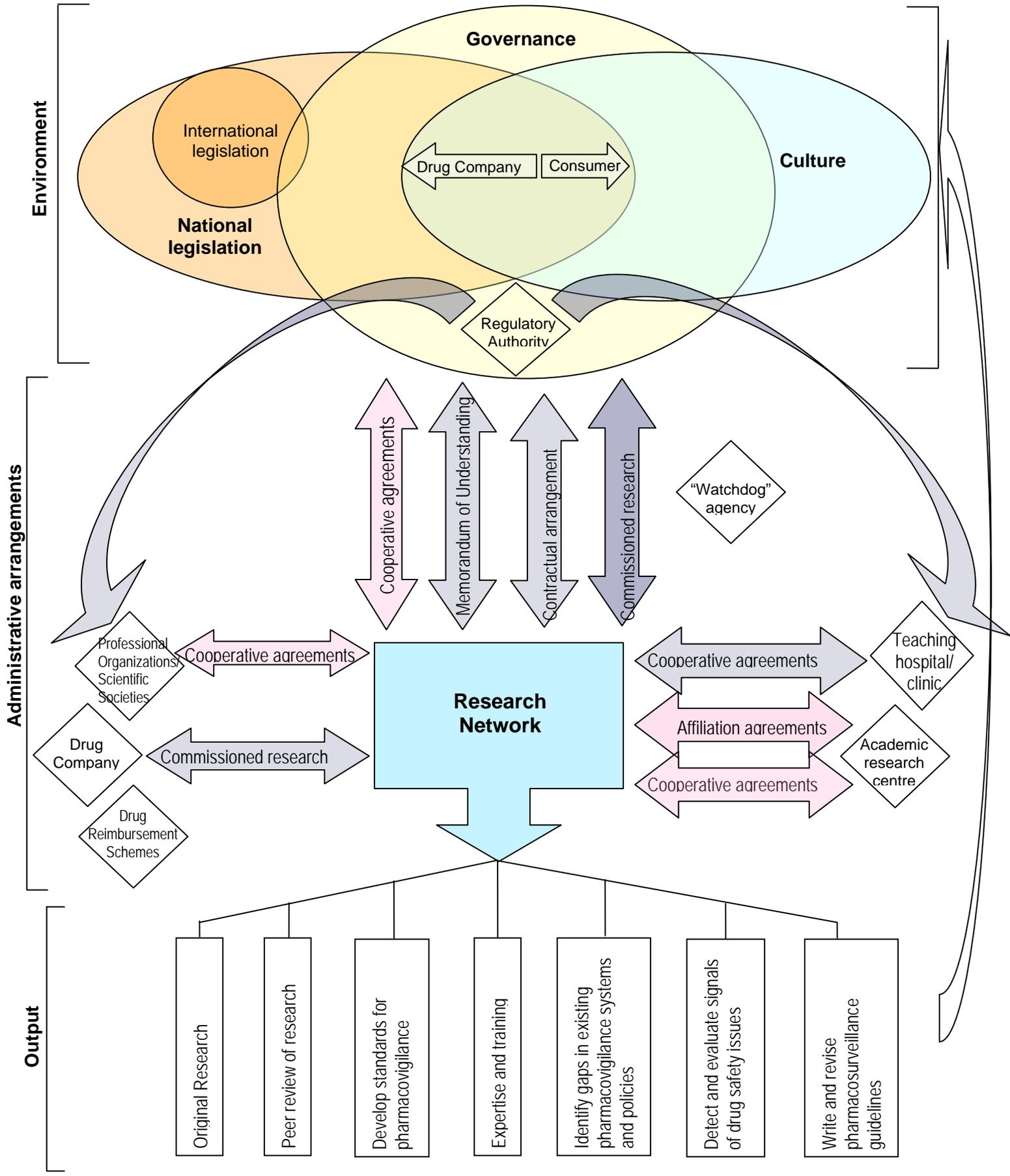
(Accessed January 5, 2008, at

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_063445](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063445).)

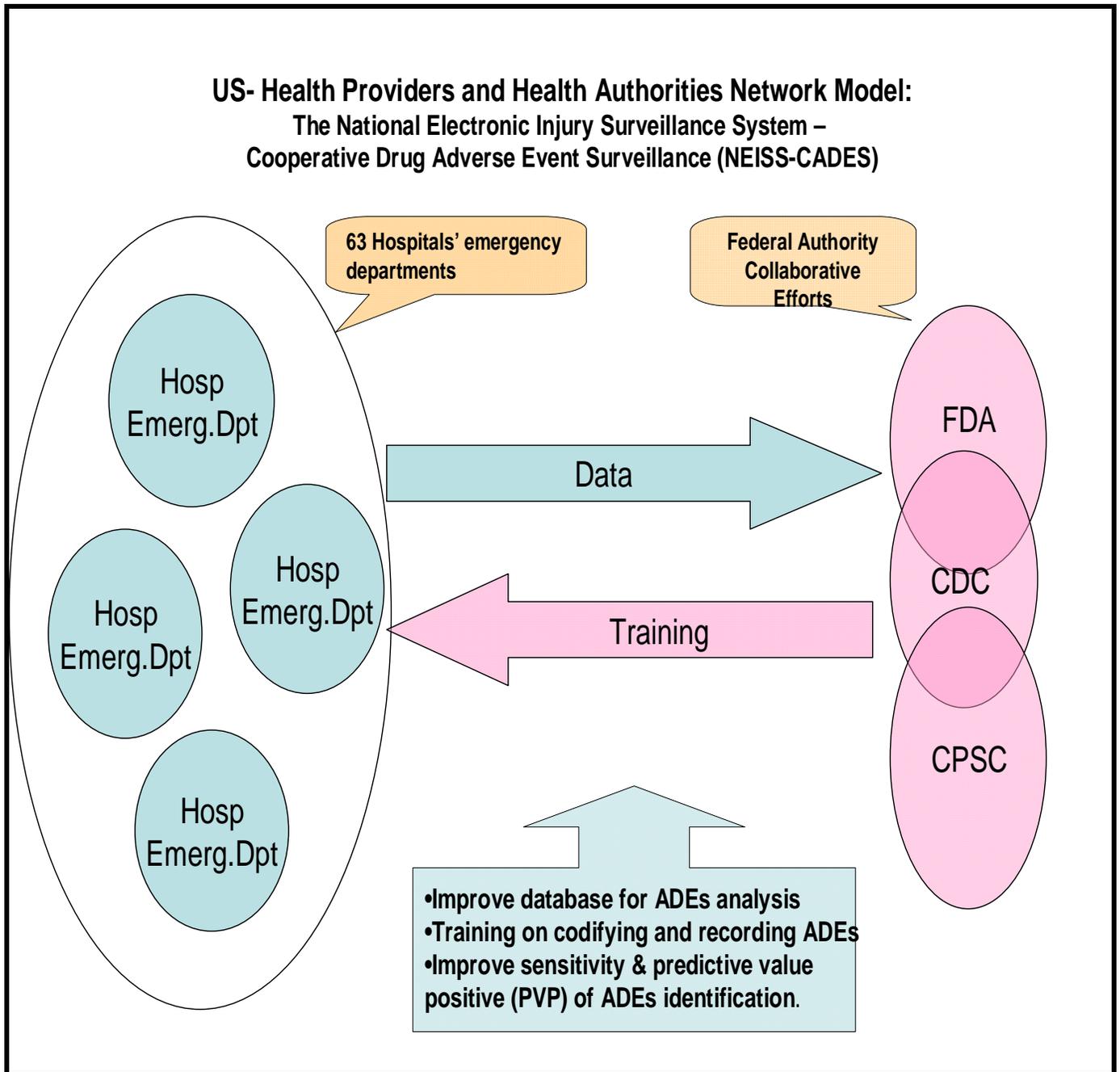
64. Abenhaim L. The new French paradigm : the public health impact assessment of drugs. *BMJ* 2004 (Accessed January 5, 2008, at <http://www.bmj.com/cgi/eletters/329/7471/867#81156>.)
65. VA-MedSAFE, VHA-PBM, VA-MAP. Pharmaceutical use outside of approved indications: guidance on “off-label” prescribing. Department of Veterans Affairs (VA) Center for Medication Safety And Veterans Health Administration (VHA) Pharmacy Benefits Management Strategic Healthcare Group and the VA Medical Advisory Panel 2004. (Accessed January 5, 2008, at <http://www.pbm.va.gov/directive/Guidance%20Off%20Label%20Prescribing.pdf>.)
66. National Institute for Health and Clinical Excellence. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer’s disease (amended). 2007. (Accessed January 5, 2008, at <http://www.nice.nhs.uk/nicemedia/pdf/TA111QRGSept07.pdf>.)
67. UK Clinical Research Collaboration. Progress report 2004-2006. n.d. (Accessed January 5, 2008, at <http://www.ukcrc.org/pdf/UKCRC%20PR%202004-2006.pdf>.)
68. UK Clinical Research Network. NIHR comprehensive clinical research network. n.d. (Accessed January 5, 2008, at <http://www.ukcrn.org.uk/index/networks/comprehensive.html>.)
69. UK CRC R&D Advisory Group to Connecting for Health. Report of research simulations. UK Clinical Research Collaboration, 2007. (Accessed January 5, 2008, at <http://www.ukcrc.org/pdf/CfH%20report%20June%2007%20full.pdf>.)
70. Caldwell EG, Ades DM, Higgins AE. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331:897-900.
71. Begaud B, Chasierie A, Haramburu F. Organization and results of drug vigilance in France. *Revue Epidemiologique Sante Publique* 1994;42:416-23.

72. MEMO - the Medicines Monitoring Unit. HIC - health informatics centre. University of Dundee, 2004. (Accessed January 5, 2008, at <http://www.dundee.ac.uk/memo/hic.php>.)
73. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Archives of Internal Medicine* 2007;67:1752-9.
74. Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. *British Journal of Clinical Pharmacology* 2003;57:127-34.
75. Will B, Nobrega K, Berthelot J-M, et al. First do no harm: extending the debate on the provision of preventive tamoxifen. *British Journal of Cancer* 2001;85:1280-5.
76. Turner EK, Matthews AM, Linardatos E, Tell R, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine* 2008;358:252-60.

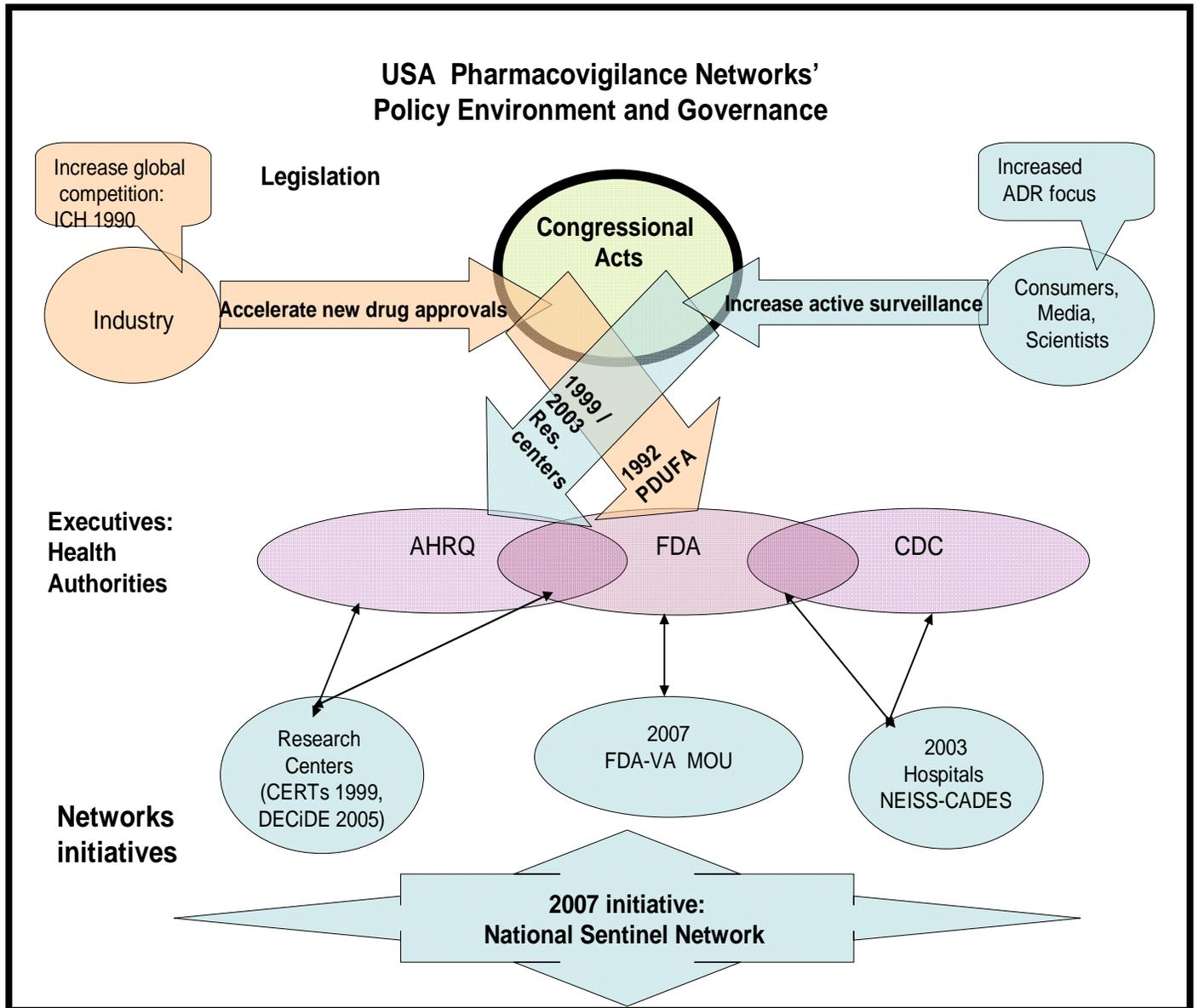
**Figure 1**  
**International Pharmacovigilance Research Network Framework**



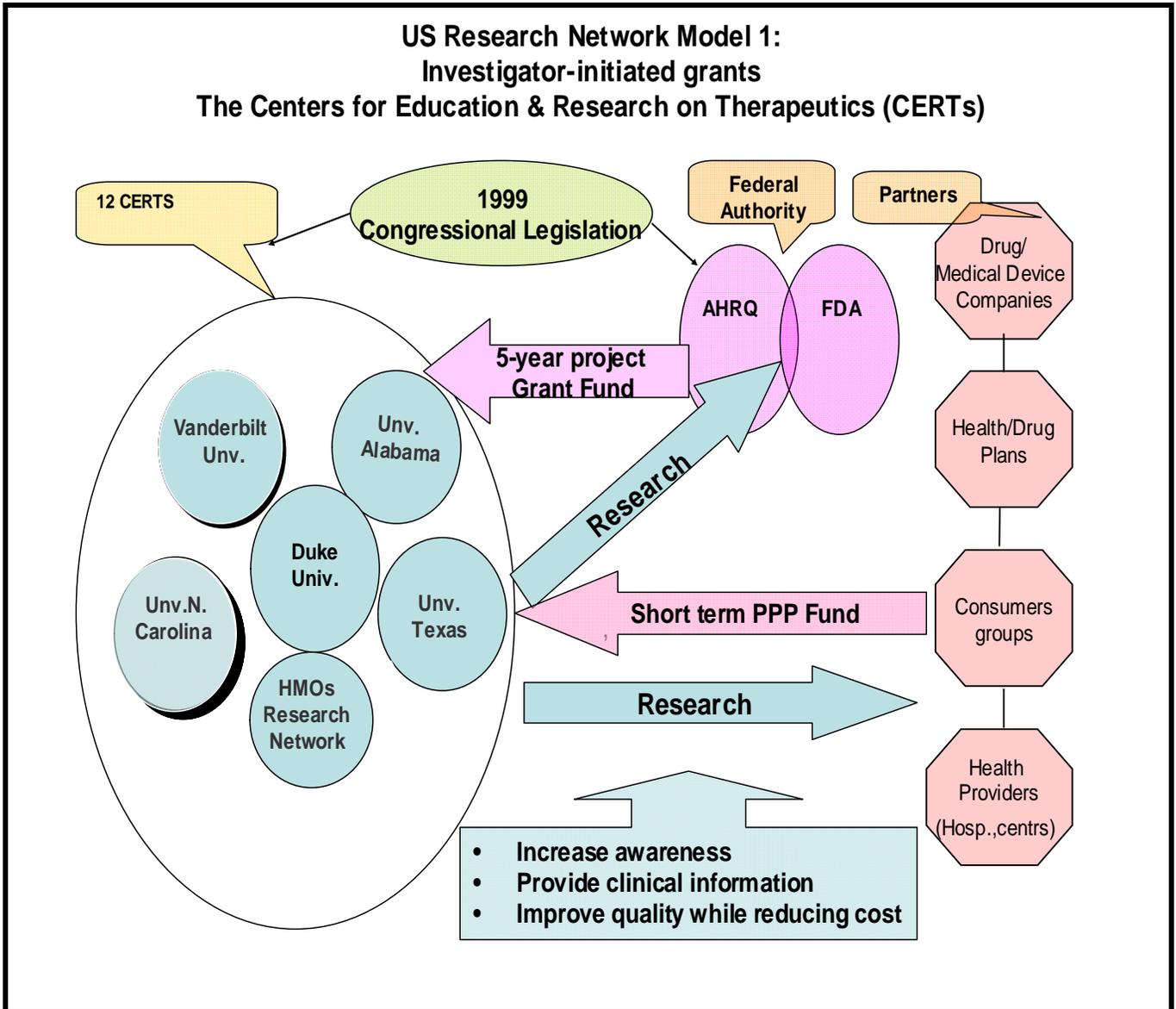
**Figure 2 US Health Providers and Health Authorities Network Model**



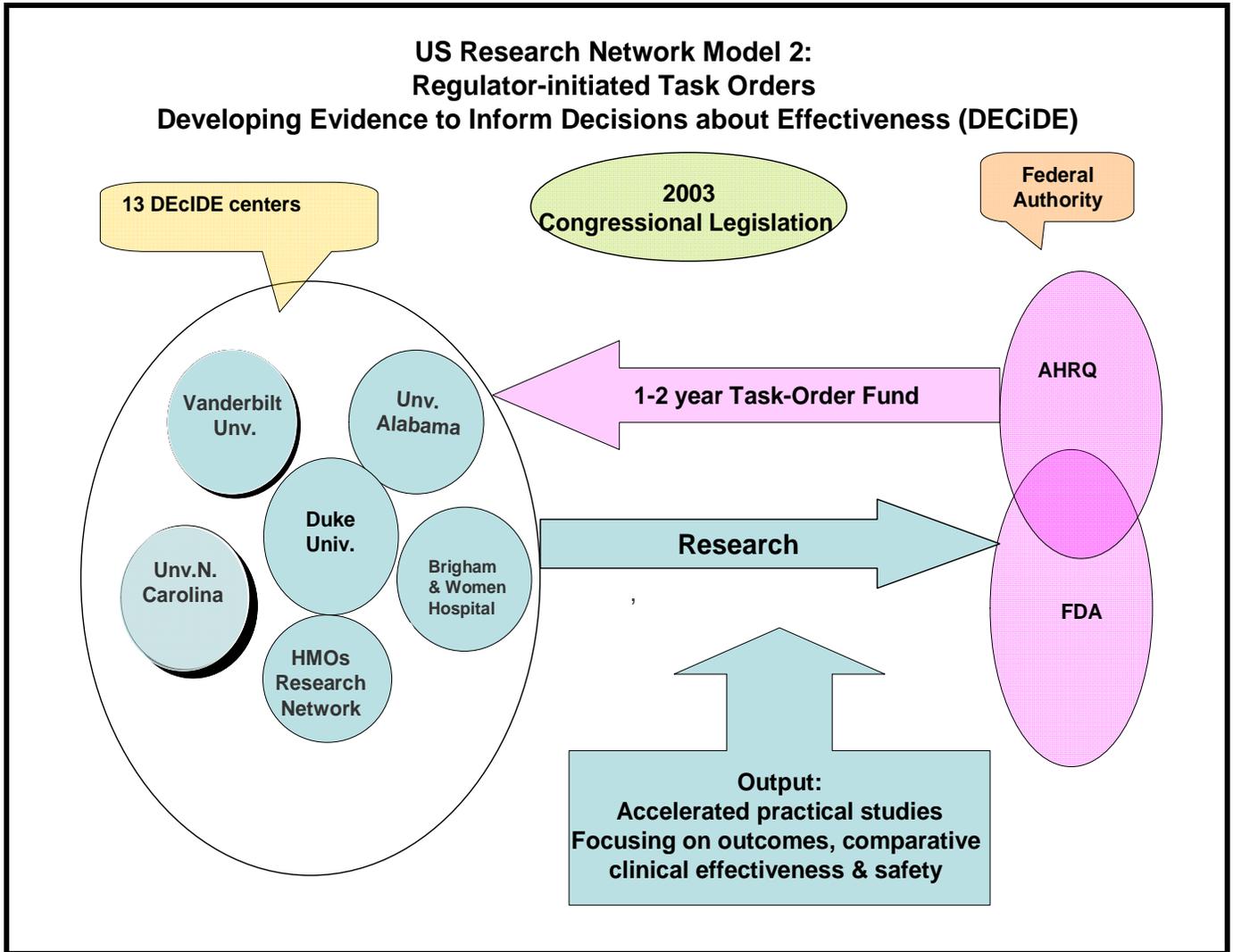
**Figure 3 US Pharmacovigilance Network's Policy Environment and Governance**



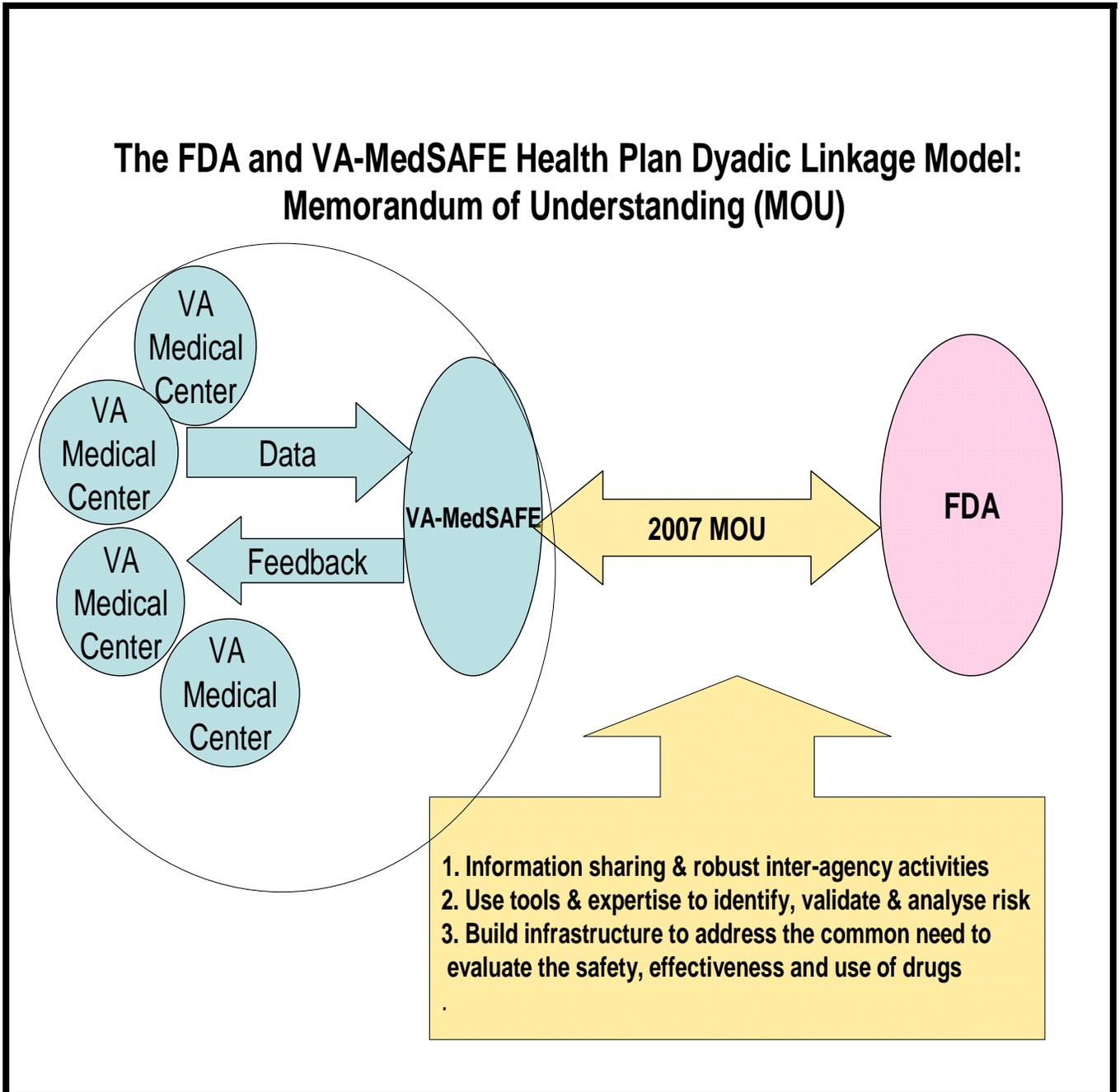
**Figure 4 Centres for Education & Research on Therapeutics**



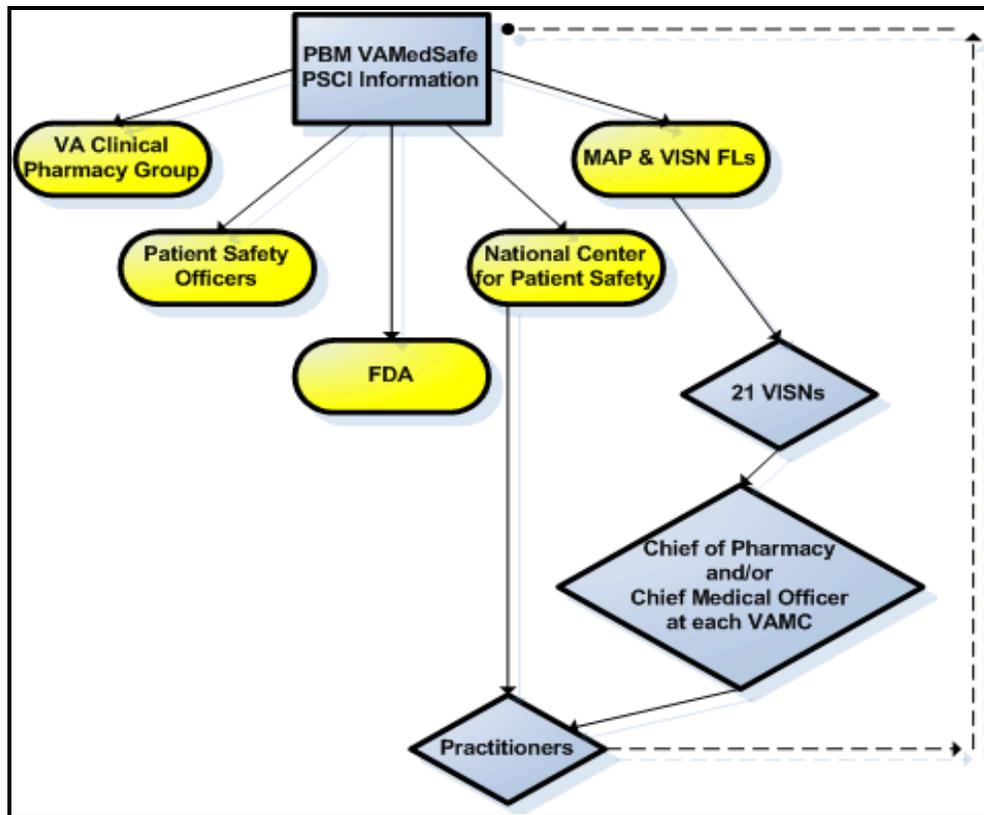
**Figure 5 Developing Evidence to Inform Decisions about Effectiveness (DECIDE)**



**Figure 6 FDA and VA-MedSAFE Health Plan Dyadic Linkage Model**

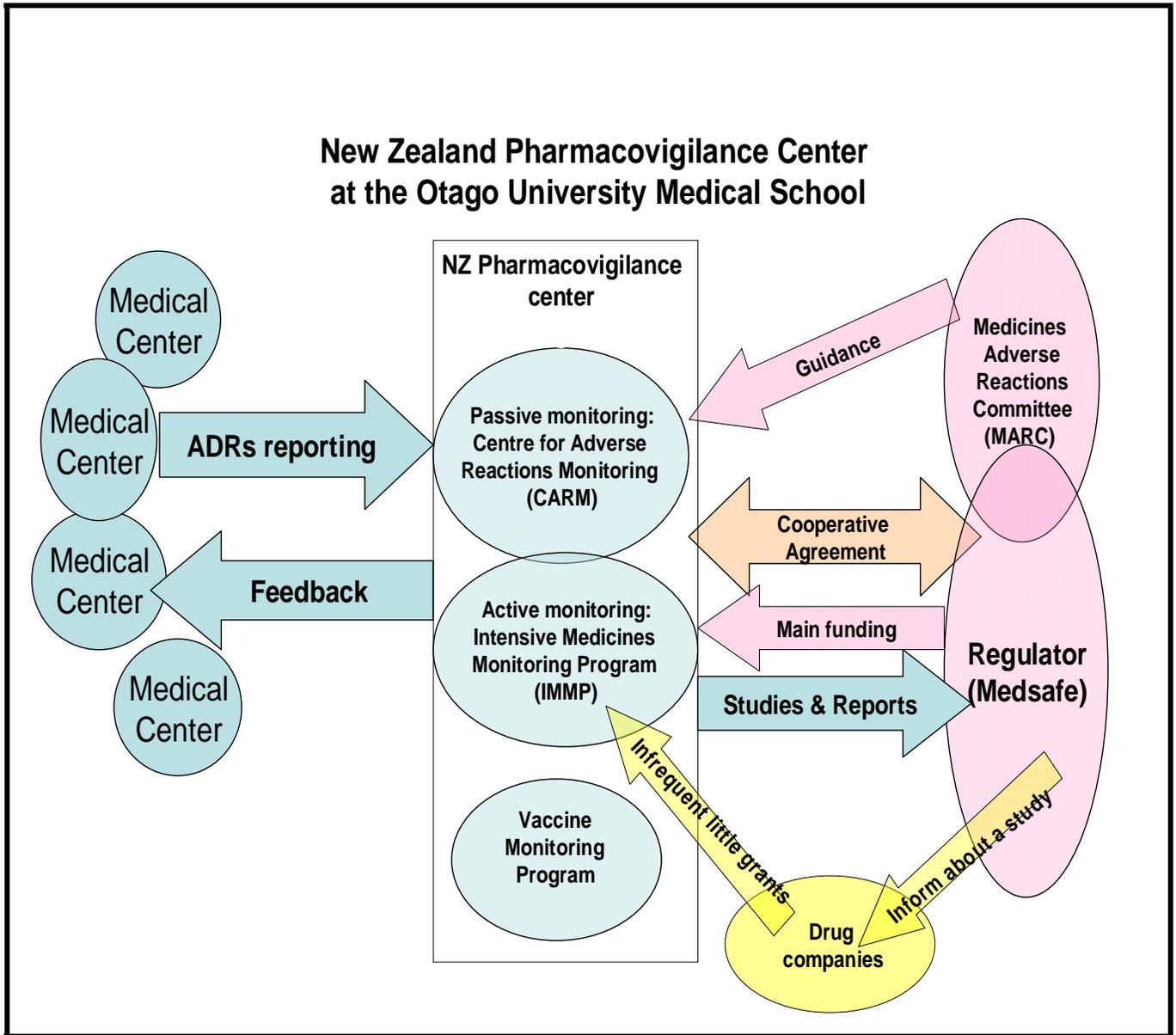


**Figure 7 VA-MedSAFE Channels for Communication and Dissemination of Information**

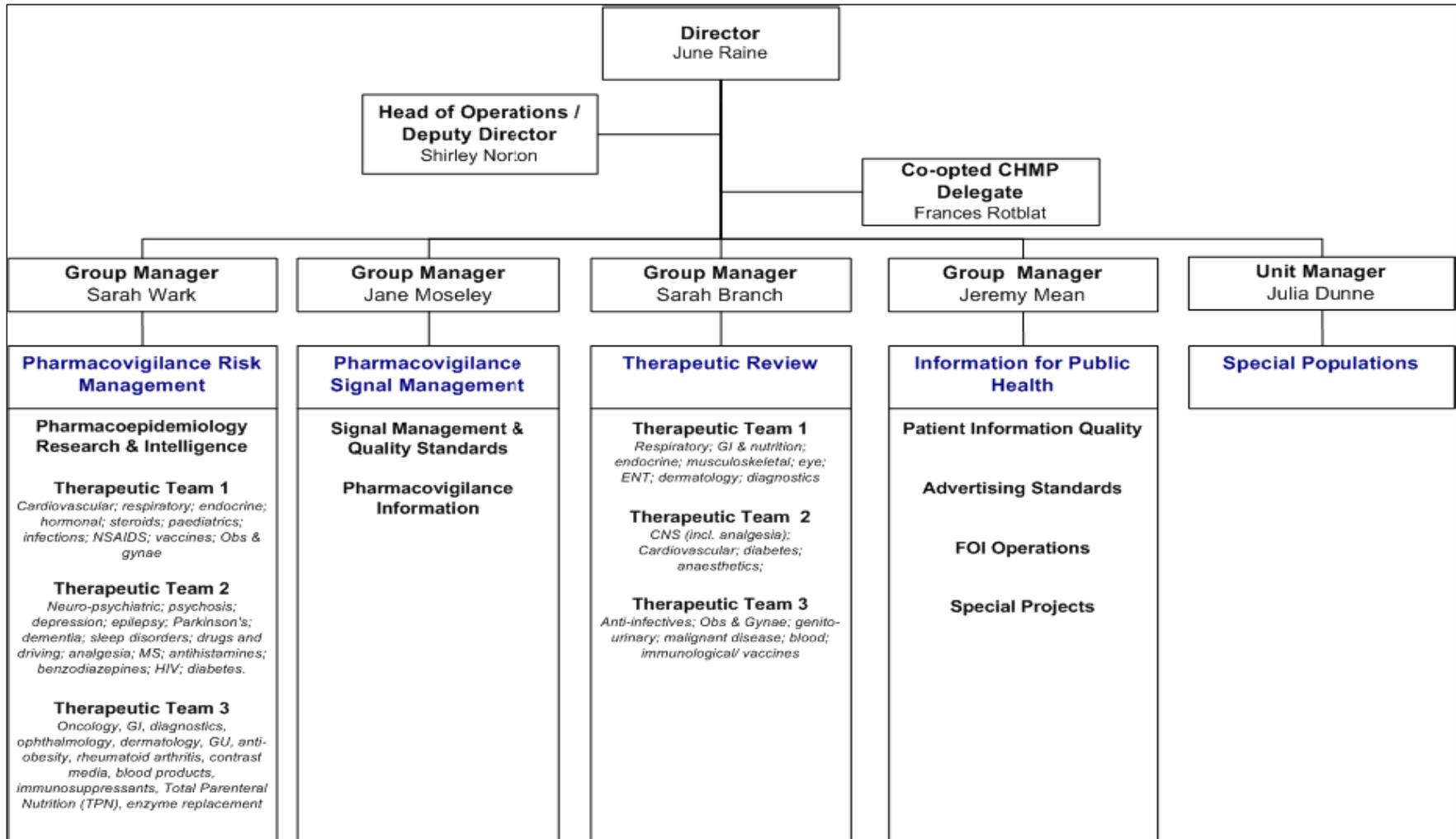


Source: VAMedSAFE (2007)

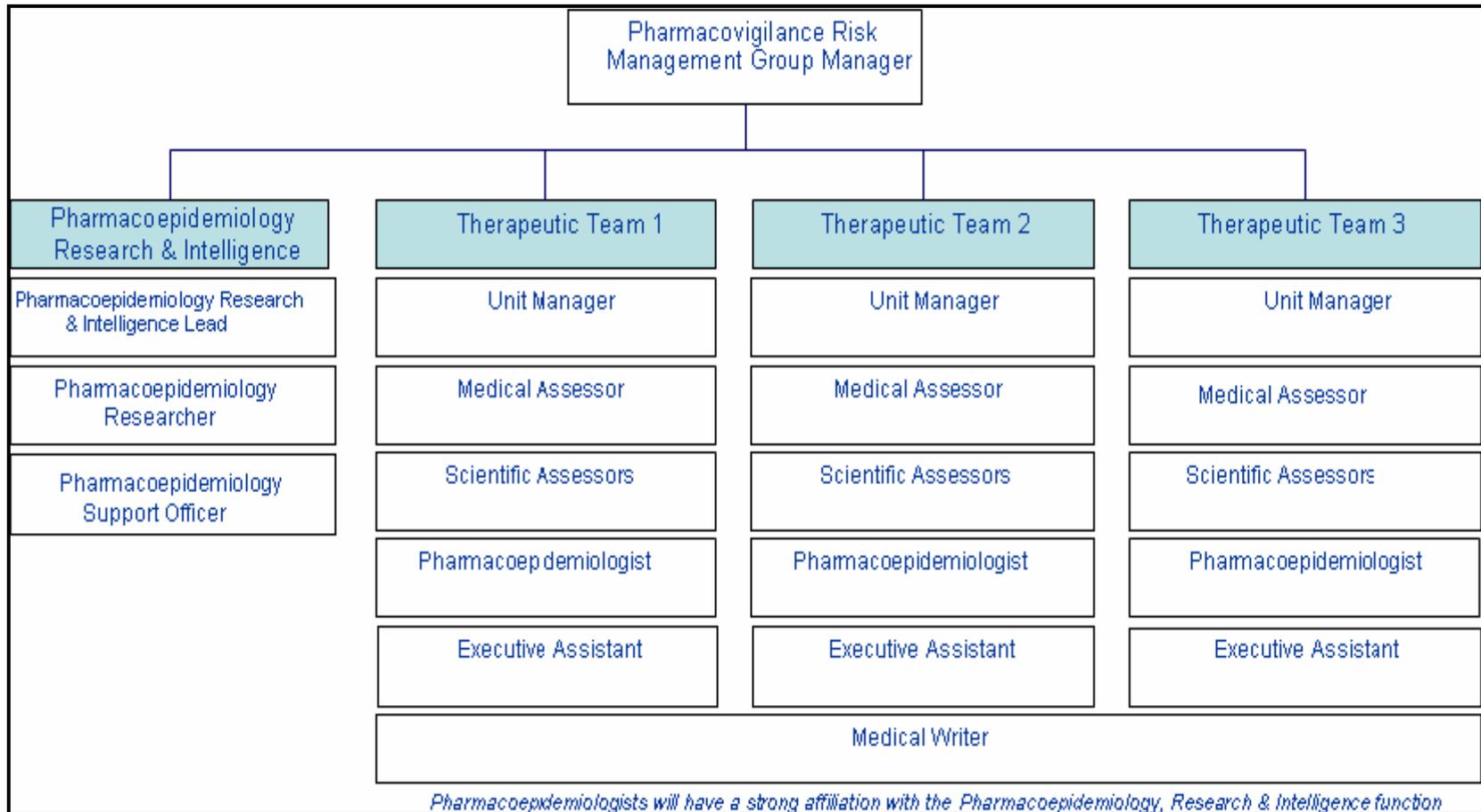
**Figure 8** New Zealand Pharmacovigilance Center at the Otago University Medical School



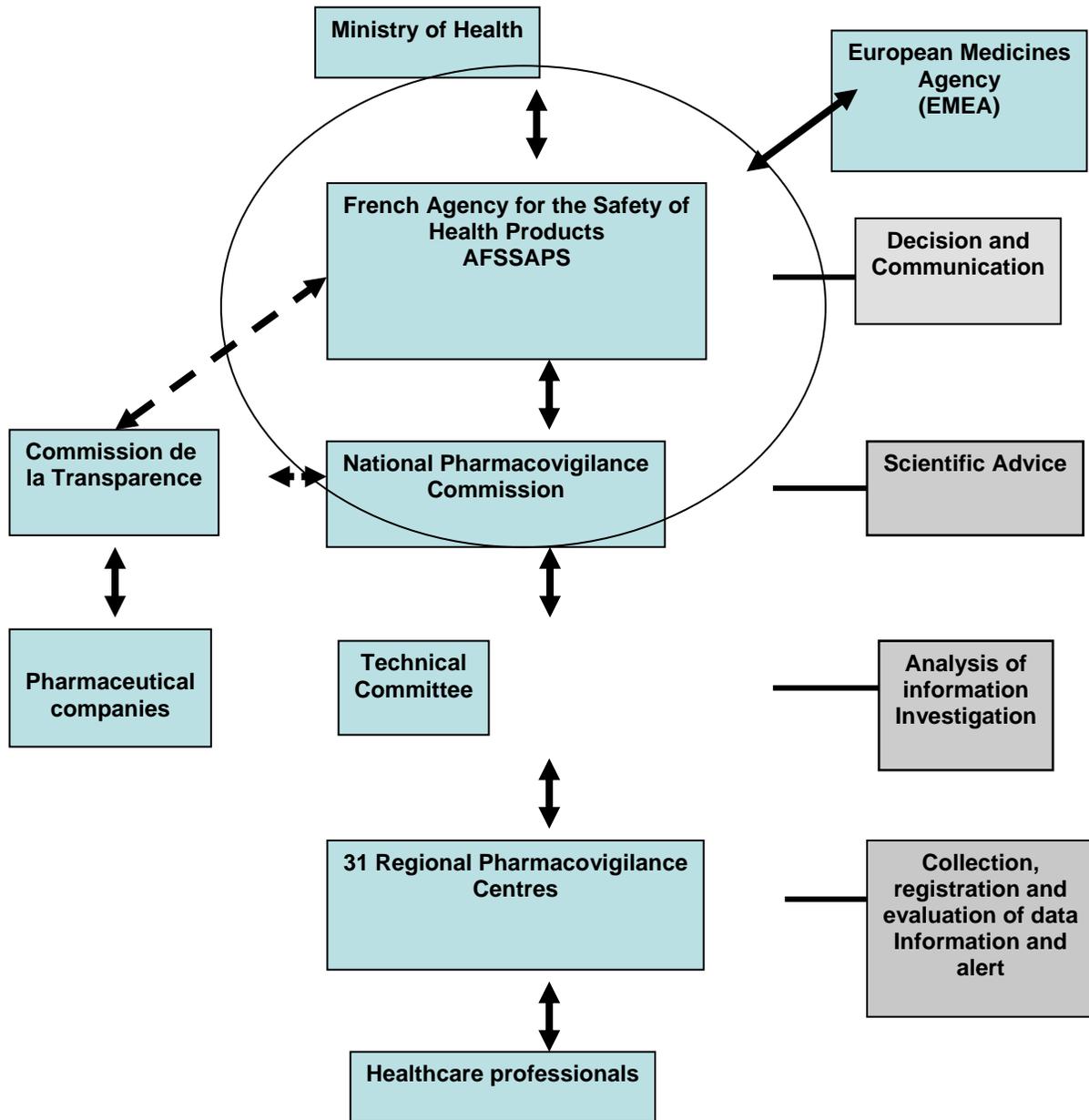
**Figure 9 - Vigilance Risk Management of Medicines Division (VRMM)**



**Figure 10 – MHRA Pharmacovigilance Risk Management**

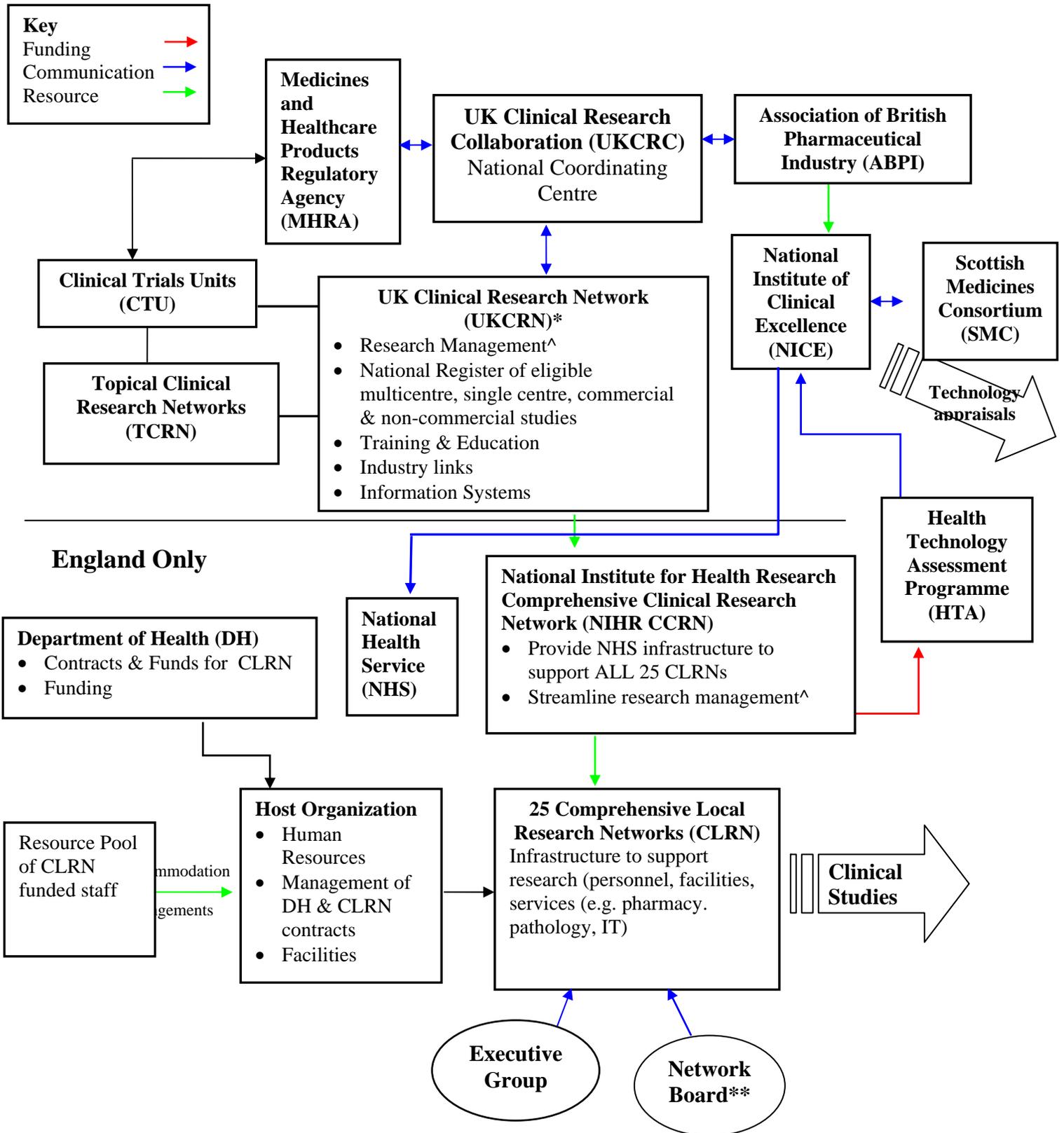


**Figure 11 French Pharmaco-surveillance Systems**



Adapted from: Moore N, Kreft-Jais C, Dhanani A Spontaneous reporting – France Chapter 16 in *Pharmacovigilance* Mann RD. and Andrews EB. editors. Chichester: Wiley, 2007: 217-27.

**Figure 12 UK Research Network**



\* UKCRN portfolio is England, Scotland, Wales and Northern Ireland. DH defines 'eligibility' for England. Emphasis is national competitive funding  
 ^ Research Management includes: study approvals, research governance, overseeing on-going studies, support to researchers, infrastructure, monitoring of activity for UKCRC, DH and the Industry Road Map Group and generates reports for CLRNs  
 \*\*Network Board: Area topic specific CLRN, academia, Constituent NHS Trusts, Host Organization clinical director