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CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 6 **CX/EURO 16/30/7(REV)**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

FAO/WHO COORDINATING COMMITTEE FOR EUROPE

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CODEX WORK RELEVANT TO THE REGION

(Prepared by the Coordinator)

Discussion of Zilpaterol hydrochloride in Codex

Introduction

- The issue of growth promotors (and other stimulators of production) in Codex has proven to be a very controversial issue during the past years. Especially the European region expressed great concerns about adopting standards for growth promotors (and other production stimulators) in Codex. This was the case during the past years for ractopamine, and more recentlty for rBST.
- Zilpaterol hydrochloride (ZH) is scheduled to be discussed at Step 3 under agenda item 6.2 of the 23rd Session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF). Being a growth promotor, like ractopamine, it has already proven to be a controversial discussion point in CCRVDF (see history).
- As discussions on these issues have proven to be sometimes disturbing and harmful for the Codex process in general, it is important to stay very critical about the input in this kind of discussions. It is important to reconsider strategies in light of what has been learned in the past.
- On the other hand, it is important to develop new positions very carefully, being also able to explain these positions to the broader Codex audience.
- Therefore, an exchange of views on Zilpaterol in CCEURO can help in rethinking the issue of growth promotors, in carefully developing positions and in preparing strategies.

BACKGROUND

Description Zilpaterol hydrochloride

- ZH is a β2-adrenoceptor agonist, and used as a growth promotor in bovine species. It is marketed by Merck Animal Health as Zilmax®, a feed supplement that 'improves cattle's natural ability to convert feed into more lean beef'. It is given orally to cattle for a short period of time – the last 20 days – when they become less efficient at metabolizing their feed, and typically gain excess fat. There is a three-day feed withdrawal prior to harvest. Treated cattle can be harvested up to seven days following the three-day withdrawal and maintain the performance benefits. It is not for use in animals intended for breeding, veal calves or horses or other equines (www.merck.com).

History CCRVDF/JECFA

- At CCRVDF20, the United States of America (USA) nominated ZH for inclusion in the priority list for evaluation by the Joint Expert Committee on Food Additives (JECFA), the risk assessment committee for Codex (CX/RVDF 12/20/11 Add.1);
- CCRVDF20 could not reach consensus on inclusion of this compound on the Priority list and, therefore, decided to request advice and direction from the Commission regarding the appropriate steps to take regarding making a decision whether or not to include a veterinary drug in the Priority List (REP12/RVDF paras 110-114 and 118);

- CCRVDF20 forwarded a Priority List to the Commission for approval as new work, as contained in Appendix IX, Part A of its report, with ZH included in Part B of the same Appendix, pending the outcome of the Commission's discussion;
- CAC35 concluded that ZH should be included in the Priority List for JECFA evaluation, that no further guidance was required for the CCRVDF, that risk management decisions should follow the risk assessment and that the Commission approved the Priority List with the addition of ZH. On this basis, the CCRVDF would initiate work based on the recommendations of the JECFA evaluation. The Delegations of China, Croatia, Egypt, European Union, Norway and Switzerland expressed their reservation to this decision (REP12/CAC, para 177-178);
- JECFA78 evaluated ZH. The committee considered tremors, observed in humans and consistent with the compound's β2-adrenergic agonist activity, to be the most relevant and sensitive adverse effect from which to derive an Acceptable Daily Intake (ADI). The committee established a toxicological ADI of 0-0.04 µg/kg bw but data were insufficient to recommend Maximum Residue Limits (MRLs). Further clarification had been provided on data needs to the sponsor and additional data had been received by the JECFA Secretariat for consideration at the 81st JECFA (November 2015) with a view to completing the evaluation (JECFA78 report, REP15/RVDF, para 41);
- JECFA81 reaffirmed the ADI of 0-0.04 µg/kg bw and established an Acute Reference Dose (ARfD) of 0.04 µg/kg bw based on acute pharmacological effects observed in a single-dose human study.
- JECFA 81 recommended the following draft MRLs for Zilpaterol (free base)

Species	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Cattle	3.3 µg/kg	3.5 µg/kg	0.5 µg/kg

  There were insufficient zilpaterol residue data to adequately consider exposure to residues in lungs and other edible offal of cattle apart from liver and kidney.
- The draft MRLs are now scheduled for discussion at Step 3 under Agenda item 6.2 of CCRVDF23.

Status in EU

- Council Directive 96/22/EC[1] prohibits the use of β2-adrenoceptor agonists in the EU, with the exception of therapeutic use, which in the case of beta-agonists is to induce tocolysis (inhibition of uterine contractions) in cows when calving as well as to treat respiratory problems, navicular disease and laminitis (foot disorders) and to induce tocolysis in equidae.
- MRLs have not been established for ZH in the EU, CVMP nor EFSA has assessed ZH. EFSA however has reviewed the JECFA assessment.

Status in other regions

- Zilmax registration is approved in Brazil, Canada, Colombia, Costa Rica, Dominican Republic, Ecuador, Guatemala, Honduras, Kazakhstan, Mexico, Nicaragua, Panama, Peru, South Africa, South Korea and United States. Registration is in process for Zilmax in eight additional countries: Argentina, Australia, Chile, Indonesia, New Zealand, Pakistan, Taiwan and Uruguay (www.zilmax.com, accessed 27 July 2016).
- Zilmax treated cattle is banned by major meat packers and processors in the US (FeedNavigator, 2015).

Discussion points

- Effects in humans. The undesired effects of ZH are tremors in humans, used as the basis for the ADI and acute pharmacological effects in humans, used as the basis for the ARfD. It should be noted that no MRLs have been recommended by JECFA for other tissues than kidney, liver and muscle.
- Animal welfare. A recent overview of animal welfare issues related to the use β- agonists can be found on the website of the Animal Veterinary Medical Association (AVMA, 2014).

[1] COUNCIL DIRECTIVE 96/22/EC of 29 April 1996 concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists, and repealing Directives 81/602/EEC, 88/146/EEC and 88/299/EEC (OJ L 125, 23.5.1996, p. 3).

There have been several reports on ZH-treated cattle losing hooves during severe heat stress. The actual cause of the hoof loss has not been established to date but researchers concluded that it was probably multifactorial (Thomson et al., 2015). Merck responded to the reports of hoof loss by temporarily stopping sales of Zilmax and has placed a statement on their website 'when these very infrequent reports have occurred, Merck Animal Health has worked closely with feeders to resolve the issues through various farm management practices and protocols that ensured proper usage of the product. It is a responsibility we take very seriously'. One observational study indicated that β- Adrenergic agonists are 'most likely causally associated with increased cumulative incidence, incidence rate, and hazard of death when they are administered in accordance with the FDA-approved label directions' (Loneragan, Thomson and Scott, 2014). Merck rejected the study (FeedNavigator, 2014).

The use of ZH is contra-indicated for equine species, oral administration of zilpaterol to horses at the dosage indicated for use in cattle may result in prolonged adverse effects, including tachycardia, muscle tremors, and renal damage (Wagner et al., 2008).

- Use of resources. ZH artificially induces growth of healthy animals. Zilmax treatment gives 24 to 33 pounds additional hot carcass weight and an increase in live weight from 11-19 pounds. The producer of ZH argues that as Zilmax helps improve cattle's natural ability to convert feed into more lean beef instead of excess fat, this requires less cattle, and as a result, requires less use of natural resources, and keeps meat affordable (www.zilmax.com).
- Consumer perception. In the European region, most consumers would prefer to be able to choose the product based on its production and not to be unknowingly eating animal products which are produced using growth enhancing treatments. Studies show that they are willing to pay more for untreated products (Food demand survey US May 2016, Lusk et al, 2003)
- Trade disputes. At this moment, no international MRLs have been established for ZH, so countries can reject products containing ZH based on their own legislation. Once Codex MRLs have been established, the situation becomes very different.

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