

# Regulatory challenges in product characterization

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**Health Products and Food Branch**  
**Direction générale des produits de santé et des aliments**

# OUTLINE

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- 🔔 Main elements of DS Characterization.
- 🔔 Related submission requirements, guidance and responsibilities.
- 🔔 Main deficiencies related to DS process, impurity profile and associated challenges.
- 🔔 Case study of DS process impact on genotoxic impurity content.
- 🔔 TPD's approach to minimize deficiencies and improve the review process.
- 🔔 Some final thoughts.



# Product characterization

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- 🔔 Involves quality control testing programs consisting of a meaningful array of in-process and final product tests that provide reasonable assurance of product safety, quality, and purity (FDA website).
  - Drug substance characterization
  - Drug product characterization
- 🔔 Process of using measurements to gain insight and improve design (Agilent Technologies).
- 🔔 Process understanding and appropriate setting of quality control programs (QbD?).



# Drug substance characterization

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- 🔔 Starts with the synthetic process (impact all other aspects)
- 🔔 Main aspects:
  - Chemical properties
    - ▲ DS molecular structure (neutral, free acid/base, salt, chiral)
    - ▲ Related Impurity profile (DS related, reagents, solvents)
    - ▲ Stability profile (degradation)
  - Physical properties
    - ▲ Amorphous/crystalline
    - ▲ Polymorphic forms/solvates
    - ▲ Particle size
- 🔔 Support/justification for DS/DP specifications
- 🔔 Impact of DP process (C&P properties change?)



# Related submission requirements

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- 🔔 “Quality (C&M) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)”
  - S 2.2-2.6 (DS synthetic process & controls)
  - S 3.1-3.2; S7 (DS C&P properties)
  - S 4 (DS Specifications)
  - P2 (Impact of DP process on C&P properties)
- 🔔 ICH CTD (M4) Guidelines should be consulted on formatting issues.



# Related Specific Guidance

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- 🔔 Potential impurities (ICH Q3s)
- 🔔 Stability profile (ICH Q1s)
- 🔔 Specifications (Q6A)
  - Decision tree # 1 & 2 (impurity/degradants)
  - Decision tree # 3 (particle size/polymorphism)
  - Decision tree # 5 (chirality)
- 🔔 Method validation (ICH Q2)



# Responsibilities

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- 🔔 DP manufacturer (sponsor) is responsible for the quality of the DS used to formulate their product(s).
- 🔔 The DMF holder is responsible for updating the DMF every 5 years, regardless of whether any changes are made. A letter confirming that no changes have been made is acceptable.
- 🔔 **Communication challenge for all.**



# Drug substance information

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## In the submission

- All, CTD format + QOS
- All except reference to DMF closed part
- Open part DMF information not substitute for sponsor's own analysis (ID, impurity, polymorph, part. size ...)

## Type I DMF

- Draft DMF Guidance for comments (Sept. 5, 2008, 60 days)
  - ▲ All DMF types (I to IV) for pharmaceuticals, NHPs, biotech/biol.
  - ▲ Clarified procedures (administrative and review)
  - ▲ Reflects ICH adopted guidelines

## EDQM CEP

- Pilot project for acceptance in lieu of DMF closed part.



# Main deficiencies (S 2.2-2.6)

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- 🔔 Lack of information on the starting material.
  - ID and Source(s). (significant structural fragment of DS)
  - Synthesis (brief description, reagents, solvents, intermediates).
  - Justification for specifications (ID, potency, impurities).
- 🔔 Lack of information on intermediates.
  - Justification for specifications of isolated intermediates.
  - Justification for not isolating an intermediate.
  - How obtaining a non-isolated intermediate is ensured?
- 🔔 Lack of information on synthetic process (from SM to DS)
  - Reaction completion monitoring (continuous process)
  - Level of details insufficient (quantities, equipment, conditions, in-process controls, work-up procedures at each step..).
  - Details of isolation and purification steps of DS.
- 🔔 **Lack of discussion linking process to impurity control.**

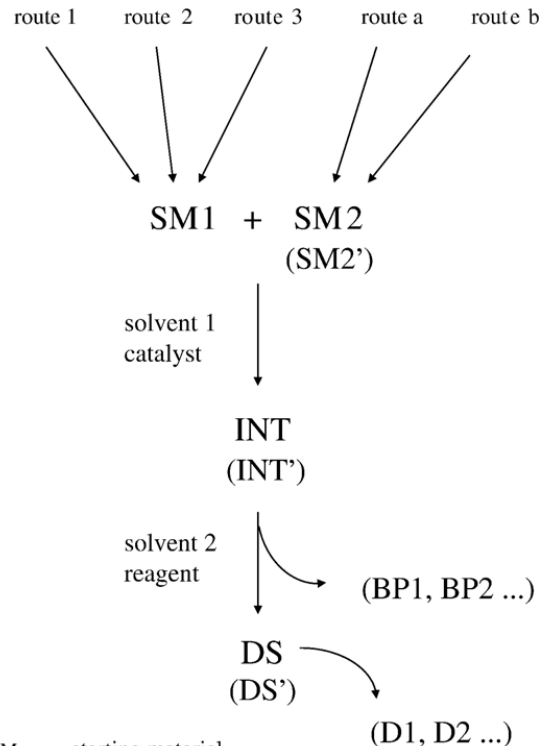


# Main deficiencies (S3.2)

- 🔔 Certain potential impurities not considered or investigated.
  - Too much reliance on compendia (do not cover all DS sources and processes).
  - Apparent lack of consideration for non-API related impurities, (e.g. reagent-solvent side reaction).
  - Assumptions? (e.g. SM not included as potential impurity?)
- 🔔 Lack of discussion/justification on potential impurity control
  - **Origin (specific), fate and rejection mechanism of potential impurity.**
  - Static control (limits in SM, Intermediates, API specifications)
  - Dynamic control (in-process reduction/elimination, how?, C&P properties)
  - **Justification for (not) including in DS specifications (and of limits).**
- 🔔 Insufficient consideration for potential genotoxic impurities
  - Genotoxic reagents widely used in synthesis (not easy to avoid using).
  - Residues in API should be avoided whenever possible.
- 🔔 **Lack of discussion linking impurity control to process**



# DS General Synthetic Process



SM = starting material  
 INT = intermediate  
 DS = drug substance  
 SM' = starting material impurity with potential to form INT' and DS'  
 BP = reaction by-product  
 D = degradation product

- 🔔 Different paths to a given SM.
- 🔔 Different paths to a given DS (SM to INT to DS).
- 🔔 Different process conditions to a given path to a given DS.
  - Different solvent(s).
  - Different reaction time, T°...
  - Different stoichiometry.
  - Different work-up.
  - Different isolation/purification.
  - Isolated/non-isolated INT.
- 🔔 All (±) impact on impurity profile.
- 🔔 Each DS process is unique.
- 🔔 Thorough understanding key to appropriate setting of quality control programs.

M.D. Argentine et al. / Advanced Drug Delivery Reviews 59 (2007) 12–28



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# Associated regulatory challenges

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## Missing information:

- Considerable time spent searching for it.
- Increase questions and reviewing answers.
- Increased review time. Impact NON.

## No clear link of process & impurity control:

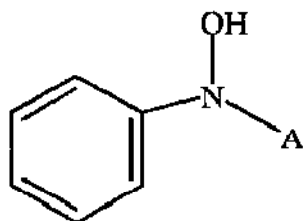
- Similar impact as for missing information
- Reviewers do not guess (they ask questions).

## Limited guidance available (variable)

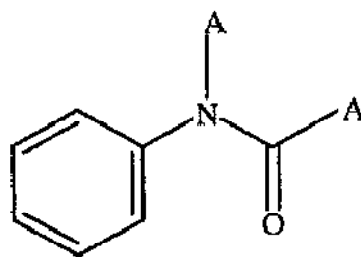


# Alerting Structures

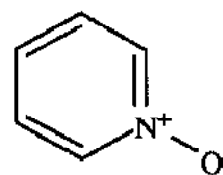
## Group 1: Aromatic Groups



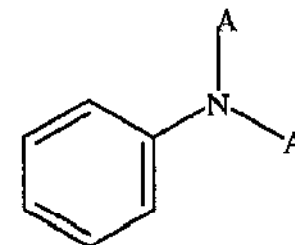
N-Hydroxyaryls



N-Acylated aminoaryls



Aza-aryl N-oxides



Aminoaryls and alkylated aminoaryls

Purines or Pyrimidines, Intercalators, PNAs or PNAHs

 A = Alkyl, Aryl, or H

 Adapted from L. Müller et al., Regulatory toxicology and Pharmacology 44 (2006) 198-211

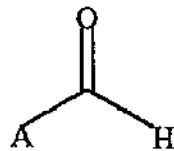


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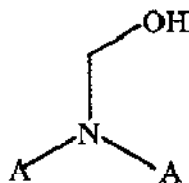
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# Alerting Structures

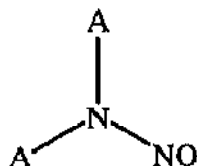
## Group 2: Alkyl and Aryl Groups



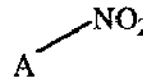
Aldehydes



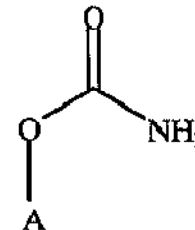
N-Methylols



N-Nitrosamines



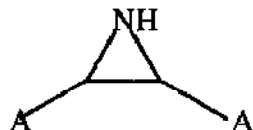
Nitro Compounds



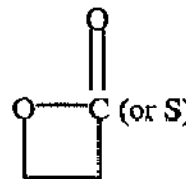
Carbamates (Urethanes)



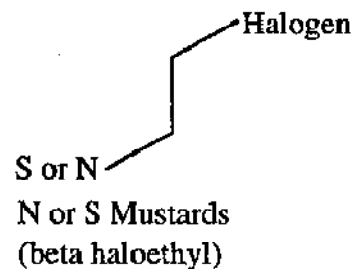
Epoxides



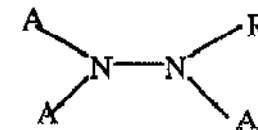
Aziridines



Propiolactones  
Propiosultones



S or N  
N or S Mustards  
(beta haloethyl)



Hydrazines and  
Azo Compounds

- 🔔 A = Alkyl, Aryl, or H
- 🔔 Halogen = F, Cl, Br, I

🔔 Adapted from L. Müller et al., Regulatory toxicology and Pharmacology 44 (2006) 198-211

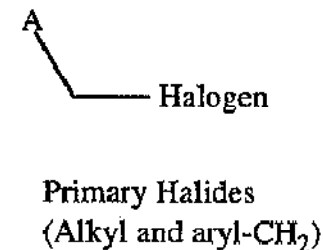
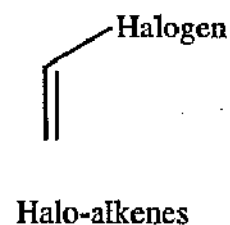
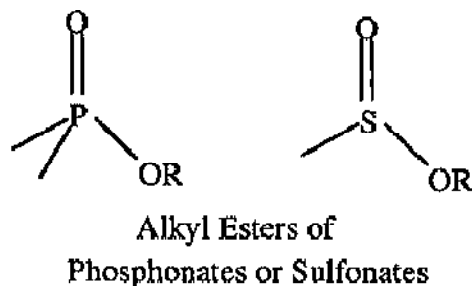
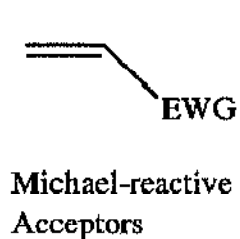


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# Alerting Structures

## Group 3: Heteroatomic Groups



↑ EMS

- 🔔 A = Alkyl, Aryl, or H
- 🔔 Halogen = F, Cl, Br, I
- 🔔 EWG = Electron withdrawing group (e.g., -C≡N, -C=O, ester etc...)

🔔 Adapted from L. Müller et al., Regulatory toxicology and Pharmacology 44 (2006) 198-211





# EMS contamination of Roche's Viracept

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- 🔔 DS is nelfinavir mesylate salt.
- 🔔 EMS is genotoxic.
- 🔔 Strange smell of DP reported (March 2007).
- 🔔 Investigation & recall (June 2007).
  - EMS levels up to 2300 ppm found in DS.
  - ~ 920 ppm in Viracept.
  - ~ 2.8 mg daily intake for patients.
  - All markets affected except Canada, Japan, US.
- 🔔 Suspension of MA in EU (August 6, 2007).
- 🔔 MA reinstated following corrective actions (Sept. 2007).



# Typical mesylate salt formation

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- 🔔 DS free base dissolved in an organic solvent or mixture of solvents (can include an alkyl alcohol).
- 🔔 Water usually present (co-solvent, in organic solvent).
- 🔔 Equimolar amount of MSA added (dropwise or mix).
- 🔔 Reaction at varying temperatures (salt ppt)
- 🔔 Isolation of salt and further processing (washing, filtering, recrystallizing...)

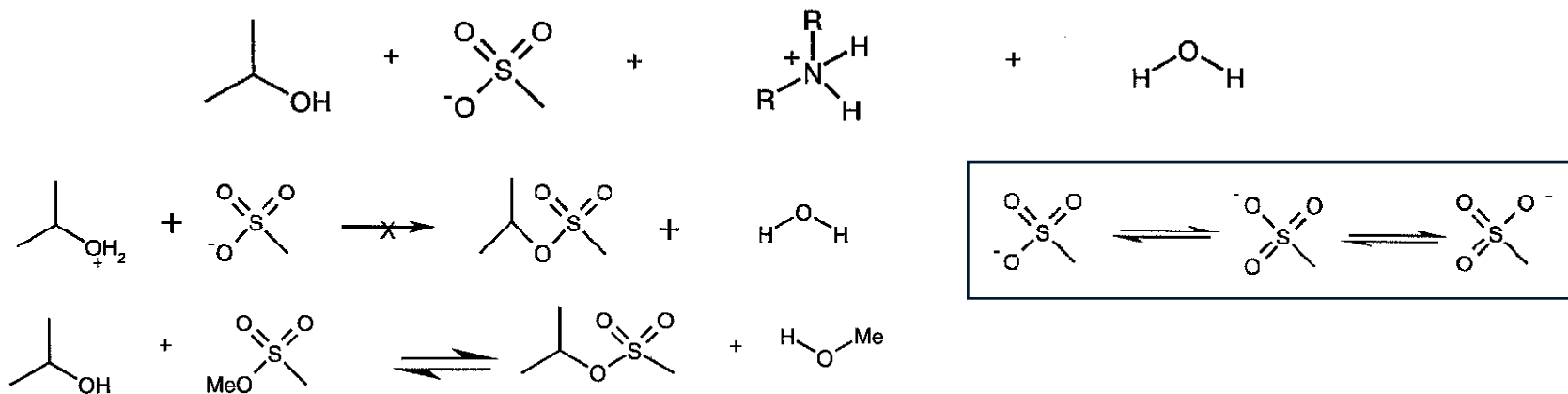
Adapted from: Snodin, D. J., Regulatory Toxicology and Pharmacology, 45 (2006) 79-90



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# Mechanistic considerations



- 🔔 Reaction of an alkyl alcohol with MSA in typical conditions of mesylate salt formation should not occur<sup>1</sup>. (pH control, alternative non-alcohol solvents, water?)
- 🔔 Low levels of MSC and/or MMS in MSA could be the source of alkyl mesylates. (MSA specifications).
- 🔔 Even if trace levels formed, process elimination (washing, mother liquors).
- 🔔 Testing DS with an appropriately validated method.

1. Adapted from: Snodin, D. J., Regulatory Toxicology and Pharmacology, 45 (2006) 79-90



# EMS C&P Sigma Aldrich

## Ethyl methanesulfonate

Product Number **M 0880**  
Store at Room Temperature

### Product Description

Molecular Formula:  $C_3H_8O_3S$   
Molecular Weight: 124.2  
CAS Number: 62-50-0  
Boiling Point: 213-213.5 °C<sup>1</sup>  
Density: 1.17 g/ml  
Molarity: 9.4 (neat liquid)  
Synonym: EMS

Reaction rate constants and half-lives for aqueous solutions of this product were calculated at increasing temperatures and at several pH's. The rate of hydrolysis is unaffected by varying (acidic) pH.

Temperature (°C)	Half-life in hours <sup>3</sup>
0	1716.0
5	796.6
10	378.7
15	185.7
20	93.2
25	48.5
30	7.8
45	4.6
50	2.7.

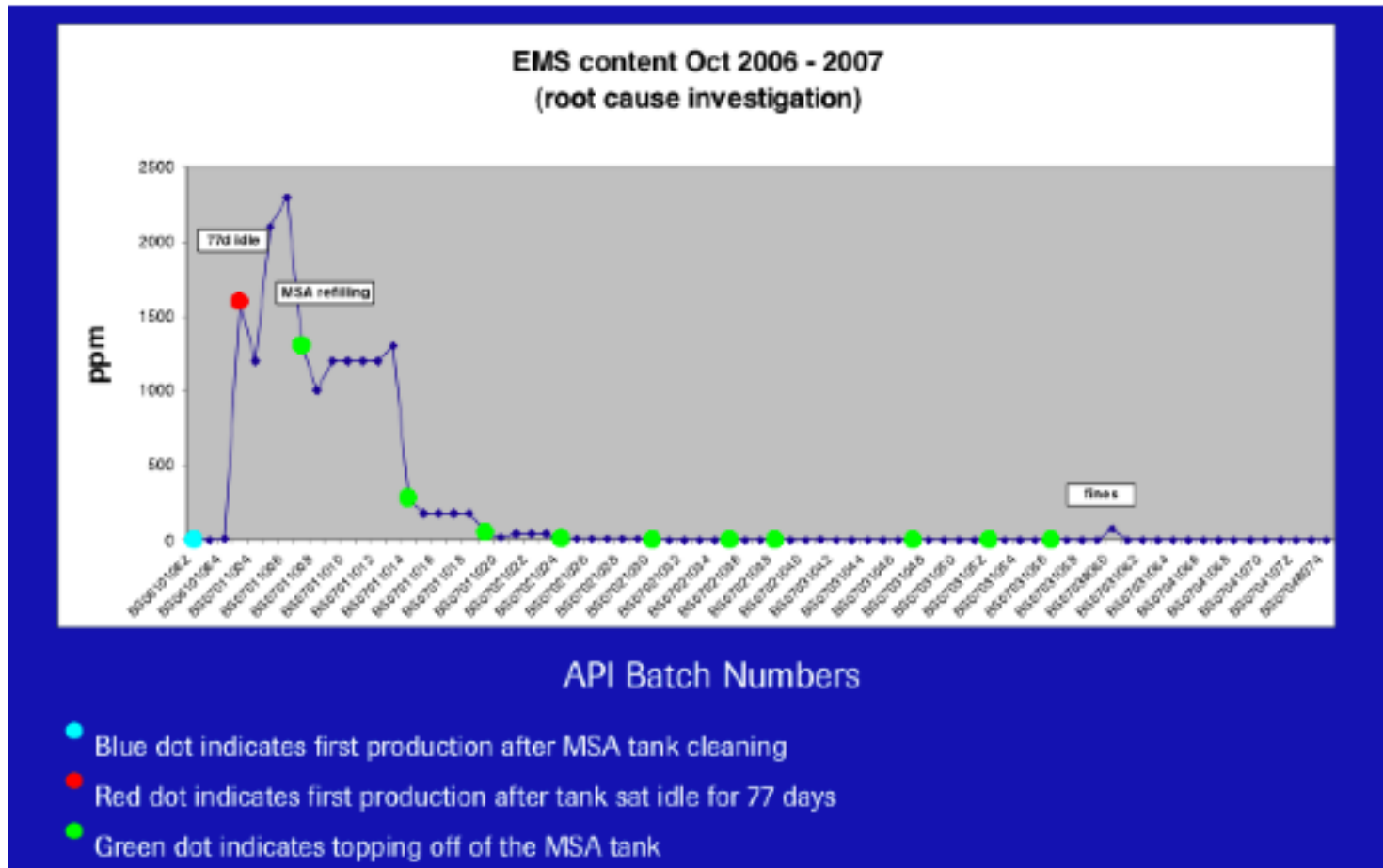
1. IARC Monographs, 7, 245-252 (1974).
3. Froese-Gertzen, E. E., et al., Nature, **198**, 447-8 (1963).



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# Investigation



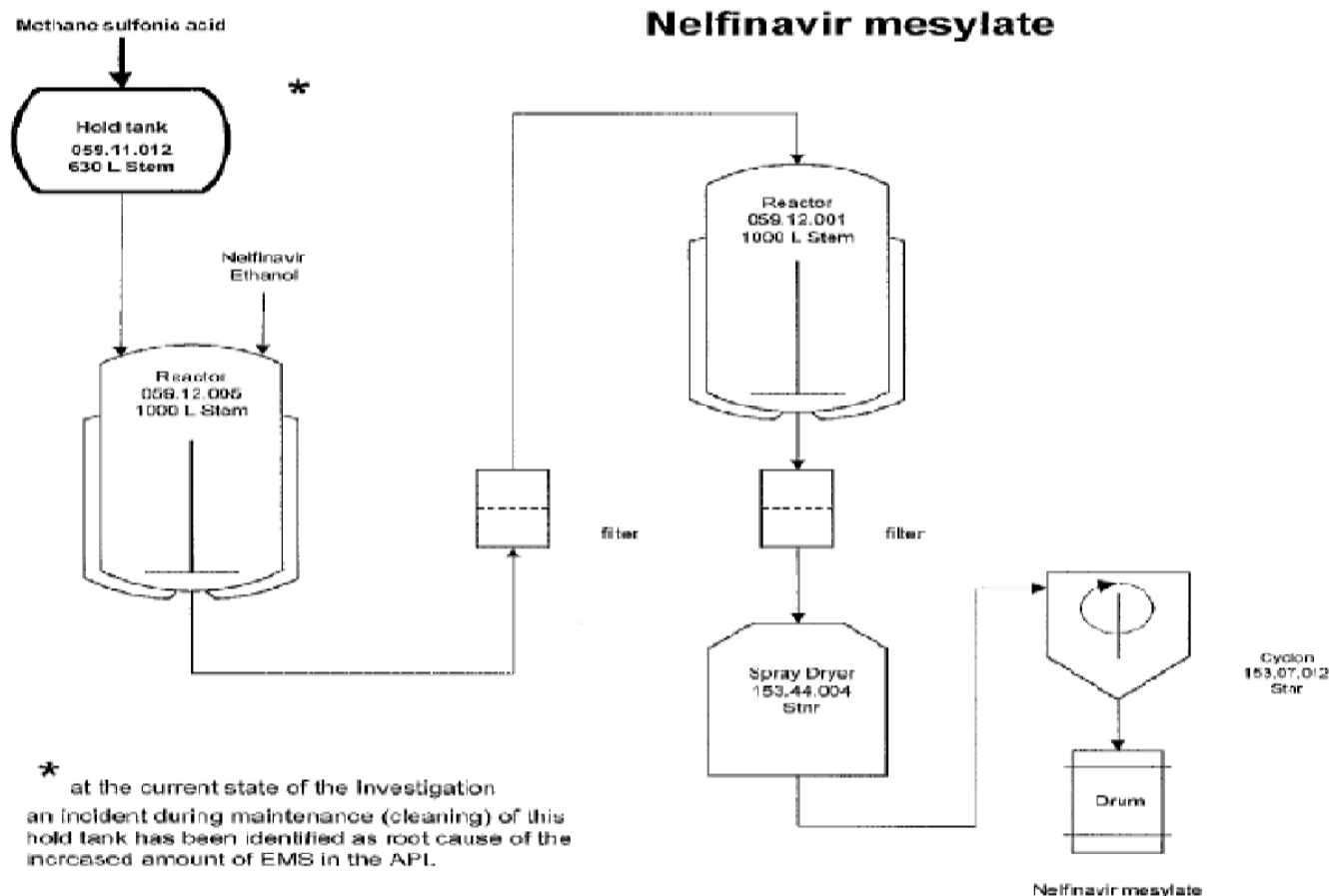
Adapted from: Roche's Viracept NGO Update and Advisory Meeting, Geneva, August 30, 2007



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# Nelfinavir mesylate salt process



Adapted from: Roche's Viracept NGO Update and Advisory Meeting, Geneva, August 30, 2007



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# Corrective actions taken in Viracept

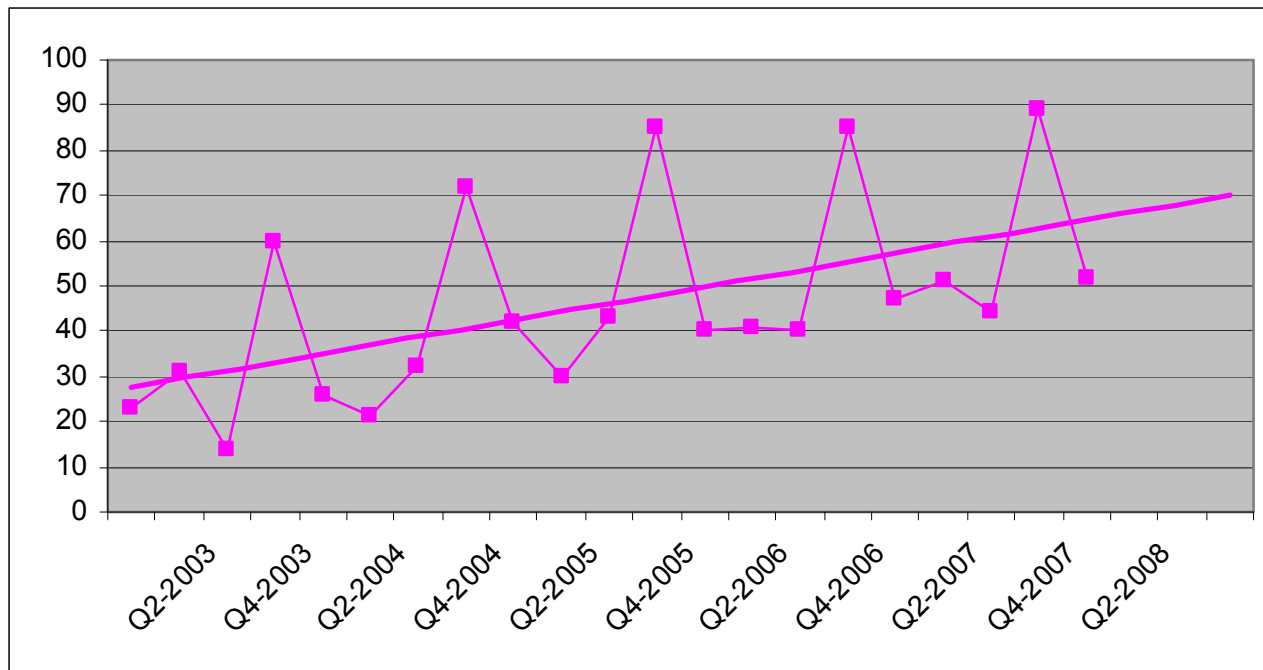
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- 🔔 Elimination of the MSA hold tank and direct charging from supplier's disposable container.
- 🔔 Revised procedure of mixing Viracept with MSA, which avoids any excess of MSA to be present.
- 🔔 Routine testing for EMS in DS (NMT 0.6 ppm, ~ 1.5 µg/day DI / EMEA ).
- 🔔 Testing of MSA for MMS/EMS had been implemented in 2005.
- 🔔 MA reinstated in September 2007.



# Generic Drug Submissions



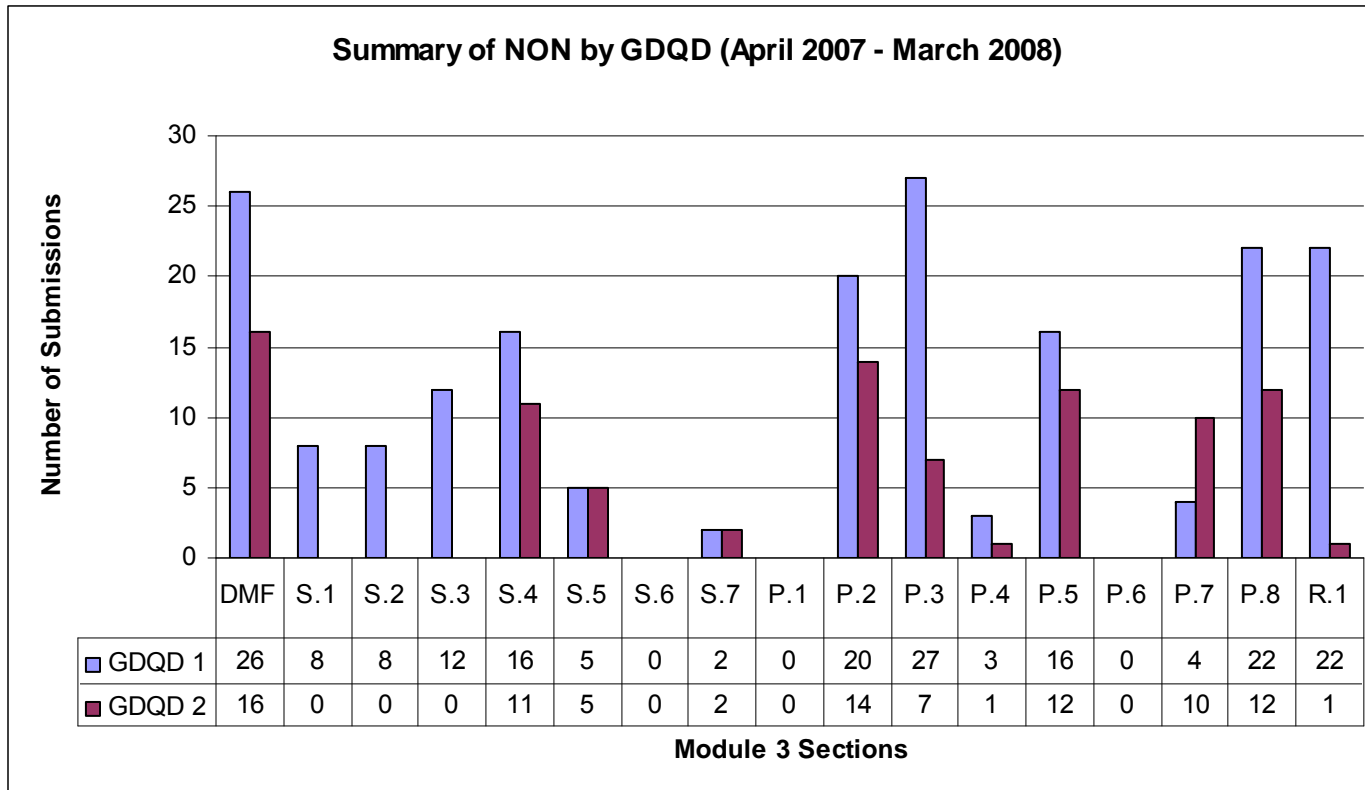
Annual Growth rate of 15%



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# DMF (S2.2-2.6) main source of NON



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# Integrated review (ANDS)

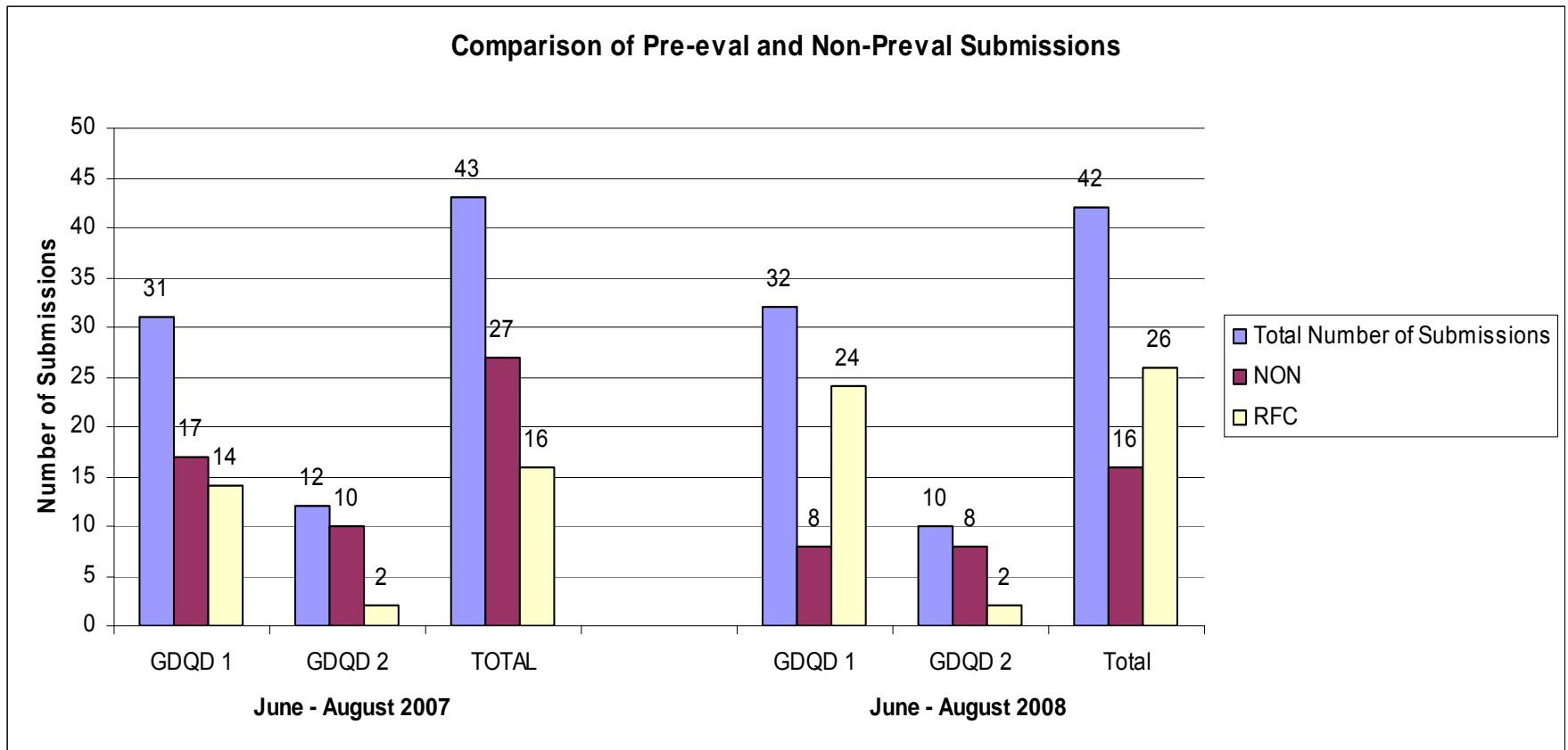
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- 🔔 Notice to stakeholder (October 1, 2007)
- 🔔 Implementation (January 1, 2008)
- 🔔 Focus on areas typically leading to NON (11) including:
  - significant deficiencies on the manufacturing process or controls for the drug substance, (e.g., incomplete information on the starting material or route of synthesis).
  - insufficient data or studies (e.g., impurity investigation, process validation for a sterile product, compatibility studies, stability studies)
  - insufficient safety/toxicological data to qualify a proposed impurity limit.
- 🔔 [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/annonce-annonce/notice\\_and\\_s\\_rev\\_avis\\_padn\\_pro-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/annonce-annonce/notice_and_s_rev_avis_padn_pro-eng.php)



# Integrated review results



 25% reduction in NON

# ICH Q11 Concept Paper (1)

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## High level Technical Guidance

- To address development and manufacture of DS.
- Chemical and biotech./biological entities (ICH Q6A).
- EWG 1<sup>st</sup> meeting June 2008.
- Step 2 and 4 Sign-off target (4Q 2009 and 4Q 2010)

## Goals:

- Harmonizing S&T principles relating to CTD S 2.2-2.6.
- Integration of Q8, Q9, Q10 principles as appropriate.
- Common terminology and definitions.
- Encourage submission of relevant process information and its justification.
- Facilitate the regulatory evaluation process.



# ICH Q11 Concept Paper (2)

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 Harmonization of principles needed for:

- Selection of materials and components.
- Identification and control of critical intermediates.
- Identification and justification of :
  - ▲ Critical manufacturing steps.
  - ▲ Process controls and parameters.
  - ▲ Analytical procedures and acceptance criteria.
- Process capacity to reduce/remove impurities.
- Evaluation of process robustness (e.g., scaling)



# Some final thoughts

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- 🔔 Each DS manufacturing process is unique.
- 🔔 Beware of assumptions (define the context).
- 🔔 Beware of continuous processes (extra justification).
- 🔔 Special attention to potential genotoxic impurities.
- 🔔 Justify Justify Justify
  - Process and controls (SM & INT specifications).
  - Impurity control choice (dynamic vs static).
  - All impurity limits in DS specifications (ICH Q3s).
- 🔔 Comprehensive discussion of the relationship of the DS quality attributes and the manufacturing process (link).
- 🔔 Clearer information and rationale improves review time.

