# Formulation Changes

## A Must for Plant Protection Products in a Changing World

**Seventh JOINT CIPAC/FAO/WHO MEETING**
**(54th CIPAC Meeting and 7th JMPS Meeting)**
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# Formulation Changes
# – Agenda -

1. Introduction

2. Typical reasons for formulation changes

3. Overview of some defined approaches

   3a. Product equivalence
   3b. CropLife Monograph No.19
   3c. CRD (UK) approach
   3d. EPA (U.S.) approach
   3e. BVL (Germany) approach
   3f. Comparison of approaches

4. Changes and the EU

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# 1. Formulation Changes
## - Introduction -

***Formulation Changes*** **to authorized Plant Protection Products (PPPs) may be required for a number of reasons e.g.**

- **New manufacturing site**
- **Withdrawal of co-formulant by supplier**
- **Improved performance**
- **Improved classification**

**National regulatory frameworks and guidelines are very different or, in some cases, non-existent .**

**Therefore time to get approval for formulation changes varies widely - between 0 to 48 months (simple notification to full submission!).**

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**However, it is very important that *Formulation Changes* are authorised in order to keep PPPs fully compliant.**

# 2. Typical reasons for formulation changes - External Triggers

- Critical co-formulant policy,
  - e.g. ban of NPEs, formaldehyde in EU
  - naphthalene containing solvents
- Shortage/unavailability of a co-formulant e.g.:
  - REACH in EU – Driver for phase-out of co-formulants
  - Raw material feedstock not available to co-formulant supplier
- Consolidation of the 'Co-formulant Industry' including product divestments

# 2. In EU phased-out co-formulants (surfactants, solvents…)

Formulator's tool box is shrinking

| Phased-out co-formulants | Examples |
|---|---|
| **Solvents** | Dichlorobenzene, chlorobenzene,<br>Isophorone<br>**DMF** (dimethylformaldehyde,<br>**NMP** (N-Methylpyrrolidone)<br>Aromatic solvents (restriction on naphthalene cont.) |
| **Emulsifiers** | **NPE** (nonylphenol ethoxylates) – formerly most important and best performing group of surfactants |
| **Dispersing agents** | Polyfluoroalkyl sulfonates & carboxylates |
| **Bactericides** | Me-, ethyl-, propyl parabene<br>Formaldehyde (even 1 g/l) |

***In EU through REACH, a mid term out-phase of approx. 10 to 20% of esp. monomeric co-formulants is expected (ref. VCI).***

# 2. Typical reasons for formulation changes - Internal Triggers

- Alternate sourcing - Ai.'s & co-formulants
- Change of technical grade Ai. purity

  Example: a higher purification TGAi. grade can lead to formulation instabilities – eg. sedimentation, poorer emulsion properties etc.

- Co-formulant quality
- Manufacturing process change (site/scale/equipment)

  • May require minor adjustments to the composition to maintain good phys/chem properties e.g. suspending agent levels, surfactant levels etc.

  •The composition is usually submitted before large scale trials/production and so changes may be needed

# 3. Overview of some defined approaches

# 3a. Product equivalence

- The new formulation should demonstrate performance equivalence to the existing registered product if a notification (and not a new authorisation) is to be sufficient.
    - No adverse safety data of new materials.
    - No change in formulation type
    - No adverse differences in phys/chem properties
- Unfortunately the legal frameworks vary greatly between countries and Industry seeks consistency which would bring benefits to both industry and the authorities
- It's in everyone's interest to bring improved formulations to market as soon as practicable without increasing risk.
- Managing production of 2 product compositions for same product due to different approval timelines is difficult.

# 3b. CropLife's Approach – Monograph No. 19

- **General requirements**
  - **Same use, same formulation type, same/better hazard classification**
  - **Environmental & biological properties are unchanged or improved**
  - **Technical performance not adversely affected**
  - **dose, concentration & frequency of application is unchanged**
- **Changes of co-formulants:**
  - **Co-formulant must have the same purpose/function**
  - **Must belong to same chemical class or have a similar identity**
  - **formulant amount not changed by more than ±25% (relative) or ± 2.5% (absolute) (whichever is the greater).**
  - **Exceptions are permitted for changes greater than those above and for non-alternative formulants: applicant must declare the change will not have any adverse effects on: phys/chem, tox, ecotox properties, the use/application of the product and its shelf life.**

# 3c. CRD, UK approach

**Minor changes (no new phys/chem data required):**

- **Dilution of a SL with water.**
- **Substitution of a formulant by a chemically identical one - evidence must be provided demonstrating identically.**
- **Any change in existing co-formulant content not greater than 10% relative of the component content.**
- **For other changes in formulation, e.g. a change of solvent, a reasoned case supporting a claim that the change will not affect the physico-chemical properties of the preparation may be appropriate.**

# 3d. E.P.A, U.S. approach

- **Notification (send letter, wait for acknowledgement)**
  - New source of co-formulant with same identity or CAS number
  - Change in co-formulant nominal level (whilst remaining within certified limits) or standard certified limits
    - ≤1% of formulation then ±10% relative is permitted
    - between 1% and ≤20% of formulation then ±5% relative allowed
    - >20% of formulation then ±3% relative allowed

- **Minor formulation amendment (apply for alternate formulation approval– typically 2-3 months)**
  - Alternate formulation
    - same certified limits for each ai, same label text, same analytical method
    - bridged to basic formulation acute tox and phys/chem data
  - Add one or more co-formulants
    - co-formulants are known, of no significant concern (old lists 3 & 4), and have same purpose
  - Exceptions will follow the same process with argumentation and/or data.

# 3e. BVL, Germany, approach

**BVL guideline document on formulation or composition change requirements**

**<u>Case 1: Procedure of Notification:</u>**

**– where chemicals are identical an instant product change is permitted**

**<u>Case 2: Procedure of Change:</u>**

- **±5% co-formulant change (relative) of similar function does not need comparative studies**
- **Other minor changes will require comparative studies or a reasoning**
- **Before changing, applicant has to wait for the official BVL approval (typically 6-12 months).**

**The BVL practice could be a model for the pending EU zonal and mutual recognition process, and for countries currently without a specific process for approving minor formulation changes.**

# 3e. BVL Practice – an Example

**Due to close chemical similarity, a slightly different fatty acid methyl ester can be used via the quite simple 'notification' procedure – even in 500 g/l scale and with CAS no. change !**

EC with 500 g/l ester

| old | new |
|---|---|
| Supermax 2 | Primawet 4 |
| CAS 67762–39-4 (C6 – C12 – Methyl ester) | CAS 85566–26-3 (C8 – C10 – Methyl ester) |
| Xi R 36/38 | No classification |
| Phys.-chem. characteristics slightly different | |

# 3f. Comparison of Approaches

| | Crop Life | UK | EPA | BVL |
|---|---|---|---|---|
| General requirements | | | | |
| same use | y | | y | y |
| same formuln type | y | | y | y |
| same/better hazard class | y | | y | y |
| environmental props same/better | y | | y | y |
| biological props same/better | y | | y | y |
| dose, concn, frequency of applicn unchanged | y | | y | y |
| | | | | |
| Formulant specific | | | | |
| same purpose/function | y | | y | y |
| identical chemistry | y | y | y | letter only |
| different chemistry, same purpose | exception | exception | y | y |
| same chemical class | y | y | y | y |
| similar identity | y | exception | y | y |
| Change level permitted as minor | ±25% max relative or ±2.5% absolute | ±10% relative | ±3 - ± 10% relative | ±5% relative |
| Exceptions allowed | y | y | y | y |
| Time frame | 45 days | ? | 2 - 3 months | ? |

# 4. Changes and the EU reg. (EC) 1107/2009

**About (EC) 1107/2009:**

- **Article 44: Member states may review an authorization at any time.**
- **Article 45: An authorization may be amended at the request of the holder of the authorization.**

**But, still no framework on formulation changes, and no regulation on zonal and so far mutually recognized PPP changes.**

**ECPA is supportive of a zonal approach to formulation changes in the EU and will be discussing with the commission**

# ECPA's view on the development of a common EU procedure for formulation changes within the framework of Regulation 1107/2009

- **Published 2 June 2010**
- **Within the zonal guidance documents currently under preparation, it would be appropriate to provide a clear procedure to deal with formulation changes.**
- **Procedure should be based on the May 2008 BVL document with reference to the CLI monograph 19**
- **Recommendation is that the application for a formulation change is submitted to only 1 Member State who is either the RMS for the active, or the ZRMS.**
- **Evaluation time should take a maximum of 6 months for the RMS/ZRMS, and a maximum of 3 months for mutual recognition by all other Member States as appropriate[1].**

[1] ***These timelines are consistent with the timelines needed for re-authorisation of products based on the guidance document being developed as a process for compliance with Article 43 of Regulation1107/2009 (Renewal of authorisations).***

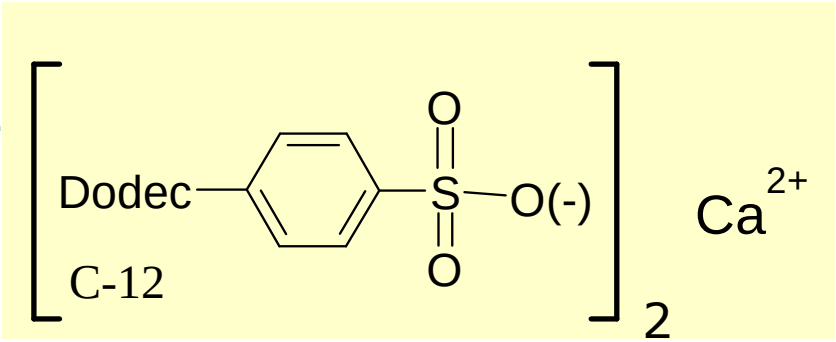
# 5. About Chemical & CAS No Identities

- **CAS number is commonly used to compare the chemical identity of exchanged co-formulants.**
- **Different CAS numbers do not necessarily mean chemical non-equivalence (as recognised by BVL in their document "Changes in the chemical composition of plant protection products")**
- **The next slides show some examples in detail.**

# 5. About Chemical & CAS No. Identities

**Example 1:**

An anionic dodecyl-phenyl-sulfonate dispersing agent may have 3 different CAS no.s:




**26264-06-0 Dodecylbenzenesulfonic acid, calcium salt**

**or**

**68584-23-6 Benzenesulfonic acid, C10-16-alkyl derivs., calcium salt**

**or**

**70528-83-5 Benzenesulfonic acid, dodecyl, branched calcium salt**

Note: typically all dodec.-alkyl chains are branched

# 5. About Chemical & CAS No. Identities

**Example 2:**

An non-ionic C-11-Polyethoxylate surfactant may have
3 different CAS No.s – due to CA nomenclature:

**68439-45-2 Alcohols, C6-12, ethoxylated**

**68439-46-3 Alcohols, C9-11, ethoxylated**

$C_{11}$-O-EOx-H

**or compare another nomenclature:**

**34398-01-1 Polyoxoethylene monoundecyl ether (= C11 ether)**

Result: 3 CAS No.s for one identical co-formulant

# 6. Formulation Changes Summary

- **Formulation changes will occur during a product's life and a consistent, pragmatic approach to authorisation is needed.**
- **A pragmatic approach to authorisation of formulation changes should also be reflected in different data requirements and time scales depending upon the type/level of change.**
- **Existing frameworks for changes are potentially good models for new & more consistent national regulations.**
- **Within the EU it is hoped that a zonal approach will bring consistency.**
- **Industry is ready to join with authorities to develop a new framework for formulation changes**

# Thank you for your attention

## Comments and questions are most welcome