

FEDESA-HEVRA INFODAY

5 October 2000, Paris

Review 2001 - what should be improved

FEDESA-HEVRA INFODAY

AIM OF THE INFODAY

The purpose of the Infoday was to gather for the first time representatives of the Heads of European Veterinary Regulatory Authorities for Medicinal Products (HEVRA) and Animal Health Industry, namely FEDESA, in order to have an open exchange on the functioning of the Mutual Recognition Procedure (MRP) in relation to the Review 2001.

After the role and priorities of HEVRA and FEDESA have been presented by respectively J. Boisseau (Current chairman of HEVRA, AFSSA, F) and J. Vanhemelrijck (Secretary General of FEDESA), the project of Veterinary Regulation 2000 was introduced by B. Boenisch (FEDESA) and complemented by R. Kroker (Chairman of CVMP and HEVRA member, BgVV, D).

The main part of the day was devoted to parallel workshop discussions on procedural aspects and the functioning of the Mutual Recognition Procedure (WS 1), the maintenance and renewal procedures (WS 2), and the application of risk analysis in relation to MRLs (WS 3). The discussions and conclusions are summarized in the enclosed attachments.

Overall, the participants expressed their satisfaction to the most constructive and open dialogue during the whole day.

Many issues have been brought up and alternative solutions being proposed to be elaborated further.

It was recognized that in fact many changes could be introduced without the need for legal amendments. For that purpose continuous dialogue in the regular VMRFG/FEDESA Liaison meetings, the continuation of the joint survey on the functioning of the MRP, and the setting up of a joint training programme have been mentioned and fully supported by the participants.

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PROGRAMME

Review 2001 – what should be improved

08:30 Registration and Coffee

09:00 Opening of the meeting G. Follet / J. Boisseau

Chairpersons: M. Schneidereit + J. Boisseau

09.10 – 09.40 What is FEDESA – How does it work J. Vanhemelrijck

09.40 – 10.10 Status and mission of HEVRA J. Boisseau

10.10 – 10.40 Introduction to Veterinary Regulation 2000 B. Boenisch / R. Kroker

10.40 – 11.00: **Coffee break**

11.00 – 13.00 *Breakout in discussion groups on Veterinary Regulation 2000 proposals*

Group 1: Which dossier in which procedure - Future of the Mutual Recognition Procedure

Group 2: 5-year renewal versus Pharmacovigilance + variations + GMP

Group 3: MRL: residue testing – minor species

13.00 – 14.30: **Lunch**

14:30 – 16.00 Reports from the discussion groups and general discussion

16.00 – 16.30 Conclusions of the Day's discussions and the way forward G. Follet / J. Boisseau

16.30: **End of the meeting & coffee**

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Conclusions of the Workshops

Conclusions of Group 1:

Which dossier in which procedure – Future of the Mutual Recognition Procedure

Chair: Mike Rutter/ Roger Cook

Rapporteur: Roger Cook

It was highlighted that the Mutual Recognition Procedure (MRP) is only mandatory since 1997, but that in general this procedure is working satisfactory. Based on the review 2001 and the joint FEDESA/ VMRFG survey some areas for improvement have been identified that were discussed in the workshop 1:

1. **Access of all product types to both centralized and mutual recognition procedure** (Annex to Council Regulation 2309/ 93)
 - The group agreed that both procedures should be kept, but that there is a need to revise the definitions of the Annex A & B and that equal access to both procedures should be possible with exception for specific products derived from biotechnology (definition to be used from the European Pharmacopoeia). There were fears that, without a better definition, mutual recognition would wither as Biotech became common place, for example an established product could be forced into the centralized procedure due to just a change in manufacturing processes.
 - Marketing flexibility should be provided within the scope of the centralized procedure to respect the sometimes geographically limited needs of a veterinary medicinal product.
 - The definitions of a “veterinary pharmaceutical product” and related to this a “marketing authorization” should be reviewed. Currently there is one Regulation, but two definitions apply depending on whether the centralized or the mutual recognition procedure is applied.
2. **Role of Reference Member State in the Mutual Recognition Procedure**
 - The group agreed that the role of the Reference Member State (RMS) should be strengthened to prioritize the questions addressed by the Concerned Member States (CMS), effectively active as “Rapporteur”.
 - The Veterinary Mutual Recognition Facilitating Group (VMRFG) should have a legal status, but not become a second CVMP.
 - It was suggested that the chair of the VMRFG should be extended to e.g. up to 3 years, as in CVMP, to ensure continuity.
 - In scientific matters the VMRFG should seek advice from the CVMP.
 - EMEA should continue to provide secretarial support.
 - Above all, the group emphasized the need to reinforce the spirit of mutual recognition and mutual trust into the system.

3. Arbitration

- The group noted that no case of arbitration took place for veterinary medicinal products had occurred. The major reason given is that once an arbitration procedure is running the license in all CMS, even those that have no objections will be stopped and therefore the cost, time and conflicts involved lead the company to withdraw the application rather to go to arbitration.
- The group acknowledged that there is no legal reference that exists to prevent CMS to grant a marketing authorization (MA) in case of arbitration.
- The group therefore proposed that the current practice to stop all MA in case of arbitration should be reviewed. If a majority of CMS agree to recognize the MA, the VMRF group should decide that there is no risk for public health, and the MA should be granted in these countries.

11

The CMS that opposed to the MA should have the choice to reconsider its decision or to ask systematically for arbitration

- The group recommended that the reasons for withdrawals of applications from CMS should be analyzed, and a way found to involve “excluded” Member States to harmonize their experience.

4. Simplified Mutual Recognition Procedure

- The industry proposal for a simplified MRP of “old” existing products to get a pan-European license, when authorized in 3 MS (pre 1995), was discussed. Currently, an application to extend to a further MS required the product to be regarded as “new”, with a full dossier etc, and ignoring “real life” experience. In reality the majority of products would be “old” for many years to come.
- As this proposal involves most-likely a change of legal requirements, there is a need to discuss it in more depth.
- In view of the different SPCs a harmonized core document needs to be developed.
- The idea of “old drug policy” was suggested to minimize the work to review the dossiers of the products involved.
- The group recognized that this policy is also of importance in view of the EU enlargement.

5. Training of authorities assessors and industry experts

- The group proposed to set up a programme to ensure continuous professional development of industry and authority experts on different topics to increase mutual understanding.
- A joint programme should be developed based on the proposals emerging from the VMRF and FEDESA.
- It was noted that the Carolus Project, now ended, had provided opportunities to exchange staff between agencies. This should be repeated, providing agencies had sufficient staff to participate.

6. Other issues raised

- Delays in the issue of licences in some MSs following completion of MRP. This is partially due to translation problems of SPC and leaflets. Consequently it was requested for SPCs to be issued by companies to CMS in the in own language early in the MRP to avoid last minute delays.
- Concerns that while the Authorities debated legislative change, the reality of open borders and the Single Market was creating de facto “Mutual Availability” of VMPs in advance of “Mutual Recognition”.

Conclusions of Group 2:

5-year renewal versus Pharmacovigilance + variations + GMP

Chair: Professor Reinhard Kroker

Rapporteur: Martin Schneidereit / Ulrich Jänicke

- It should be highlighted that it was a lively and open discussion, a good mix of EU and company representatives from North (SF) to South (P).
- Two discussion rounds took place where regulators and industry representatives expressed their views.

1. Regulators viewpoint

Regulators gave the following reasons for maintaining the 5-year renewal system:

- to have a defined date to control the marketing authorization in the light of new data; to make sure the dossier is up-to-date, and to check the marketing authorisation holder is fulfilling his duties;
- renewal fees form a substantial part of the budget plan of an authority.

2. Industry viewpoint:

- it was stressed that the intention of industry is not remove controls but to make it workable by removing duplicate levels of control;

- a high level of control is now possible with the broadened scope of pharmacovigilance, expected improvements to the variations regulations, and GMP inspections;
- the present system creates administrative and financial obstacles due to the differing renewal dates and requirements in the member states.

3. Conclusion:

Consensus was reached within the group that as a precondition for the replacement of the existing 5-year renewals system, pharmacovigilance was to be fully implemented across Europe, and the proposal includes a revision of the current variations regulation and the functioning of GMP inspections.

Conclusions of Workshop 3

Risk Analysis – MRLs/extrapolation – residue analysis

Chair: Jacques Boisseau/ Jacques Cuvelier

Rapporteur: Peter Schindler

1. Risk Analysis

Risk analysis concept comprises

- Risk assessment – to be done by scientists, who also recommend appropriate risk management strategies
- Risk management – to be enforced by authorities.

Risk assessment and risk management procedures for residues of veterinary medicinal product, culminating in the ADI, MRL and withdrawal period, are designed to reduce risk to consumers to 'practically zero' by using worst case assumptions at every step, and by applying additional safety factors. While the objective of this approach is laudable, the procedure could be improved by considering more realistic exposure factors, particularly when the 'close to zero risk' approach creates undue problems. For example:

- Every day consumption of the MRL is not realistic.
- Not all animals are treated; only sick animals or at risk groups are treated.
- Exposure to residues from minor species is less likely than from major species.
- Consumption of an injection site residue is as an acute exposure event, and not a chronic exposure event.
- Consumers are unlikely to consume 500g of meat and 1.5 L of milk every day.

Currently the biggest hurdle facing both industry and regulators is convincing DG SanCo that proposals for increased use of risk analysis, for example when extrapolating MRLs from one species to another, will not affect consumer safety. The difficulty lies in explaining the significance of the ADI and MRL. A consumer will demand 'no residues at all', and will have difficulty accepting the concept of 'no harmful residues'.

The group concluded that effective communication with DG SanCo was essential on both MRLs and analytical method development. In turn DG SanCo must give the right messages to consumers about the registration procedures, which ensure the safety of veterinary medicines, and that residues are kept at 'insignificant' levels. This would include the publication of residue surveillance data.

2. MRLs and extrapolation to all species

The chairman opened the discussion by making the following observations:

- A CVMP guideline on establishing MRLs for minor species was adopted in 1997, but it had little practical impact.
- The new draft CVMP guideline (EMEA/CVMP/187/00) on a risk analysis approach to residues does not represent a significant progress in the practical situation.

The group recognised the following elements:

- The CVMP risk analysis paper concludes "an analysis of all published MRLs clearly demonstrates... it would be possible to set identical MRLs for different species".
- Furthermore the paper concludes "that specific MRLs for specific target species may not be necessary to ensure" consumer protection.

- However the final recommendations of the paper are mollified for political reasons (to be “politically prudent”), so that data are required on 3 major species before an “all-species” MRL can be considered for that substance.
- The group observed that in fact it would be better to focus on the generation of one good data set, rather than less data on each of 3 species.

The following conclusions were agreed:

- All must continue to promote to the European Commission and the Council the logic and benefits of setting MRLs for all species (i.e. MRLs should be published without specifying individual species).
- The mechanism to trigger the extension of existing MRLs to further species needs to be discussed.
- How the interpretation of the guideline can be harmonised should also be discussed, as it includes several loosely defined requirements.

3. Residue surveillance

3.1. Regulatory analytical methods

The group noted that there had been an EMEA Workshop on analytical methods in January 2000. The group reached the following conclusions:

- Reference laboratories do not require a *validated* analytical method, as the validation data is not relevant to them (as they will modify the method and revalidate).
- Reference laboratories only require a full description of the analytical method and the possibility to communicate with the company analyst.
- Companies should validate the analytical method, but only for the purposes of supporting the tissue residue depletion studies (i.e. certain validation criteria are not relevant).
- The MRL dossier should be based on data on one major species, and will include a validated analytical method (as above). This can be used as the basis for method development by the reference laboratories.
- Validated methods for other major species will be part of subsequent applications for marketing authorisations.
- There should be further workshops on this subject, involving DG SanCo and the reference laboratories.

3.2. Withdrawal periods

- It is technically possible now, with existing EU guidelines, to harmonise withdrawal periods.
- The problem lies in harmonisation of interpretation.
- This should be the subject of training days, as part of an assessor’s ‘continual professional development’.



FEDESA-HEVRA Info Day

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List of Attendees

<i>Attendees</i>	<i>Company Name</i>	<i>Pays</i>
Mr. Appleby Guy	ELANCO ANIMAL SCIENCE RESEARCH	UK
Ms. Barthelemy Marie-Anne	SIMV	FRANCE
Mr. Bell James	INTERVET INTERNATIONAL GmbH	GERMANY
Ms. Beuvier Anne	VETOQUINOL	FRANCE
Dr. Boenisch Brigitte	MERIAL	FRANCE
Dr. Boisseau Jacques	AGENCE NATIONALE DU MEDICAMENT VETERINAIRE	FRANCE
Ms. Chaton - Schaffner Mireille	CEVA SANTE ANIMALE	FRANCE
Ms. Cillo Nicola	FATRO SpA	ITALY
Mr. Clayton Rick	FEDESA	BELGIUM
Mr. Cook Roger	NOAH	UK
Dr. Cornez Bob	JANSSEN ANIMAL HEALTH B.V.B.A.	BELGIUM
Dr. Cuvelier Jacques	SIMV	FRANCE
Ms. De Bock Anne	PHARMACIA & UPJOHN COORDINATION CENTER	BELGIUM
Dr. De Ridder Erik	ELANCO ANIMAL HEALTH	BELGIUM
Dr. Doutel Mascarenhas Ramiro	DIRECCAO GERAL DE VETERINARIA	PORTUGAL
Ms. Falize Françoise	MINISTERE SANTE PUBLIQUE & ENVIRONNEMENT	BELGIUM
Ms. Finderup Birthe	SCHERING PLOUGH AH	DENMARK
Dr. Follet Ghislain	FEDESA	BELGIUM
Dr. Geilhausen Horst	BAYER AG	GERMANY
Mr. Henriksen Per	DANISH MEDICINES AGENCY	DENMARK
Dr. Hentges Andrea	BAYER AG	GERMANY
Dr. Hoerstermann Dirk	BOEHRINGER INGELHEIM VETMEDICA GmbH	GERMANY
Dr. Jaenicke Ulrich	BAYER AG	GERMANY
Dr. Jones Peter	EMEA (EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL	UK
Dr. Jungback Carmen	PAUL-EHRlich INSTITUT	GERMANY
Dr. Klostermann Ludwig	BAYER AG	GERMANY
Prof Kroker Reinhard	BgVV	GERMANY
Dr. Lewis David	PFIZER CENTRAL RESEARCH	UK
Ms. Liebaut Danielle	JANSSEN ANIMAL HEALTH B.V.B.A.	BELGIUM
Dr. Loontjens Louis	AGIM	BELGIUM
Dr. Marion Hervé	FEDESA	BELGIUM

Attendees	Company Name	Pays
Mr. Masseback Lennart	BAYER AB	SWEDEN
Dr. Meisel Marta Leonor	INFARMED	PORTUGAL
Dr. Moreau Alain	SCHERING PLOUGH ANIMAL HEALTH	UK
Mr. Moulin Gérard	ANMV - AFSSA	FRANCE
Mr. Obermayr Eugen	BMAGS	AUSTRIA
Dr. Peeters Walter	PHARMACIA & UPJOHN	BELGIUM
Dr. Ramiro Casimiro Elena	AGENCIA ESPANOLA DE MEDICAMENTOS	SPAIN
Dr. Roestel Barbara	ANMV - AFSSA	FRANCE
Dr. Rutter J. Michael	VETERINARY MEDICINES	UK
Dr. Schindler Peter	MERIAL GmbH	GERMANY
Dr. Schneidereit Martin	BfT (BUNDESVERBAND FUER TIERGESUNDHEIT e.V.)	GERMANY
Dr. Stewart Fraser P.	PFIZER CENTRAL RESEARCH	UK
ProfTokola Olavi	NATIONAL AGENCY FOR MEDICINES	FINLAND
Dr. Vallisneri Alessandra	FATRO SpA	ITALY
Dr. Van Leemput Leo J.J.	JANSSEN ANIMAL HEALTH B.V.B.A.	BELGIUM
Dr. Vandaele William	BVD CONSULTANTS S.A.	BELGIUM
Dr. Vanhemelrijck Johan	FEDESA	BELGIUM
Dr. Vanhooren Meike	PFIZER ANIMAL HEALTH	BELGIUM
Mr. Vanlerberghe Johan	SCHERING-PLOUGH	BELGIUM
Dr. Vollset I.	NORWEGIAN MEDICINES CONTROL AUTHORITY	NORWAY
Dr. Walters John	ELANCO ANIMAL HEALTH	UK
Dr. Zaenker Susanne	FEDESA	BELGIUM