Viracept NGO Update and Advisory Meeting

Geneva
30th August 2007

Meeting Objectives

- Share an update of the situation
- Work in partnership to gain insights and expertise on establishment of patient registries
- Focus on resource-limited countries with the weakest health systems (primarily sub Sahara Africa)
- Meeting notes will be circulated

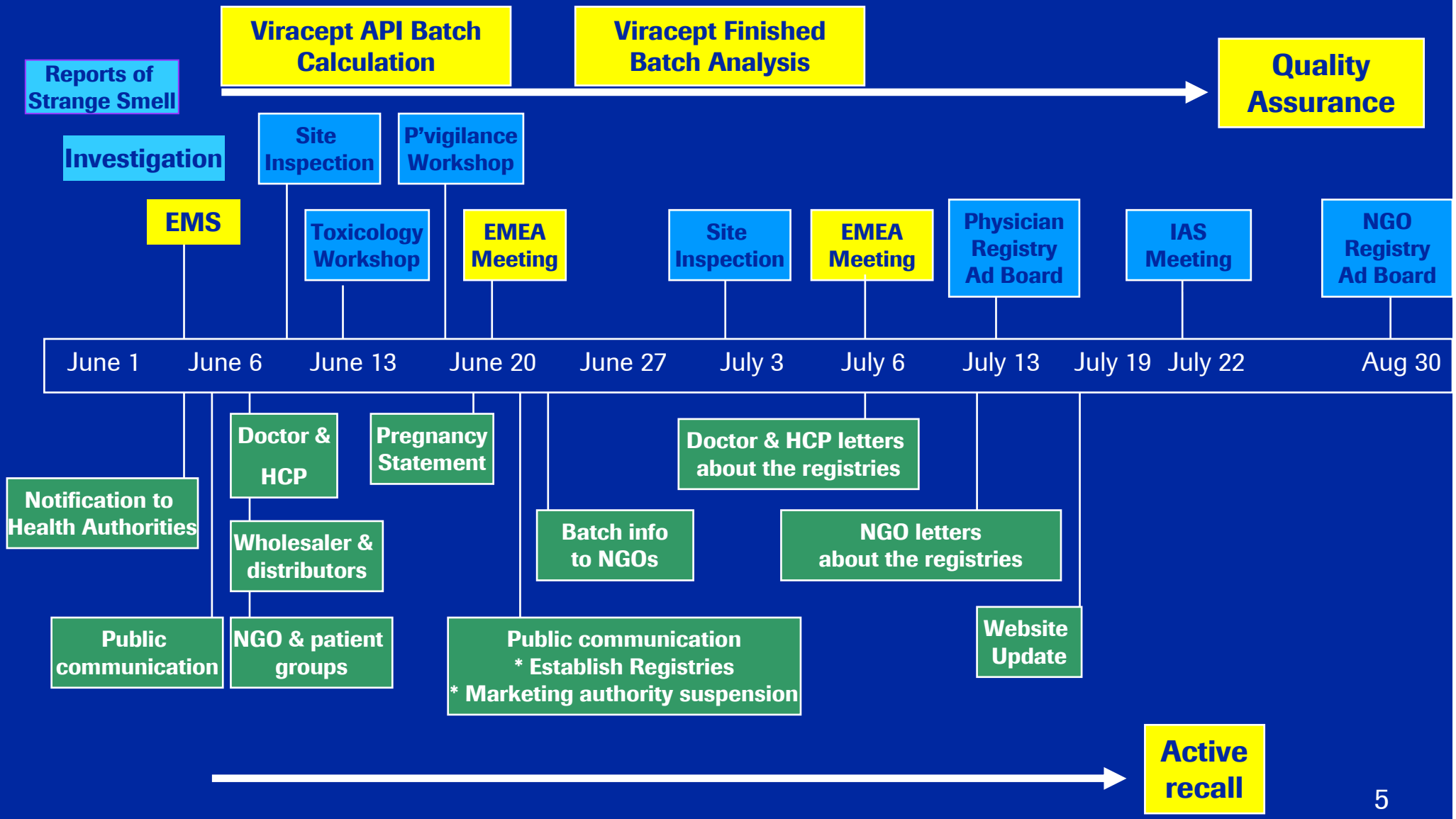
Agenda

9.30	Welcome and introductions	Maria Vigneau
9.45	Summary of the situation	Jenny Edge-Dallas
10.00	What we know about EMS	Malte Schutz
10.30	Coffee break	
10.45	Viracept manufacturing process	Malte Schutz
11.15	Overview of patients registries	Malte Schutz
12.00	Sub-Saharan Africa: Recall actions to date	Georges Koffi
12.30	Lunch	
13.30	Discussion: Health infrastructures in resource limited countries	Joep Lange
14.00	Discussion: Running the registries	Joep Lange
15.00	Open discussion and conclusions	Maria Vigneau
15.15	Departures	

Summary of the Situation

Jenny Edge-Dallas

General Summary of Findings and Communications



Date: Aug 22, 2007

NGO treatment providers in resource-limited countries – Roche Actions

- Written communications on the recall commenced June 8
  - Contacted purchasers of no profit and reduced priced Viracept ex Basel
- Transparent and open in all communications
  - Briefings at IAS conference, materials publically posted on www.roche-hiv.com
- Roche provided:
  - Communications for governments and HCPs
  - EMS levels by batch
  - Process and contacts for reimbursement of recalled Viracept and associated expenses
- Briefed Roche African management team and reprioritized and recruited additional African staff to assist recall process
- Working with African distributors to identify clinics supplied with Viracept
- Supported recall process for NGOs through Roche affiliates

Recall Reimbursement

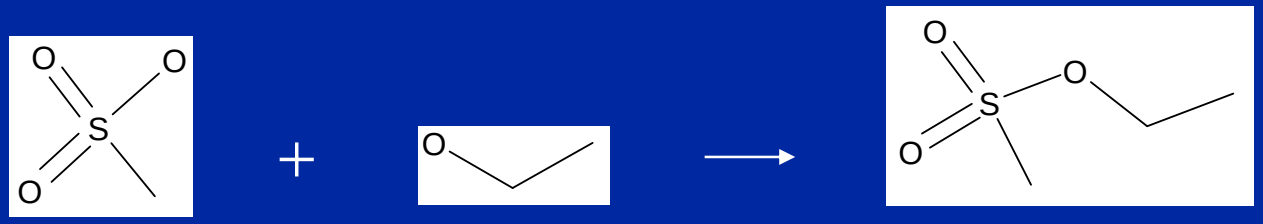
- Roche reimburses for
  - Healthcare provider visits facilitating change in therapy
  - returned or locally destroyed Viracept
  - Shipping and freight cost
  - Clearing charges
  - Duties
  - VAT
  - Import declaration form fees
  - Transport to warehouse and warehousing of recalled goods
  - Incineration costs
  - Certificate costs

What we know about EMS

Malte Schutz

What is EMS?

- EMS is ethyl methane sulphonate (sometimes called methanesulfonic acid ethyl ester)



MSA Ethanol EMS

- Known genotoxic substance
  - Reacts with DNA leading to alkylation of specific nucleotides
  - Evidence shows threshold level for DNA damage
  - Cellular DNA repair mechanisms are the likely explanation for the threshold levels of genotoxicity of EMS

- Only animal data exists on EMS

Chemical properties of EMS

- EMS has poor bioavailability
  - About 65% of orally administered EMS undergoes partial hydrolysis to ethanol and methanesulfonic acid in the mouse
  - Accumulation is not expected due to very rapid metabolism of EMS
- EMS reacts with proteins and DNA
  - Direct alkylation by transfer of the ethyl group
  - No metabolizing enzymes needed for the reaction
  - Alkylation occurs in all mammalian species, i.e. no species differences expected or known
  - This means that animal data can be used for human risk assessment

Carcinogenicity – evidence from the literature

- IARC Monographs: categorized as Group 2B agent = possibly carcinogenic to humans (no human data, sufficient evidence in animals)
- Most of the literature on EMS is for the parenteral route:
  - Alexander & Connell (1963): mouse, i.p. → kidney and lung tumours
  - Frei (1971): mouse, i.p. -> lung tumours
  - Clapp (1973): mouse, i.p. → lung tumours
  - Swann & Magee (1969): rat, i.p → kidney tumours, 1/22 rat with brain tumour
  - Hrushesky et al. (1972): rat, i.p. → "variety of benign and malign tumours" incl. lung carcinomas
  - Montesano et al. (1974): rat, i.p. → kidney tumours
  - Roe et al. (1962, 1963): newborn mouse, s.c.: → lung tumours
  - Walters et al. (1967): newborn mouse, s.c.: → lung tumours
- Limitations of these studies:
  - Parenteral route without exposure data
  - I.P. doses 33 and 372 mg/kg used (single dose and up to three doses with weekly intervals)
  - Most i.p. doses close to LD_{50} (rat: 350 mg/kg, mouse: 435 mg/kg)

Carcinogenicity – evidence from the literature

- Two publications looked at carcinogenicity of EMS given via drinking water to rats:
  - Ueo H et al. (1979): over 12 weeks
  - Ueo H et al. (1981) : over 2-12 weeks
- Result: Primarily mammary carcinomas (MC), also renal and uterine mesenchymal tumours
- Limitations for these studies:
  - Limited ability to accurately determine actual daily EMS intake values
  - Doesn't allow establishment of NOEL (**N**o **O**bserved **E**ffect **L**evel)

Potential exposure of Viracept patients to EMS

- Maximum impurity in affected Viracept tablets: 920 ppm of EMS*
- Maximum duration of use of batches with impurity: 3 months
- Maximum calculated daily dose of EMS: 2.8 mg or 0.06 mg/kg

  (based on daily dose 2.92g of Viracept base for a patient weighing 50 kg)

Calculation of daily intake in animal studies

- Using the lowest reported dose that produces tumors in young rats when EMS is taken orally via drinking water[1]
- **~40 mg/kg/day**
  - calculation based on 100 g body weight, 30 ml water intake/day, concentration: $1X10^{-3}$ M **= 0.124 mg/ml**
- This dose is at least 200 x higher than the maximum dose possible from affected Viracept

1. Ueo *et al* (1979)

* Originally calculated as 2300 ppm based on the amount of EMS in the API

Genotoxicity of EMS

- EMS damages the DNA by alkylation[2]
  - Covalent attachment of ethyl group within nucleotides
  - EMS induces mainly adducts at the N7 position of Guanine and to a minor extent O6 alkylations
  - O6 alkylations are known to transform more readily into mutations

➔Risk assessment for alkylating agents is normally based on a linear dose-response expectation,

➔Recent evidence suggests a non-linear dose-response for EMS-induced genetic damage *in vitro* and *in vivo*[2]

2. Doak et al., Cancer Res. 67, 2007, 3904-3911

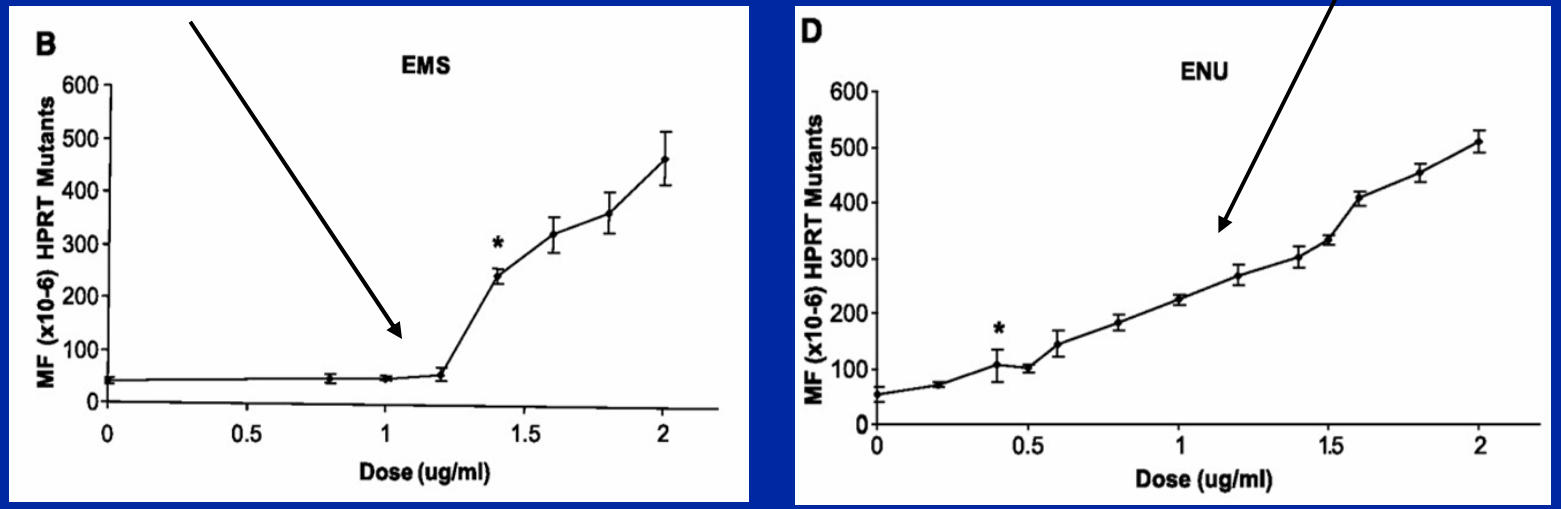
Evidence for a threshold of EMS effect

➡ *in vitro* results with evidence for a threshold

- Evidence of efficient repair of EMS-induced DNA damage at low concentrations
  - Repair conducted via base excision repair (BER) and O^6-methylguanine-DNA methyltransferase (MGMT)

Threshold dose response

Linear dose response



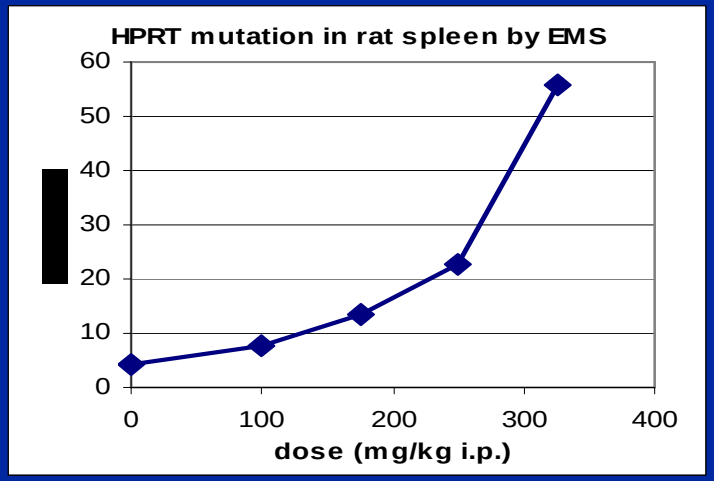
Dose-response for HPRT mutations in human cells *in vitro*

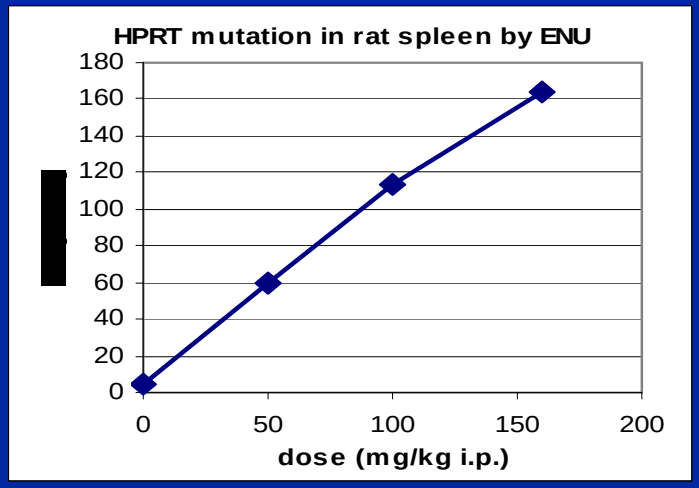
Doak et al., Cancer Res. 67, 2007, 3904-3911

Genotoxicity of EMS

➡ *in vivo* results with evidence for threshold

- *In vivo* mutation induction studies show a 'sublinear' dose response curve in rats after single intraperitoneal injection of EMS[3]
  - In contrast, ENU shows a linear dose response





3. Jansen et al., Cancer Research 55, 1995; 1875-1882

Risk Assessment for Human Embryo/Fetus

- Risk assessment, in mice, gives a hypothetical 0.1% incidence level at ~3 mg/kg
  - Based on linear extrapolation of dose-response for embryofetal effects
- Human highest potential exposure (0.06 mg/kg body weight) gives a hypothetical risk of below 0.005%, i.e. less than 1 in 20,000
- In comparison, the spontaneous incidence of malformations in the human population is between 2.5 and 3%

Platzek T, et al, (1995). Teratog, Carcinog, Mutagenesis; 15:81-92

Lack of complete toxicity data requires a responsible study plan

- Study 1: Induction of LacZ gene mutations
  - Aim: provide evidence of a sublinear/threshold dose response for EMS in low doses
  - Endpoint: LacZ mutations in mice

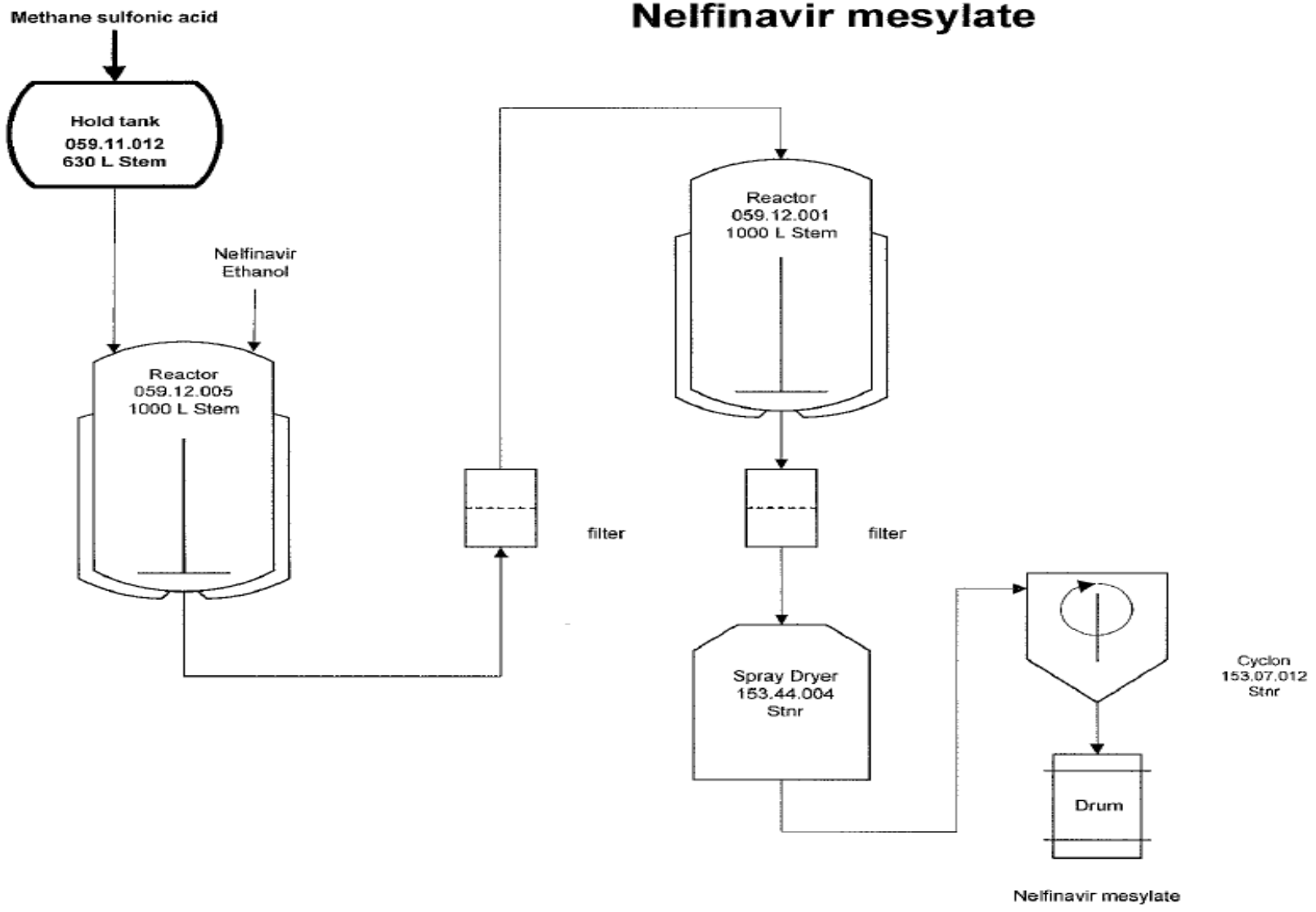
- Study 2: Induction of chromosomal damage
  - Aims: * provide evidence of a threshold dose response for EMS in low doses
    * provide further data for dose setting in the gene mutation study
  - Endpoint: Micronuclei damage

- Scheduling
  - Studies started in mid August 2007 with an interim update due in November 2007
  - Results expected January 2008

Viracept Manufacturing Process

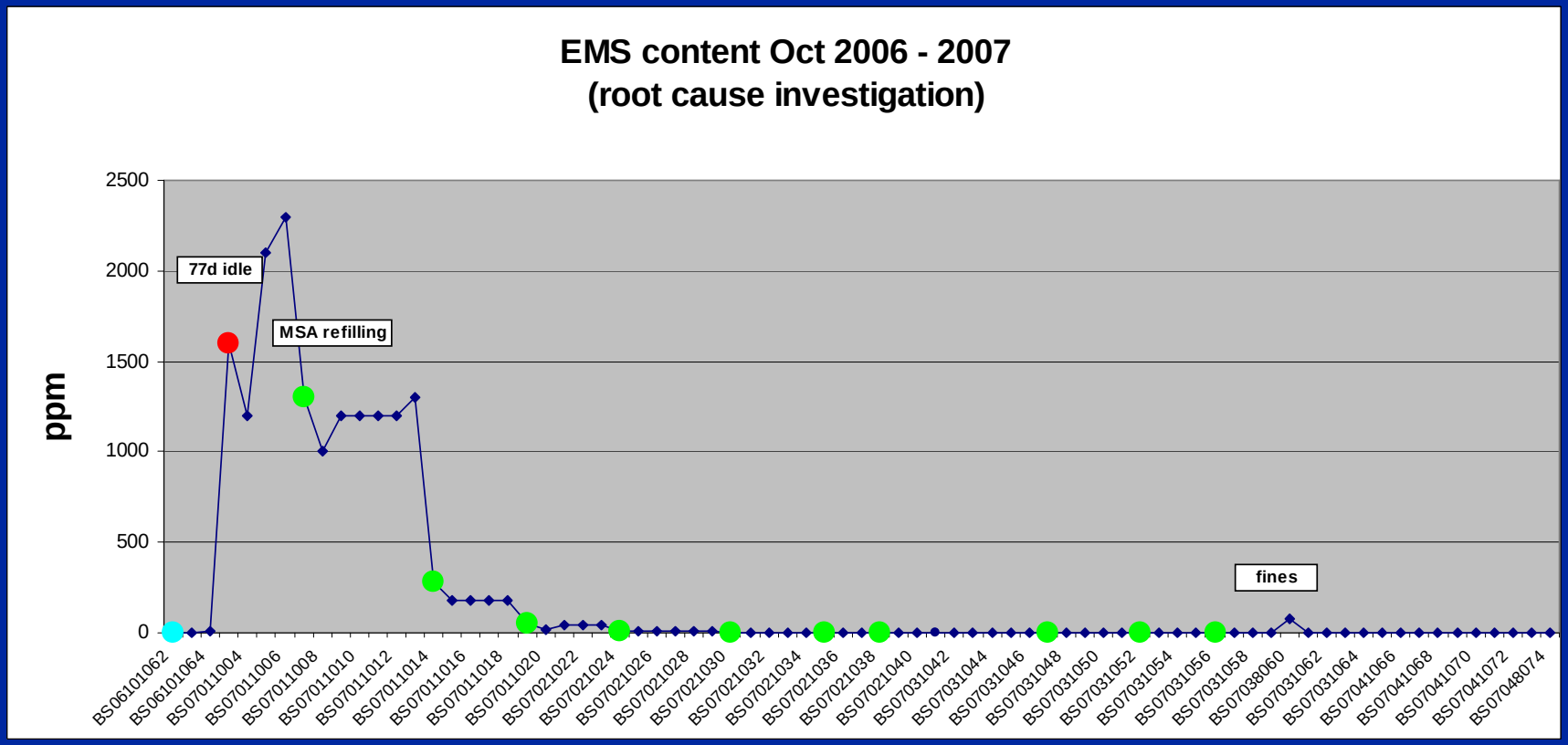
Malte Schutz

Nelfinavir mesylate



Viracept Production

EMS Formation in MSA Holding Tank



API Batch Numbers

- Blue dot indicates first production after MSA tank cleaning
- Red dot indicates first production after tank sat idle for 77 days
- Green dot indicates topping off of the MSA tank

EMS measurement was not required by health authorities; now part of the Viracept specifications

- Impurities like EMS are formed during the manufacture of pharmaceuticals and are not always part of the steps to release a product [1,2]

- In 2001, EMEA asked pharmaceutical manufacturers to evaluate EMS in production of medicines
  - Testing of sequential batches showed levels of EMS in production of Viracept within specification

1. CHMP Guidelines on the limits of genotoxic impurities, 28 June 2006

2. Muller L. Regulatory Toxicology & Pharmacology, 2006; 44: 198-211

EMS impurity levels in Viracept

- Since launch of Viracept, the majority of batches contained less than 1 ppm
  - Highest EMS level, by exception, in Active Pharmaceutical Ingredient (API)
    - 1999-2003: highest batch reading 25 ppm
    - 2004-March 2007: highest batch reading 132 ppm
    - March 2007-now: highest batch reading 2,300 ppm
- New analysis (developed and validated since June 5)
- During the final steps in the production of Viracept tablets, EMS level decreases by about 60%
  - Highest concentration found in tablets: 920 ppm (March 2007)
  - [Original calculation based on amount of EMS in API at 2,300 ppm]

Viracept oral powder not affected at levels greater than 1.3 ppm of EMS impurity

Countries which received shipments of Viracept produced from API containing EMS > 1,000 ppm

- Estimated total of 45,000 patients were taking Viracept at time of recall
  - Several large countries (i.e. Brazil = 30% of Viracept sales) were not affected
  - Rough estimate that up to 20,000-25,000 patients are from countries that received supply manufactured from > 1,000 ppm API

Country	Estimated Pts on Viracept*	Packs shipped	Country	Estimated Pts on Viracept*	Packs shipped	Country	Estimated Pts on Viracept*	Packs shipped
Botswana		639	**Iran**		2,593	**Portugal**	~860	2,271
Burkina-Faso		1,000	**Italy**	~2,000	2,206	**South Africa**	~340	1,976
Cameroon		1,200	**Kenya**		2,000	**Spain**	~1,700	2,029
Egypt		240	**Mali**		103	**Taiwan**	~260	1,053
France	~1,500	3,196	**Mexico**	~2,600	6,584	**Uganda**		417
Germany	~500	950	**Mozambique**		64	**Ukraine**	~630	7,975
Great Britain	~700	1,956	**Nigeria**		18			

* Estimated total number pts. on Viracept in country at time of recall based on sales, etc.

Corrective Actions Taken in Viracept Manufacturing

- Elimination of the MSA hold tank and direct charging from supplier's disposable container
- Testing of MSA for MMS/EMS has been implemented in 2005
- Revised procedure of mixing Viracept with MSA, which avoids any excess of MSA to be present
- Routine testing for EMS

Viracept Manufacturing
Next Steps

- Market Authorization has been withdrawn by EMEA
- All corrective actions have been implemented and production has been resumed
- Validation of new production process is ongoing
- Market authorization may hopefully be reinstated by October

- Viracept with EMS levels of <0.6 ppm is ready for shipment, awaiting market authorization by EMEA

Overview of Patient Registries

Malte Schutz

Two Viracept Registries planned

1. All patients potentially exposed to Viracept containing EMS at >1000 ppm in the API.
   - Registry will be restricted to patients in countries that received Viracept produced from API with EMS > 1000 ppm from time the material entered the distribution channel in March 2007 to the time of recall in June
   - to be revisited on review of data from the planned animal studies on mutation induction and exposure assessment
2. All pregnant women, children (under 18 years) and children exposed in utero since license approval at all levels of potential exposure to Viracept containing EMS.
   - Request to include all above patients from time of marketing authorization (1998)

Expert Advisory Meeting Outcome

- **Advisory Board was supportive of Roche proposed scope of registries:**
  - Registry #1:
    - New onset neoplasms in patients with potential exposure affected Viracept (produced from > 1000 ppm API)
  - Registry #2:
    - Birth defects in newborns exposed in utero to Viracept at any exposure since introduction in 1999
    - New onset neoplasms in children exposed to Viracept (directly or indirectly via exposure in utero) at any exposure since introduction in 1999

Some HIV negative people to be included in registries

- **Advisory Board suggested need to follow additional patients;**
  - Registries #1 and #2: Non-HIV infected patients exposed to Viracept for post-exposure prophylaxis
  - Registry #2 (included in proposal): Non-HIV infected children born to HIV-infected mothers exposed to Viracept during pregnancy.

Registry of registries approach

- **For both registries, Advisory Board suggested:**
  - Focus on existing HIV registries or observational cohorts rather than trying to create new infrastructure de novo
    - Plethora of existing HIV registries and observational cohorts in many countries
      - Adult HIV registries
      - HIV Pregnancy registries
      - Pediatric HIV registries
  - Implement “Patient log” in countries / areas where there are no existing HIV registries or use of such registries problematic
    - Solicitation via Health Care Providers
      - Request to inform Registry only of any new onset neoplasms
      - No periodic updating
      - Listing of patients available in case of need for further communication

Advantages of collaborating with existing Registries

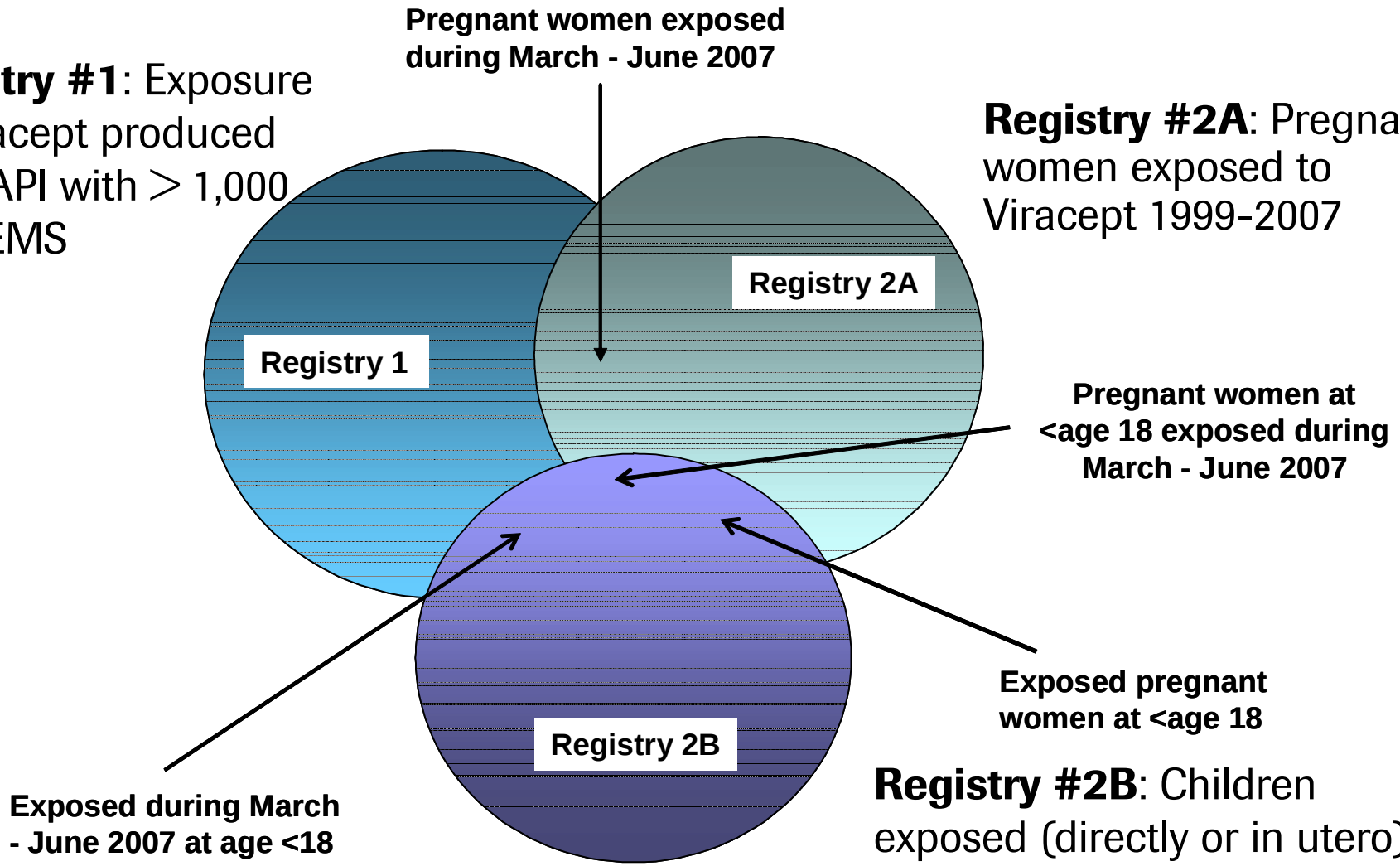
- **Working with existing HIV registries and observational cohorts will allow:**
  - Inclusion of comparator groups
    - Will allow for rigorous “within study” comparisons of incidence rates of specific new-onset neoplasms
  - Existing registries viewed as credible
    - Physicians and patients more likely to participate than in a “Roche only” program, which might be perceived as self-serving
  - Retrospective data already in existing registries/cohorts will provide some answers much sooner than would be possible if we were to create a new infrastructure *de novo*
- “Patient Log” will serve to register patients in areas where existing HIV registries/observational cohorts do not exist or would be problematic
  - Cover non-HIV infected individuals who took Viracept for post-exposure prophylaxis

Overview of Viracept Registries

- **In reality there will be "3" Viracept Registries:**
  - Registry #1: Exposure to Viracept produced from Active Pharmaceutical Ingredient (API) with > 1,000 ppm EMS
  - Registry #2A: Pregnant women exposed to Viracept 1999-2007
  - Registry #2B: Children exposed (directly or in utero) to Viracept 1999-2007
- **Common elements**
  - All will be "Registry of registries", serving to work with existing HIV registries across countries to create a consolidated database
  - Include a "Patient log" to register patients in areas where existing registries capture data on < 85% of exposed patients

Overview of Viracept Registries

Registry #1: Exposure to Viracept produced from API with > 1,000 ppm EMS



Registry #2A: Pregnant women exposed to Viracept 1999-2007

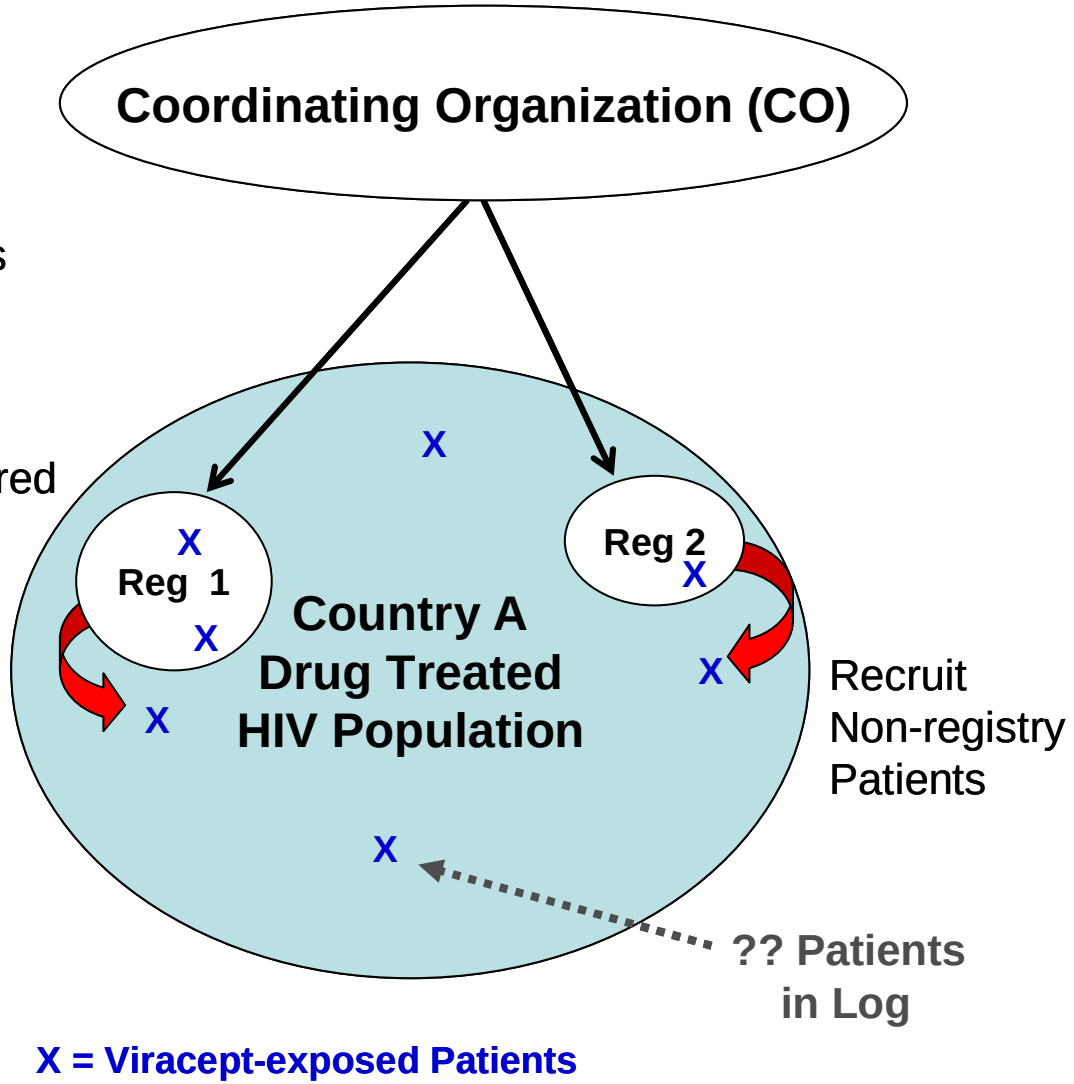
Registry #2B: Children exposed (directly or in utero) to Viracept 1999-2007

To some extent these registries will overlap, so that some activities of the registries will need to interact to prevent duplication of patient counts and effort.

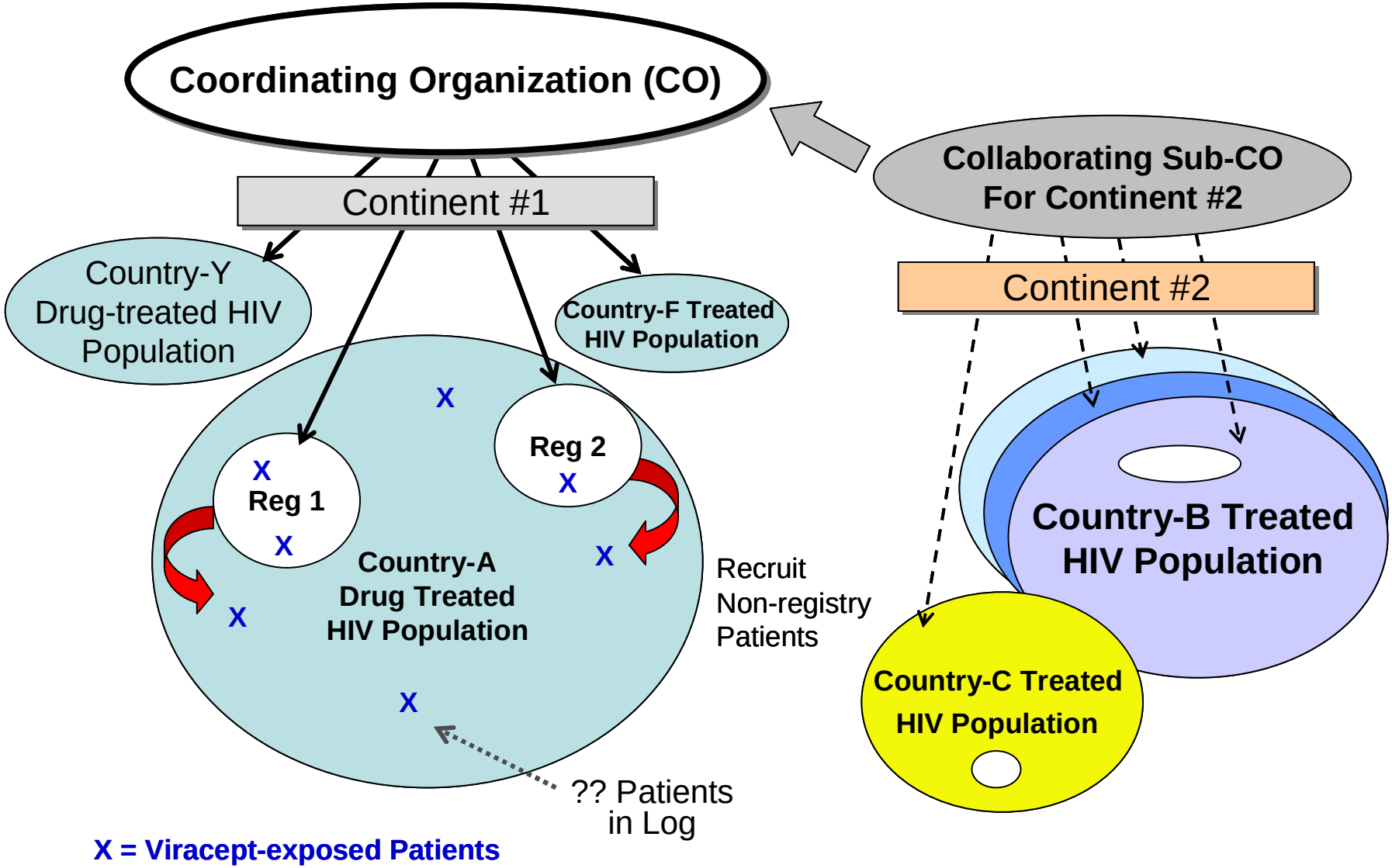
Schema of VIRA-EMS Registry 1 for One Country

Tasks

1. ID Registries
2. Determine suitability of registry
   - # exposed/eligible & controls
   - Ability to get non-registry patients
3. Obtain collaboration agreement
4. Enroll those in registry
5. Recruit non-registry pts
6. Determine proportion exposed captured
7. Determine need for additional Patient Log procedure



Schema for VIRA-EMS Registry 1 for Multiple Countries



Viracept Registries Summary

- **There will be 2 Viracept EMS Registries**
  - Registry #1: Exposure to Viracept produced from Active Pharmaceutical Ingredient (API) with > 1,000 ppm EMS
  - Registry #2A: Pregnant women exposed to Viracept 1999-2007
  - Registry #2B: Children exposed (directly or in utero) to Viracept 1999-2007
- **Registry of Registries: Focus on existing HIV registries or observational cohorts rather than trying to create new infrastructure de novo**
  - Inclusion of comparator groups
    - Will allow for rigorous "within study" comparisons of incidence rates of specific new-onset neoplasms
  - Enhanced credibility
  - Retrospective data already in existing registries/cohorts will provide some answers much sooner than would be possible if we were to create a new infrastructure *de novo*
- **Implement "Patient log" in countries / areas where there are no existing HIV registries or use of such registries problematic**

Sub-Saharan Africa: Recall Actions to Date

Georges Koffi

Roche presence in Africa

- Morocco*
- Egypt*
- Cote d'Ivoire
- Ghana
- Ethiopia
- Uganda
- Kenya
- Tanzania
- Senegal
- Cameroon
- Namibia
- Botswana
- South Africa*
- Mauritius
- Madagascar

* Denotes full affiliate presence

Roche in sub-Saharan Africa

- Small infrastructure
  - One affiliate (South Africa)
  - Liaison offices/agents in other countries
    - Non-Roche independent distributor supply chain in most countries

- Antiretrovirals supplied by various routes:
  - Except South Africa, local distributors order from Basel
  - MoH tenders
  - Orders placed by NGOs / treatment providers from
    - Roche Basel
    - Roche Affiliates (mostly until 2003)
      - Senegal and Cote d'Ivoire still placing orders from France

Update on Recall

- First information provided from Roche on 6th June 2007
  - Communication to NGOs directly from Roche Basel
- Sub Sahara Africa is divided in 5 operational regions with Regional Managers in charge of operational activities :
  - Francophone West Africa,
  - Eastern Africa,
  - Southern Africa,
  - Anglophone West Africa and
  - Indian Ocean
- Each Regional Manager contacted responsible authorities (by fax, courier or telephone) to
    - Inform them about the recall
    - To document acknowledgement of receipt of information

Update on Recall

- Authorities and key organisations contacted:
  - Ministries of Health,
  - National AIDS Programs
  - Local NGOs
  - Distributors (public and private)

- New relevant information is being forwarded to local Authorities (i.e. batch numbers, previous orders to Roche logistic, destruction process, registries, etc.)
- Regular contact with distributors & customers for update on goods in quarantine

Information to countries and feed-back from local Authorities (Anglophone Africa)

Country	First contact with MoH	Feed back on information	Action from Authorities
Angola	06 June 2007	NO	NA
Botswana	06 June 2007	YES	Letter to Hc. P & Pts associations
Burundi	06 June 2007	YES	Letter to Hc. P
Djibouti	06 June 2007	NO	NA
Ethiopia	06 June 2007	YES	Letter to Hc. P & Pts associations
Gambia	06 June 2007	NO	NA
Ghana	06 June 2007	YES	Letter to Hc, Media interview & Pts associations
Kenya	06 June 2007	YES	Letter to Hc. P & Pts associations
Liberia	06 June 2007	NO	NA
Malawi	06 June 2007	NO	NA
Mauritius	06 June 2007	YES	Press release and information to Hc at Treatment centers
Mozambique	06 June 2007	NO	NA
Namibia	06 June 2007	YES	Letter to Hc. P & Pts associations
Nigeria	06 June 2007	YES	Letter to Hc
Rwanda	06 June 2007	YES	Information to Hc
Seychelles	06 June 2007	YES	Letter to Hc. P & Pts associations
Sierra Leone	06 June 2007	NO	NA
Tanzania	06 June 2007	YES	Letter to Hc. P & Pts associations
Uganda	06 June 2007	YES	Media Advert & information to Hc
Zambia	16 July 2007	YES	Media Advert & information to Hc
Zimbabwe	06 June 2007	NO	NA

Zambia received phone notification on June 6

Information to countries and feed-back from local Authorities (Francophone Africa)

Country	First contact with MoH	Feed back on information	Action from Authorities
Benin	06 June 2007	YES	Letter to Hc & Pts associations
Burkina Faso	06 June 2007	YES	Information to Hc. P.
Cameroon	06 June 2007	YES	Information to Hc. P.
CAR	06 June 2007	NO	NA
Congo	06 June 2007	NO	NA
Cote d'Ivoire	06 June 2007	YES	Letter to Hc & Pts associations
DRC	06 June 2007	NO	NA
Equatorial Guinea	06 June 2007	NO	NA
Gabon	06 June 2007	YES	Letter to Hc & Pts associations
Guinea	06 June 2007	NO	NA
Madagascar	06 June 2007	YES	Letter to Hc & Pts associations
Mali	06 June 2007	NO	NA
Niger	06 June 2007	NO	NA
Senegal	06 June 2007	YES	Information to Hc. P.
Togo	06 June 2007	YES	Information to Hc. P.

Key Challenges in Africa

- Contact with some African Authorities has been difficult
  - fax, email, telephone not always available
- Multiple stakeholders in supply chain and care provision
- Recall procedures challenging in resource poor environments
- Lack of locally available replacement therapies

Current Activities

- Contacting Authorities again who have not replied since June 2007 (ongoing)
- Continuing to collect returned goods in all countries for destruction
- Additional staff appointed
  - To follow-up on and check goods recalled
  - To follow up & ensure proper destruction process or return to Basel
  - To work with Authorities on the establishment of registries

Discussion & Conclusions

Maria Vigneau

Facilitator