EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Consumer safety issues

Approach for injection site residues

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An agency of the European Union

Revised reflection paper (RP) on injection site (IS) residues: considerations for risk assessment and residue surveillance

Public consultation until 30/04/2014

1st RP published in June 2008

Problem statement:

- residues at IS tend to be dramatically higher than residues in non-IS muscle
- muscle with different residues levels in a single carcass
- difficult to set appropriate muscle MRL
- Withdrawal period (WP) based on IS particularly long
- MRL should ensure consumer safety and WP no longer than necessary

Conventional approach for setting MRLs

- Set MRLs in non-IS muscle, fat, liver and kidney so that Theoretical Maximum Daily Intake (TMDI) < ADI
- WP derived so that residues < MRL
- Issues:
  - High residue levels at IS and slow depletion result in long WP
  - Not justified based on consumer safety
  - May reduce availability of VMP

Option to lessen the WP

- set no MRL for muscle
- Calculate the WP according to the ADI approach

Problems at residue control:

- Muscle is tissue of choice for monitoring
- No legal value without MRL for muscle
- Sample and analyse another tissue
- No control possible to meat imported as lean cuts

Set muscle MRL based on IS residue levels ?

PROs: higher muscle MRL →→ lower WP

CONs: little relevance for residue control authorities

- IS are scarce and non identifiable by eye
- IS residues in non-IS muscle would comply with MRL-IS even if WP not respected
- Tissue distribution not respected
  - residues in other tissues < LOQ when IS-residues = MRL
  - Monitoring in non-IS muscle not informative on MRL compliance in other tissues

No practical value for substances administered by other routes

Set 2 MRLs for muscle ?

Preferred approach for CVMP: MRL for non-IS muscle

MRL for IS-muscle

- Need 2 separate samples for monitoring
- Sample1 < MRL_{IS}

  < $MRL_{non\text{-}IS}$ →→ compliant
- Sample1 < MRL_{IS}

  > $MRL_{non\text{-}IS}$ → test sample2 < $MRL_{non\text{-}IS}$ → compliant

  > $MRL_{non\text{-}IS}$ → ~~compliant~~
- <u>CONs</u>
  - Cost
  - If sample2 not available ? Sample1 > $MRL_{non\text{-}IS}$ →→ ~~compliant~~

COMPROMISE

- Establish a single MRL for muscle derived in the conventional way
- Determine an alternative value for IS muscle allowing to set WP

ISRRV: injection site residue reference value

maximal level of residues that would be expected at the IS at the anticipated WP

– *TMDI calculated based on MRLs for liver, kidney and fat(+skin)*

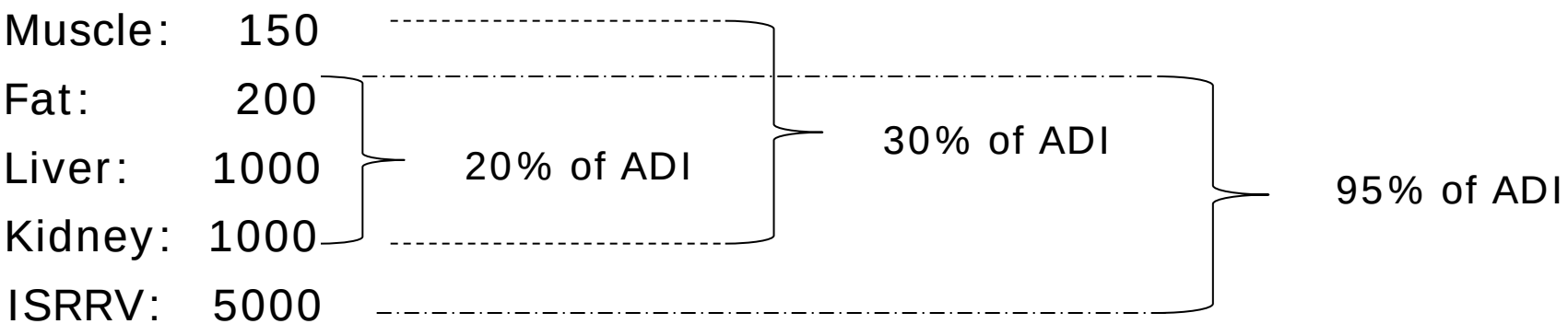
– *ADI-TMDI = value allocated to 300g injection site muscle*

– *WP:*

- *residues at IS < ISRRV*
- *residues in L, K, S/F, non-IS muscle < respective MRLs*

Hypothetical example - MRLs

Hypothetical MRLs (µg/kg):



Injection Site Residue Reference Value (ISRRV) is derived based on proportion of ADI not used by fat, liver and kidney (ie up to 80% of ADI)

CONSEQUENCES OF THE COMPROMISE

- ISRRV not published in CR 37/2010
- Published in the EPMAR
- Not used for monitoring purposes

- PROs: WP no longer than necessary
  no consumer safety concern
- CONs
  - Residues at IS > MRL at WP →→ risk of non compliance
  - Portion of the ADI available ? (ex. room for milk)
  - Compliance muscle MRL = compliance ISRRV not always possible
    - Muscle MRL not useful for controlling overall WP when residues very low in non-IS muscle

RECOMMENDATIONS

Introduce additional measures to further minimize the possibility of sampling IS:

- Injection consistently administered into one part of the animal that will not be used for residue sampling
- Include in the PL the area of the animal into which injections should be administered
  - Non-edible tissue
  - Neck for cattle, swine, sheep, goats and horses
  - Cattle: front of shoulder blade
  - Horses: breast
  - Piglets: Sc injection in the skin fold between the hind leg and the abdomen)
- Control authorities: sampling in other parts (diaphragm)
- EPMAR: recommendation on which tissue to sample

ACKNOWLEDGEMENTS

Prior to preparing the reflection paper CVMP consulted:

- Practicing veterinarians: information on injection practices - where are food animals injected, proportion of animals that go for slaughter within 3 months of being injected, division of large dose volumes?
- Residue control authorities: information on current residue control practices – tissue types used, how many tissue samples taken, which muscles used…
- Meat processing industry: information on potential fate of injection sites – amount of meat from different sites used for processed products

Thank you to all responders and in particular to FVE for coordination distribution and compilation of responses from practicing veterinarians.