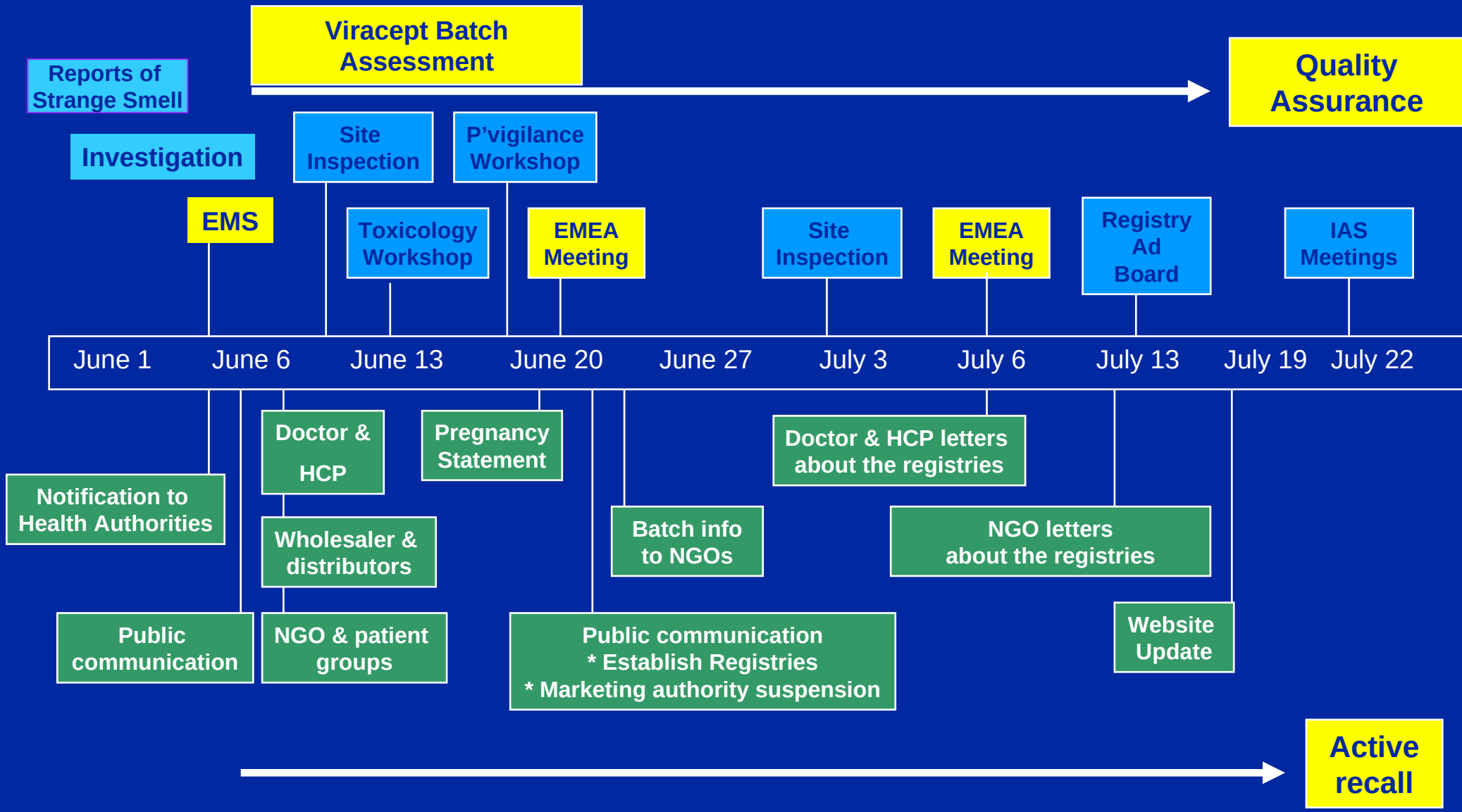
Viracept Recall – an Update

23rd July 2007

Content

- **Summary of the situation**
- NGO treatment providers in resource-limited countries
- What we know about EMS
- Viracept manufacturing process
- Patient Registries
- Questions

General Summary of Findings and Communications



Date: July 21, 2007

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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
- Roche provided:
  - EMS levels by batch supplied
  - Communications for HCPs
  - Process and contacts for reimbursement of recalled Viracept and associated expenses
- Briefed Roche African management team and reprioritized African staff to assist recall and registries process
- Working with African distributors to identify clinics supplied with Viracept
- Supported recall process by NGOs through Roche affiliates (where existing)

NGO treatment providers in resource-limited countries – Next steps

- Seek further input on local recall and registries
- August 30 in Geneva: Advisory board meeting scheduled with NGOs and key stakeholders
  - Goal - to work in partnership on local challenges across Africa to collect patient registry information

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What is EMS?

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

- 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

- Maximal exposure for affected Viracept patients to EMS is estimated to be 0.06 mg/kg/day
  - Considerably below the dose levels which induce genotoxic effects in single dose animal studies (40 mg/kg/day)

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: 960 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 nelfinavir 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

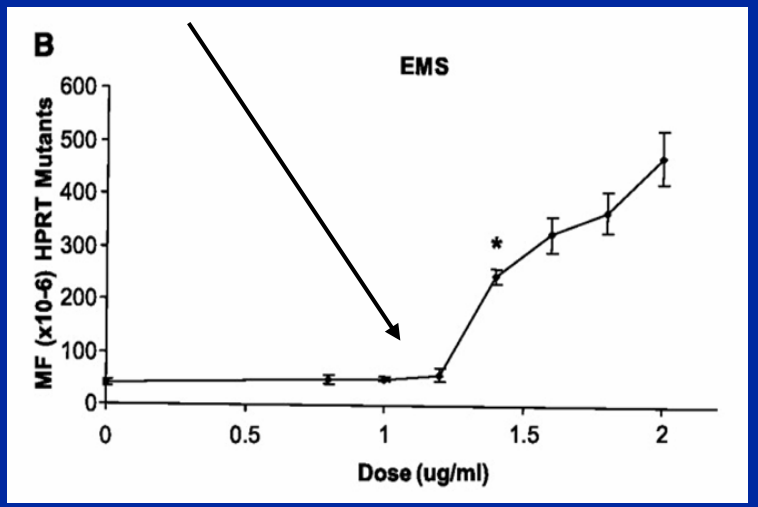
1. Ueo *et al* (1979)

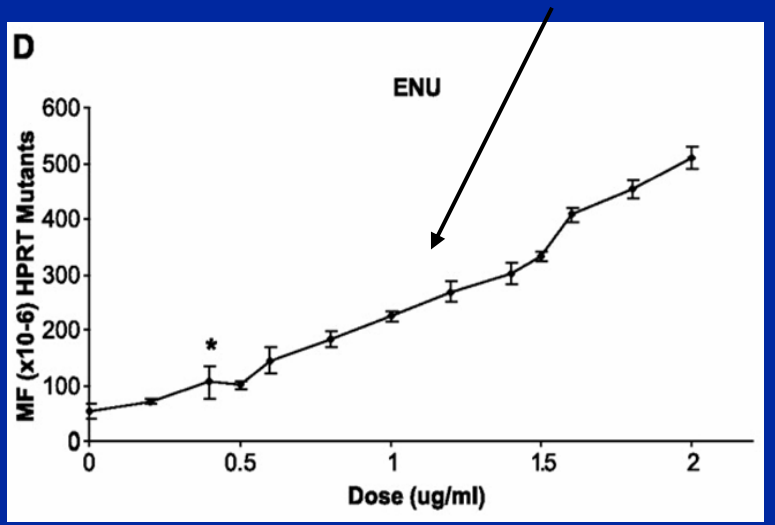
Evidence for a threshold of EMS effect

- Evidence of efficient repair of EMS-induced DNA damage at low concentrations

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

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

- Planned 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

- Planned 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 start in mid August 2007 with an interim update end of October 2007
  - Results expected December 2007

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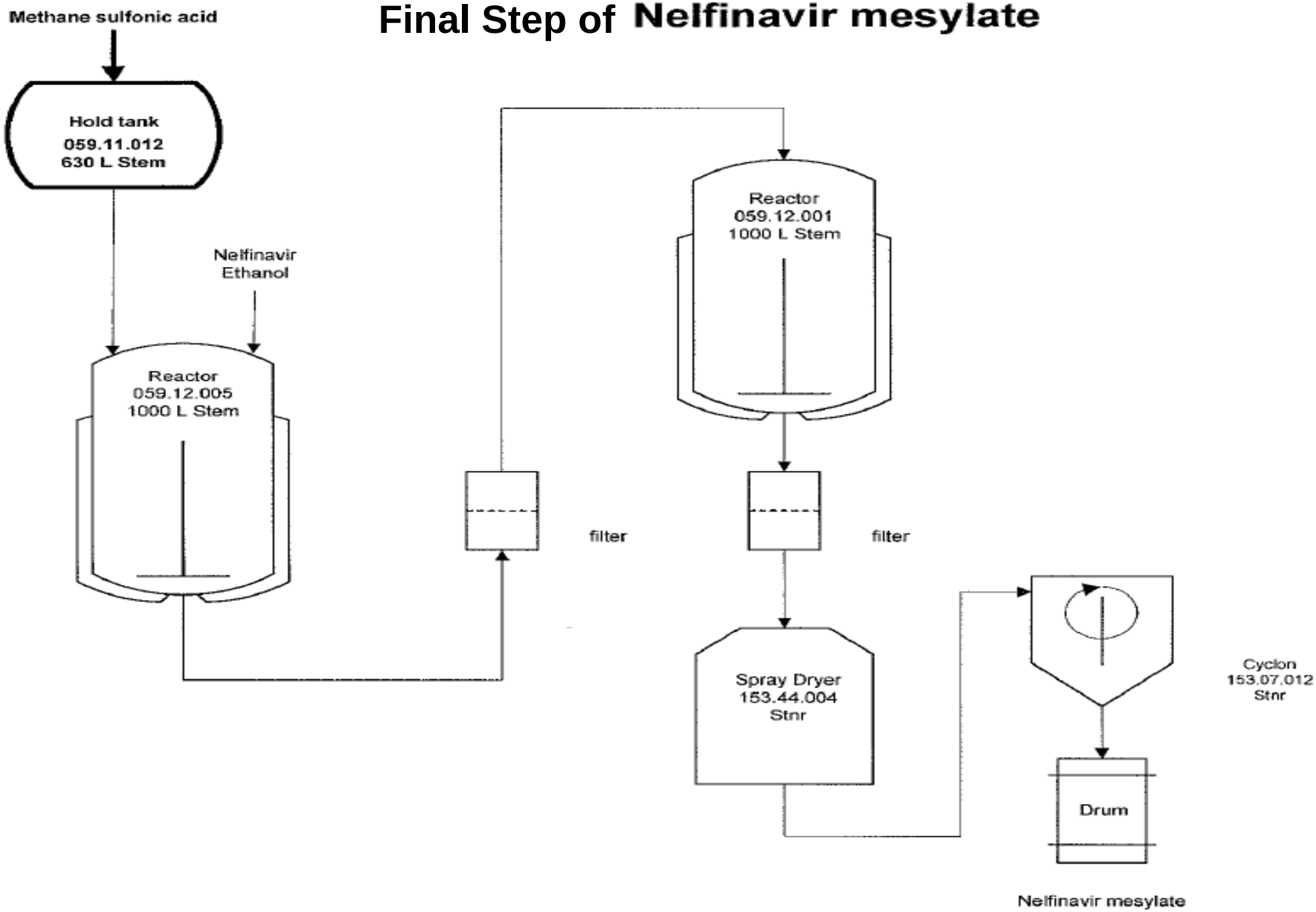
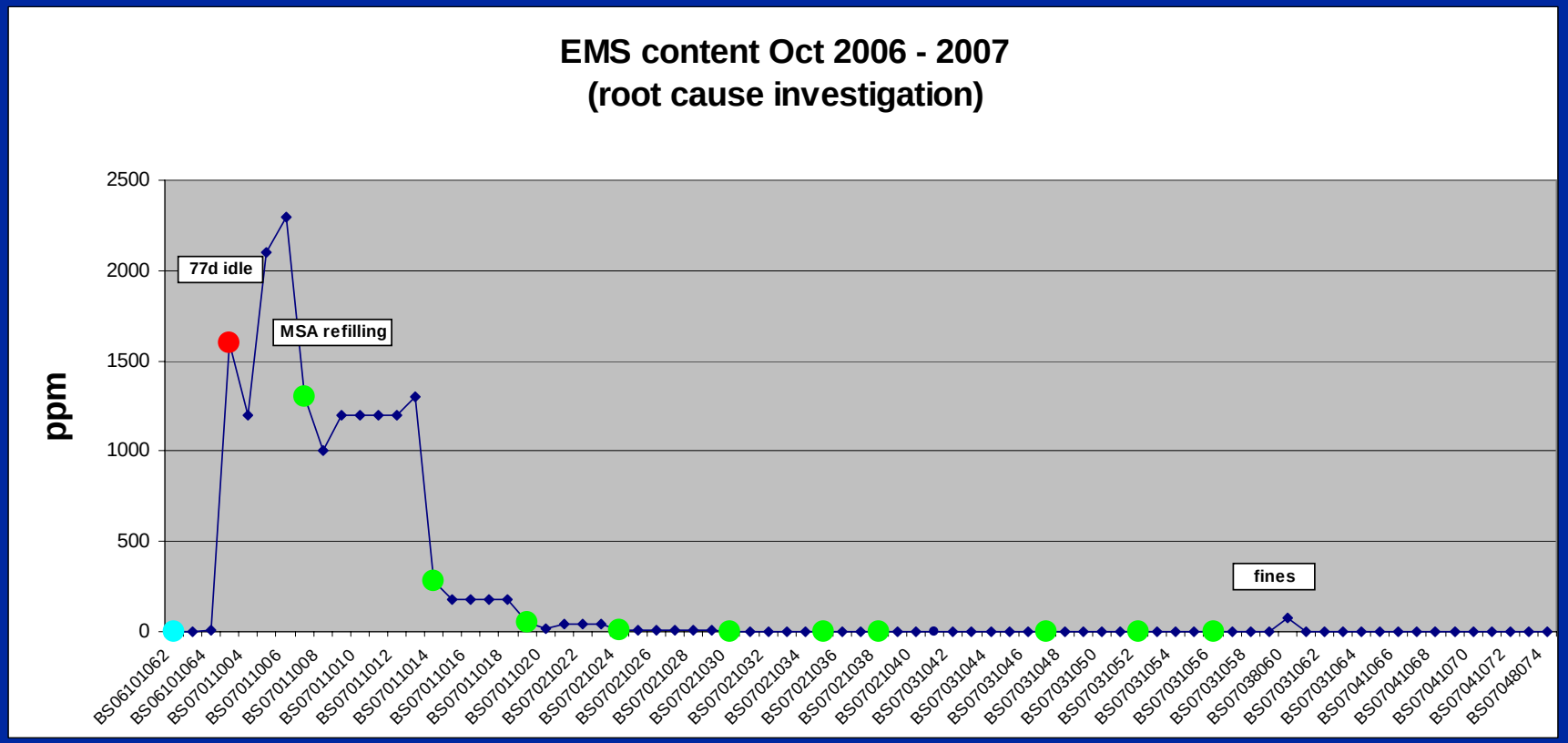
Final Step of Nelfinavir mesylate



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
  - Our tests 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)
  - 1998-2003: 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): in preparation of Viracept tablets EMS level decreases by 60%
  - Highest concentration found in tablets: 960 ppm (March 2007)

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Review of Adverse Event Databases

- Review of Drug Safety databases (Roche ADVENT and WHO) for Viracept has not demonstrated any signal of neoplasms, birth defects or any other toxicity

Viracept Registry 1

- All Patients potentially exposed to Viracept tablets produced from API containing > 1000 ppm of EMS
- Population and scope
  - Countries:
    - Botswana, Burkina-Faso, Cameroon, Egypt, France, Germany, Iran, Italy, Kenya, Mali, Mexico, Mozambique, Nigeria, Portugal, South Africa, Spain, Taiwan, Uganda, Ukraine, UK
  - Viracept prescriptions from March 1, 2007 through June 30, 2007
  - Focus on rates of malignancies

Summary of recommendations as agreed on with health authorities. Details of protocol design and implementation are under discussion with health authorities.

Viracept Registry 2:

- All women receiving Viracept while pregnant, children exposed in utero and children (<18 years) treated with Viracept
- Population felt to be potentially more vulnerable
  - All countries that received Roche-supplied Viracept
  - Viracept treatments since 1999
  - Focus on pregnancy outcome and observational follow up of children for malignancies
- Very challenging to identify these patients going back in time

Summary of recommendations as agreed on with health authorities. Details of protocol design and implementation are under discussion with health authorities.

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