

VARIATIONS :

IMPACT ON ADMINISTRATIVE BURDEN AND FEES

Rose-Marie Molina – EMA Infoday – London, 14th March 2014



VARIATIONS : IMPACT ON ADMINISTRATIVE BURDEN AND FEES

Before 1234/2008 Regulation, variation procedures in the European Union for industry was synonymous of:

- Lack of visibility about timelines
- Lack of visibility about necessary data
- Lack of visibility about outcome (without even expecting unique outcome)
- Lack of visibility about possible implementation date ...

And

- Significant resources to cope with administrative burden
- Significant fees



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Regulation 1234/2008 has indeed **improved** the previous situation:

- Type IA « Do and Tell » variations
- Grouping procedures
- Worksharing procedures
- Defined timelines
- Applicable to national products

Is the situation satisfactory or is there room for improvement ?



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First (real) example: « The Belgium subsidiary from company X, acting as Marketing Authorisation Holder in Belgium, moved from Michael Angelo avenue to Leonardo Da Vinci street »

=> administrative change (**type IA_{IN} variation**), not needing any assessment, not leading to any impact on quality, safety, efficacy ... but it is a change.

- Change of address for nationally-registered products managed locally with Competent Authority from the country

but...

- 17 products registered through MRP/DCP with different RMS and different CMS...



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Grouping of type IA variations possible but ...
because different products concerned and each product
has different RMS and different CMS concerned, need to
manage **4 grouped-variation procedures** ... and a
significant administrative burden including:

- ✓ Get convinced by your Belgium colleagues of the need to run MRP/DCP procedures
- ✓ Try to convince RMS that procedures involving all CMS were needed ... and again with colleagues in other subsidiaries
- ✓ Find the easiest way to manage the grouped-variation procedures for the 17 products ... hopefully with only 4 RMS



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Final agreed strategy:

- 1 grouped procedure involving 9 products managed by RMS n°1 and including 26 CMS
- 1 grouped procedure involving 4 products managed by RMS n°2 and including 25 CMS
- 1 grouped procedure involving 3 products managed by RMS n°3 and including 22 CMS
- 1 procedure involving 1 product managed by RMS n°4 and including 14 CMS

=> 4 RMS and 26 CMS included in **4 IA_{IN} variation procedures** (AF, fees, dispatch to all CMS)



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How it looks like:

Product	RMS	CMSs	Procedure No.
Product 1	FR	AT, BE, FI, DE, EL, IE, LU, NL, PT, ES, UK	FR/V/XXXX/001/IA/007/G
Product 2	FR	AT, BE, BG, CY, CZ, DE, EL, ES, HU, IE, IT, LV, LT, NL, PL, PT, RO, SK, SI, UK	FR/V/XXXX/001/IA/008/G
Product 3	FR	AT, BE, DK, EL, FI, DE, IT, LU, NL, SE	FR/V/XXXX/001/IA/006/G
Product 4	FR	AT, BE, DE, DK, EL, ES, FI, IE, IT, LU, NL, PT, UK	FR/V/XXXX/001/IA/004/G
Product 5	FR	AT, BE, CY, DE, DK, EL, ES, FI, IE, IT, LU, NL, NO, PL, SE, SI and UK	FR/V/XXXX/005/IA/014/G
Product 6	FR	AT, BE, CY, DE, DK, EL, ES, FI, IE, IT, LU, NL, NO, PL, SE, SI and UK	FR/V/XXXX/001/IA/014/G
Product 7	FR	AT, BE, CY, DE, DK, EL, ES, FI, IE, IT, LU, NL, NO, PL, SE, SI, and UK	FR/V/XXXX/002/IA/014/G
Product 8	FR	AT, BE, CY, DE, DK, EL, ES, FI, IE, IT, LU, NL, NO, PL, SE, SI, and UK	FR/V/XXXX/003/IA/014/G
Product 9	FR	AT, BE, CY, DE, DK, EL, ES, FI, IE, IT, LU, NL, NO, PL, SE, SI, and UK	FR/V/XXXX/004/IA/014/G

Product	RMS	CMSs	Procedure No.
Product 10	UK	AT, BE, CY, CZ, DE, DK, EL, ES, FR, HU, IE, IT, LV, LT, LU, NL, PL, PT, SK, SI	UK/V/XXXX/001/IA/002/G
Product 11	UK	AT, BE, DE, DK, FI, FR, EL, IE, IT, LU, NL, NO, PT, ES, SE	UK/V/XXXX/001/1A/016/G
Product 12	UK	AT, BE, CY, CZ, DE, DK, EE, FI, FR, EL, HU, IS, IE, IT, LV, LT, LU, NL, NO, PL, PT, SK, SI, ES, SE	UK/V/XXXX/001/1A/025/G
Product 13	UK	FR, BE, LU, DE, NL	UK/V/XXXX/001/1A/019/G

Product	RMS	CMSs	Procedure No.
Product 14	DE	AT, BE, CY, CZ, DK, FI, FR, EL, HU, IE, IT, LV, LT, LU, NL, PL, PT, SK, SI, ES, SE, UK	DE/V/XXXX/001/IA/009
Product 15	DE	AT, BE, CY, CZ, DK, FI, FR, EL, HU, IE, IT, LV, LT, LU, NL, PL, PT, SK, SI, ES, SE, UK	DE/V/XXXX/001/IA/006
Product 16	DE	AT, BE, CY, CZ, DK, FI, FR, EL, HU, IE, IT, LV, LT, LU, NL, PL, PT, SK, SI, ES, SE, UK	DE/V/XXXX/001/IA/010

Product	RMS	CMSs	Procedure No.
Product 17	Hu	BE, BG, CY, CZ, FR, DE, EL, ES, IT, LT, LV, PL, RO, SI, SK	HU/V/XXXX/001

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Conclusion:

- ✓ Fees were paid when applicable, free of charge in some countries –
- ✓ Resources at company corporate level, company subsidiary level, at 4 RMS level => Easier for Centrally-approved products because one authority only and MA valid in all countries

... just to notify National Competent Authorities of the change of address of 1 subsidiary ...

... and now again for the other subsidiaries !!!!



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Other examples of requested variations, expected to concern multiple products, where administrative burden seems excessive compared to added value (although to a lesser extent for centralised procedures) :

- Deletion of manufacturing sites (IA)
- TSE certificate of suitability: updated certificate from an already approved manufacturer (IA)
- TSE certificate of suitability: deletion of certificates (IA)
- Change(s) to an existing PhV system as described in DDPS: change in QPPV (IA)
- Change(s) to an existing PhV system as described in DDPS: Change to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH* (IA)

*the same changes to the DDPS are introduced for all medicinal products of the same MAH (same final DDPS version)



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... and fees do not seem proportionate to the service provided, included for centralised procedures.

Example of fees that a company having 20 products registered centrally would pay (Real situation):

- Deletion of manufacturing sites (if common to all products): **13.8 k€**
- Change(s) to an existing PhV system as described in DDPS: change in QPPV (IA): **13.8 k€**
- Change(s) to an existing PhV system as described in DDPS: Change to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH (IA): **13.8 k€**



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For all those examples (non-exhaustive list), the message from industry is not :

“Those changes should not be declared to competent authorities”

But rather

“Those changes should be declared to competent authorities by a **simplest way** avoiding as much as possible administrative burden with proportionate fees”



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Second (real) example: « Removal of the Target Animal Batch Safety Test (TABST) for veterinary vaccines following update of Ph. Eur. (applicable from 1st January 2013)»

Removal of TABST was already possible and data requirements were described in position paper EMEA/CVMP/865/03/Final and guideline EMA/CVMP/IWP/810769/2011 with following requirements: type II variation including for each product concerned safety data, assessment report on the last 10 batches and expert report

= > Not much incentive for industry (not a priority)



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Then possible to remove the TABST through type IA (i.e. administrative) variations: no more data requested.

Merial concerned by 103 products:

- ✓ Significant resources needed (not estimated)
- ✓ **Estimated regulatory fees (IA variation): 300 k€ (including 49.3 k€ for centralised products ... equivalent to 7 type II variations needing assessment)**

=> Still not much incentive !!!



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Proposal was accepted to manage as a notification: no AF, no procedural management, no fees ... information sent to competent authorities with a simple letter

The CMDv has endorsed a proposal from IFAH-Europe on how to handle the withdrawal of the TABST during the period between the publication of the revised (general and specific) monographs on 1 October 2012 and the implementation date of 1 April 2013. In order to inform the national authorities of the omission of the TABST from the finished product control testing of their vaccines, each Marketing Authorisation Holder (MAH) will inform the relevant authorities in writing (i.e. not via variation) of:

- the products for which they will withdraw the TABST;
- the products for which the TABST will be renamed as a 'residual toxicity test', as indicated by the Ph. Eur.;
- the date at which the changes will be implemented; this will not be later than 1 April 2013.

This approach is valid for all MAHs. After 1st April 2013, a variation will be required to withdraw the TABST.

High incentive !!! Done by IFAH-EU member companies...

... but why stopping after 1st April 2013 ?



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Some ideas for further consideration :

- ✓ Consider the possibility to enlarge management of certain administrative changes as notification (e.g. simple letter)
- ✓ Manage changes not product-specific (change of QPPV/DDPS) at site level: PhV masterfile or certification
- ✓ Delete the need to send updates of TSE certificates of suitability for already approved manufacturer already assessed by EDQM

... before Regulatory Reform



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NEXT STEPS:

CMDv and EMA confirmed their support for a joint **variations workshop**, to be held at EMA, which will include worksharing and will cover on CP/MRP/DCP/National procedures.

Suggested date is 6 June. IFAH-Europe will prepare a draft agenda.



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Thank you very much for your
attention !

Questions ???



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Abbreviations:

CMS: Concerned Member States

DCP: Decentralised procedure

DDPS: Detailed Description of Pharmacovigilance System

EDQM: European Directorate for the Quality of Medicines

MA: Marketing Authorisation

MAH: Marketing Authorisation Holder

MRP: Mutual Recognition Procedure

Ph. Eur.: European Pharmacopoeia

PhV: Pharmacovigilance

QPPV: Qualified Person for Pharmacovigilance

RMS: Reference Member State

TABST: Target Animal Batch Safety Test

TSE: Transmissible Spongiform Encephalopathies

