Variation update - Industry perspective

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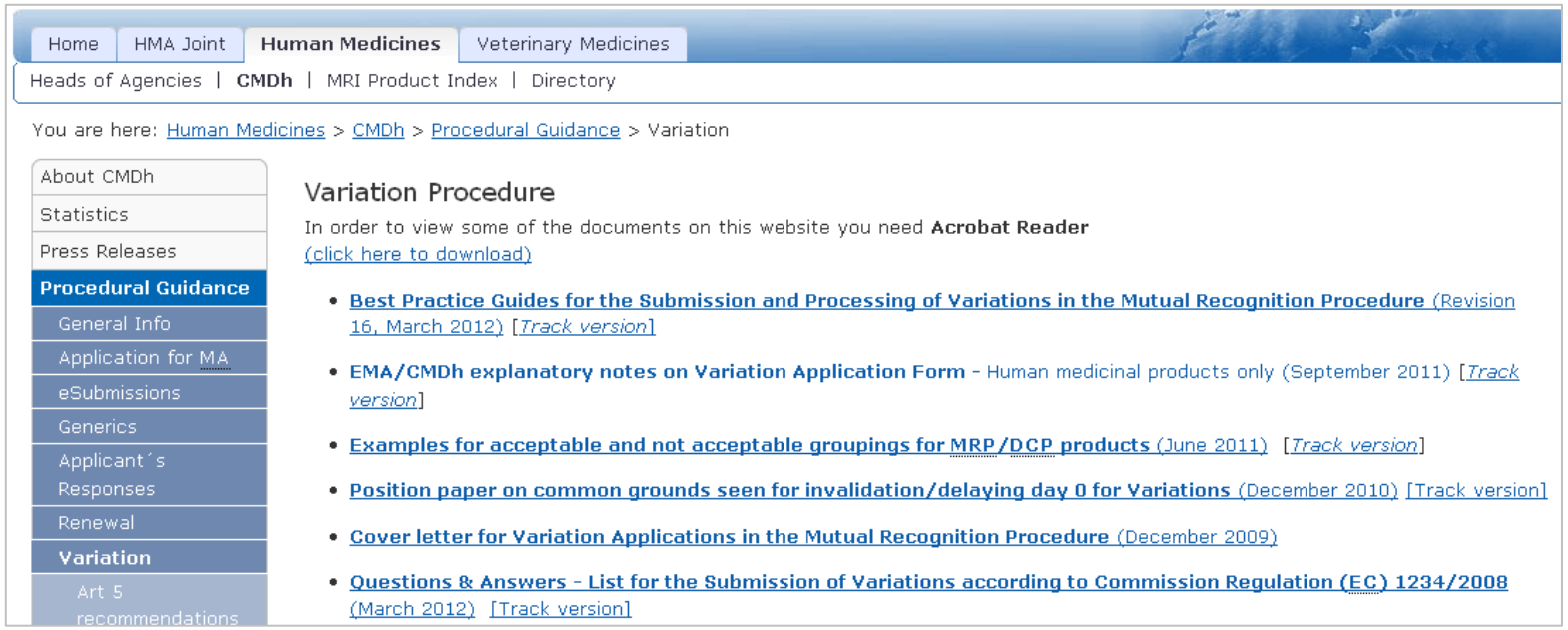
Overview of Presentation

- Background
  - Advantage of current Variation Regulation
- Industry Experience
  - Type IA
  - Type IB
  - Grouping
  - Worksharing (WS)
- ratiopharm's experience
- Fees
- Conclusions

Background on Variation Regulation 1234/2008

- Advantage of current Regulation
  - More flexibility has been introduced
  - Type IB variation by default
  - Update CMDh Best Practise Guide (Rev16, March 2012)
    - Combination of marketing authorisations of more than one RMS in one grouped application for Type IA variations (6 months pilot phase successfully completed)



Background on Variation Regulation (cont.)

- However, **...**
  - Currently only for MRP/DCP/CP authorised products

- Expectations
  - Regulation should be completely implemented with clear timelines
  - Implemented at the same time in all countries

Type IA Variations - Annual Reporting

- The principal of annual reporting NOT often used in practise due to:
  - High volume of IA and IA_{IN} changes per Marketing Authorisation (MA)
  - Having to keep track of implementation dates / submission dates
  - No significant reduction of workload by keeping them for submission within one year
  - Document Management System
  - Not fitting the electronic submission environment (especially for eCTD)
  - Rejection of the variation having impact on already marketed products

→ Nevertheless, should be kept as a possibility

Industry Experience with Type IA Variations

Type IA & Type IA_{IN} Variations - "Do and Tell"

- Real improvement, but
  - Challenging for industry, particularly for multicentred manufacturers
  - Robust change control system is needed
  - Some NCA's still not fully within the spirit of "Do and Tell"
    - IT: Bollino number only issued upon RMS approval
  - Interpretation of "immediately" still varies
  - Implementation of IA changes across EU not possible as long as national MA's are out of scope

Industry Experience with Type IB Variations

Type IB Variations - “Tell - Wait - Do”

- Working well on the whole especially as the default category
- Implementation Type IB after 30 days not possible
  - Delays in validation → takes in general 1 – 3 months
  - Industry receives later comments from some Member States on national level even after RMS approval
  - Before implementation of changes especially to the SmPC and PIL industry tends to wait for the formal approval

Industry Experience with Groupings

Grouping

- Is now becoming part of daily routine
- Growing list of proposed groupings
- Grouping with one MA most frequently used
  - Request for grouping number not needed
  - More efficient submission process
- Grouping across several MA's (with same RMS or different RMS, Type IA only)
  - Very useful but only used if high number of MA's can be combined
  - Complex for NeeS and eCTD submissions
- Consequential changes as single variation should be accepted
  - Grouping is more expensive than consequential

Industry Experience with Worksharing

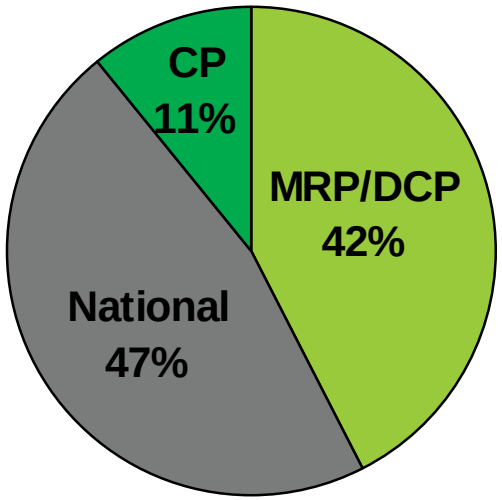
Worksharing

- In comparison to Groupings limited experience so far
- Advantages:
  - able to receive one outcome of assessment particularly useful
    - e.g. registering the same DMF for separate procedures
    - DDPS Updates
- Disadvantages:
  - Approx 1 month to receive permission for worksharing
  - When dossiers are not harmonised, worksharing may not be acceptable
  - Depending on the size of concerned MA's long preparation time needed

- Challenge for the industry to coordinate the process internally

ratiopharm's Variation Workload in 2011

- **Percentage of approved MA's per Procedure Type ***



- **The Main Reasons for Product Changes in 2011**
  - Texts
  - Pharmacovigilance System
  - CEP (drug substance)
  - Manufacturing Site (drug product)
  - Specifications (drug product)
  - Name and/or address MAH or Manufacturer
  - Stability (drug product)
  - DMF (drug substance)
  - other

→Strong influence of integration related variation triggers

* without Teva MA's, Status: December 2011

WS Example - Change in DDPS

- **Background:**
  - Based on the acquisition of ratiopharm by TEVA, a new DDPS was introduced
    - ***Worksharing Variation Type IB no. C.I.8 b)*** *- Introduction of a new Pharmacovigilance System, which has been assessed by the relevant national competent authority/EMEA for another product of the same MAH*
  - Several hundreds of EU procedures affected
  - BfArM acted as Lead RMS

- **ratiopharm Experience:**
  - Early involvement of BfArM in submission strategy discussions
  - Approval for WS received within less than 3 weeks
  - Logistic challenge to coordinate the process internally (parallel name changes, MAH transfers and/or withdrawals complicated the preparation)
  - Individual NeeS Sequences were requested for each procedure

  → **A robust Data Management and enough time for preparation needed!**

Grouping Example - Address Change

Kind of Change:

- Address Change of MAH and Batch Release Site (BRS)
  - Type IA_{IN} change on EU level → “Do and Tell”
  - Notification on national level (DE) → “Tell and Do”

- Strategy:
  - Grouping on national level
  - Grouping on EU level

Address change of MAH and BRS - on national level

- **Background:**
  - National Notification (“Sammeländerungsanzeige”) according §29 AMG
    - Address change MAH
    - Address change Batch Release Site
  - Hundreds of national MA’s affected

- **ratiopharm Experience:**
  - MAH variation submitted through PharmNet.Bund Portal
    - Easy to handle (same point of origin) → many ENR Numbers could be considered in one variation
    - Technical limitations of the Portal (upload of max. 100 ENR Numbers at once) → split of variations needed
  - Portal submission wasn’t advisable for BRS change → submission was done through “paper- way”

Address change of MAH and BRS - on EU level

- **Background:**
  - Change in the address of MAH and Batch Release Site
    - ***1st Grouping: Variation Type IA_{IN} no. A.1*** *- Change in the name and/or address of the marketing authorisation holder*
    - ***2nd Grouping: Variation Type IA_{IN} no. A.5 a)*** *- Change in the name and/or address of a manufacturer of the finished product, including quality control sites; (Manufacturer responsible for batch release)*
  - Hundreds of EU MAs affected
  - "Supergrouping" used → Grouping across several MA's with different RMS
  - BfArM acted as Lead RMS

- **ratiopharm Experience:**
  - Overall positive experience
  - Benefit from previous experience with groupings and DDPS Worksharing
  - Straightforward cooperation with RMS
  - Proactive planning is crucial in order to meet the timelines

Fees

- Variation costs have a significant impact on regulatory budget
  - General increase of fees for variations
- Grouping vs. consequential variations
  - Not always cost-effective to group (e.g. no longer combination of several CMC changes to one Type II variation)

  Example from EGA:
    - DCP procedure with 13 countries and up to 4 strengths
    - Grouping of 10 variations (7 x IB and 3 x IA) → 116.000 €
    - If submitted as one Type II variation: 47.000 €
- In general no fee reduction for same change across Marketing Authorisations
  - EMA as positive exception: reduced fees for worksharing and grouping
- Grouping fees not clearly identified across NCA's
  - Request for supplementary fees

Conclusions

- Regular update of CMDh Guidelines and Q&A Documents highly appreciated by the industry
- Industry needs to follow new publications closely
- Industry much more experienced now →reduced number of rejections
- Grouping and Worksharing are very useful but lead to internal challenges
  - Changes affecting the majority of the MA's require accurate preparation, good change management and robust tracking system
- Limit the regulatory expenses for variations
  - Differentiation between product and company related changes
  - Consideration whether real assessment is needed or not
- Harmonised inclusion of National MA's in the scope awaited

Thank You!