Zilpaterol MRLs in Codex

Status Update

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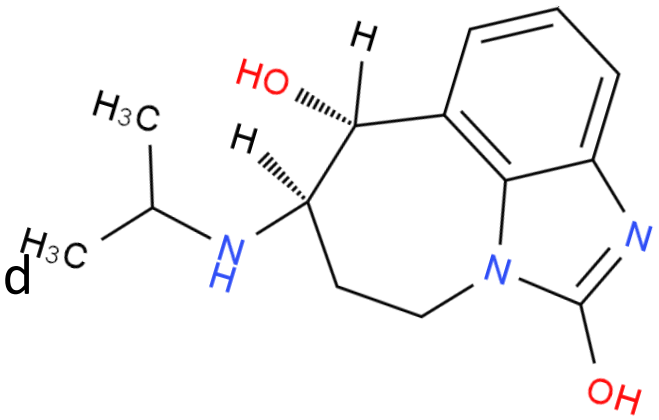
The Issue

- Proposed MRLs for zilpaterol hydrochloride (cattle fat, kidney, liver, muscle) held at Step 5 at the last Commission (CAC45)
- Proposed MRLs Previously held at Step 4 at CCRVDF 25

- The Proposed Standard Fulfils all the requirements of Codex Standard Development:
  - Favorable evaluation by JECFA
  - Extensive Discussions at CCRVDF: No technical Issue is impeding the development of the standard
  - Supportive Favorable Evaluations by other Food Safety Agencies such as US FDA, Health Canada and EFSA

Background on Zilpaterol

- Zilpaterol hydrochloride (trade name Zilmax), CAS no. 119520-06-8), is a β2-adrenoreceptor agonist that is used to **increase the rate of body weight gain**, improve feed efficiency and increase carcass muscle ratio in **cattle fed in confinement** before slaughter.
- Zilpaterol, by activation of protein kinase A, **increases protein synthesis in skeletal muscle fibers**, as well as **reduces lipogenesis and increases lipolysis** in adipose tissues.
- Zilpaterol is approved for use in several countries including: Canada, the USA, South Africa, South Korea, Mexico, Panama, the Ukraine and Brazil
- **Zilpaterol is mostly used / Sold in South Africa, Mexico, Panama, Costa Rica, Lebanon, Guatemala, Honduras, Lesotho and Nicaragua**
- **Zilpaterol is not (much) used in the United States, Canada**
- Zilpaterol is not approved in China, Taiwan, Russia, and the EU
- Zilpaterol hydrochloride has been assessed by JECFA at its 78th (2014) and 81st (2015) meetings at the request of the CCRVDF21 and CCRCDF22.



Zilpaterol: Scientific Assessments and in Codex

- JECFA Established Health Based Guidance Values for Zilpaterol:
  - **ADI value of 0.04 ug/kg bw was set as the ARfD based**
- EFSA (2016) noted that the ADI/ARfD of 0.04 µg/kg bw proposed by JECFA **is sufficiently protective for the establishment of MRLs and safe exposure levels for humans"** and considered JECFA's evaluation as **"scientifically robust**"
- MRLs held at Step 4 at CCRVDF, while exhausting all the discussions
  - Opposition is not related to Science / Health issues but Policy considerations at the national or regional level
  - Mainly: **Directive 96/22/EC prohibits the use of β-agonists in food-producing animals except for therapeutic use, under direct veterinary supervision, in cows and horses**. Likewise, meat and meat products obtained from animals treated with β-agonist for growth promoting purposes are banned in the European Union.

Positions Expressed

- ❑During discussion on whether to hold zilpaterol at step 4 or advance to step 5
  - The EU despite stating they had no human health concerns objected to advancing it to step 5 and beyond
  - EFSA had completed a review of the JECFA Risk Assessment and not only found it to be "robust" but also found no human health concerns and no animal welfare concerns at the recommended dosage
  - EU's objection based on "consumer preference" and the fact that growth promoters are not allowed in the EU
- ❑China objected to advancement as they stated that offal tissues are consumed in China and the MRL does not cover offal (muscle, fat liver and kidney per Procedural Manual)
- ❑Russia objected saying that Russia had additional data (never submitted)
  - CCRVDF has a Concern Form that delegations can submit if they have data or human health concerns for JECFA's review. No Submission was made in relation with zilpaterol

Status in CCRVDF and CAC

- The Chair of CCRVDF based on the fact there were objections to holding Zilpaterol at step 4 or advancing it to step 5 **sought advice from CCEXEC**

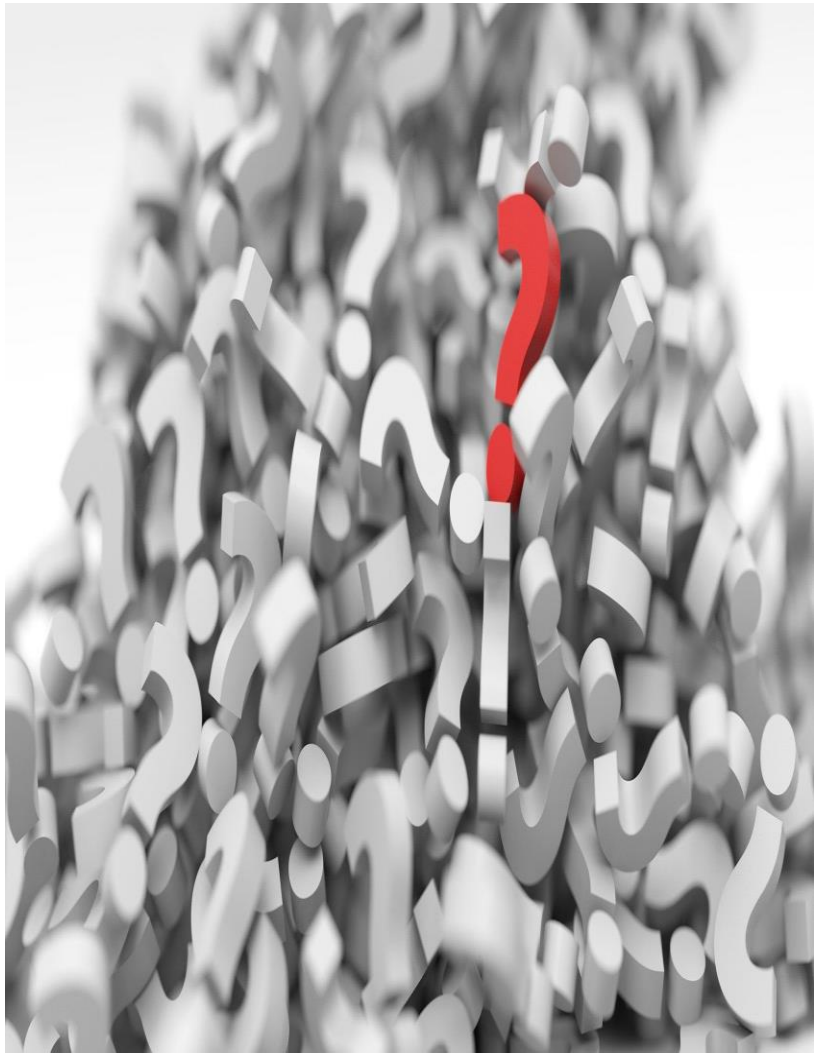
- The question was on Course of Action when the objections were not based on science, were not within the mandate of Codex (A minority of delegations objected to the discussion)

- CAC45 Voted to Adopt the Standard at Step 5

- Second Vote at CAC45 (requiring 75% of the votes) was shy of reaching the needed number to adopt the standard through the accelerated procedure (5/8)

Consideration of Positions

- Scientific Evaluation of Zilpaterol is supportive of the adoption of MRLs at Codex
- A standard Adopted at Codex does not mean that countries have to adopt it – The substance can still be not allowed in the countries that have the rationale to do so
- A codex Standard would support countries that decide to use Zilpaterol to set safe levels for its use
- Not adopting the MRLs for Zilpaterol would have impacts on **South-South Trade (minimum impacts on the exports of / trade of countries of the "North"** i.e., US, Canada)



Review of International Risk Assessment(s) of Zilpaterol (including JECFA Assessments)

Dr. Mark Feeley – Senior Food Toxicology and Scientific Advisor, GFoRSS

Review of the Science :

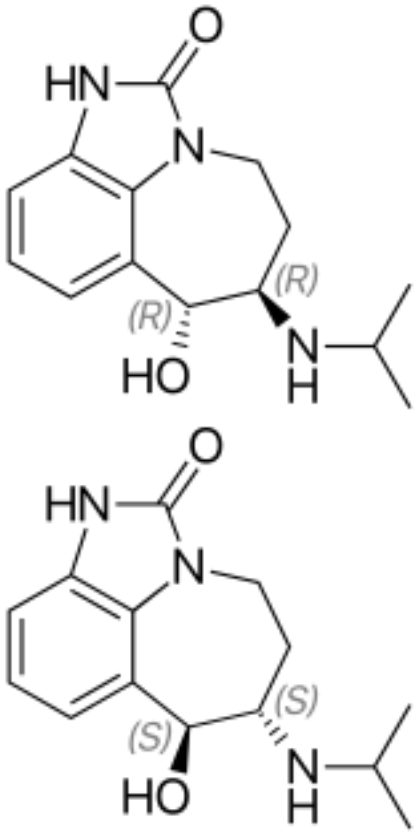
Dr. Mark Feeley

- **Senior Toxicology and Scientific Advisor, GFoRSS.**
- **Former Deputy Director, Bureau of Chemical Safety, Food Directorate, Health Canada**

https://www.youtube.com/watch?v=ACBJcjouaPY

Overview

- Zilpaterol (Zilmax®) - for increased weight gain, improved feed efficiency and increased carcass leanness in cattle fed in confinement during the last 20 to 40 days on feed; not permitted for use in lactating dairy cattle
- β2-adrenergic agonist activity (binds to the receptor); in humans, β2-adrenergic agonists cause smooth muscle relaxation of bronchial passages, vasodilation in muscle and liver, relaxation of uterine muscle, and release of insulin. Used to treat asthma and pulmonary diseases.
- Zilpaterol hydrochloride has been assessed by JECFA at its 78th (2014) and 81st (2015) meetings at the request of the CCRVDF21 and CCRVDF22.



JECFA – Zilpaterol HCl

- 78th JECFA initially established an ADI of 0.04 ug/kg bw; no issue with the safety assessment but questions remained re. residue data on which to recommend MRLs
- Full toxicological data package was available for evaluation (PBPK, short term, long term, cancer bioassays, developmental, reproductive, genotoxicity)
- The most sensitive effect was considered to be neurological (tremors); observed in human volunteers at a LOAEL of 0.76 ug/kg bw (described as slight and transitory)
- Application of a 20-fold UF gave the ADI of 0.04 ug/kg bw or an acceptable daily intake of 2.4 ug for a 60 kg person
- At the 81st JECFA, additional residue data on bioavailability and depletion was made available; in addition, as the critical study used to set the ADI was acute dosing, it was considered appropriate to set an ARfD

Food and Agriculture Organization of the United Nations

World Health Organization

JECFA – Zilpaterol HCl (2)

- Main tissues are liver < kidney <<< muscle < fat; after a 48 hr withdrawal period, residues only detected in liver and kidney
- The MRLs recommended by JECFA for bovine tissues are based on an acute dietary exposure scenario (GEADE). Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs
- 95th percentile of residue concentrations in bovine tissues at the 72-hour time point: 4.1 µg/kg in kidney, 4.3 µg/kg in liver and 0.6 µg/kg in muscle = 99% of ARfD for the general population and 117% for children.
- Considered a refined assessment with 95% residues derived at 77 hours post-dose: 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.
- GEADE of 1.9 µg/day (80% of the ARfD) for the general population and 0.57 µg/day for children (94% of the ARfD)
- It was noted that the time point at which the MRLs are calculated (77 hours) is consistent with currently approved withdrawal times (GVP).

JECFA

The Joint FAO/WHO
Expert Committee on Food Additives

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JECFA Summary

- Oral bioavailability of zilpaterol is high (almost 100%); Cmax reached within 1 hr. and similar PBPK profiles are seen with acute and repeat dosing; T1/2 humans is 3-4 hours.
- Short term GLP studies conducted in rodents (rats and mice), dogs, Cynomolgus monkeys, microswine and cattle
- Rats – decreased average HR at a LOAEL of 50 ug/kg bw/day (13 weeks); NOAEL (52 weeks) = 50 ug/kg bw/day. Monkeys - NOAEL was 10 ug/kg bw per day (4 weeks), based on reduced blood pressure; increased heart rate with a decreased QT interval at 50 ug/kg bw per day
- No evidence for reproductive or developmental toxicity (rodents) at dose up to 1 mg/kg bw/day; embryo and fetal toxicity only observed at doses > 10 mg/kg bw/day
- Humans – 0.25 mg/person (3.6 ug/kg bw) NOAEL for diastolic blood pressure, stroke volume, heart rate, bronchodilatation and tremor; LOAEL for increased heart rate (5.75 bpm) and increased blood glucose
- Asthma – 0.05 mg/person (0.76 ug/kg bw) bronchodilation NOAEL, tremor LOAEL.
- Observed effects were slight and transitory and typically related to the β2-adrenergic agonist activity of zilpaterol HCl

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FDA - 2006

- The lowest short-term No-Observed-Adverse-Effect Level (NOAEL) of 10 µg/kg bw per day was found in monkeys (reduced blood pressure, increased heart rate associated with decreased QT intervals at 50 µg kg/bw per day for 4 weeks).
- When zilpaterol was given to rats for 1 year, reversible effects on heart rate and blood pressure resulted in a NOEL of 250 µg/kg bw per day
- Human studies – single doses of $\geq$ 4.14 µg/kg bw caused HR and blood glucose increases; doses $\geq$ 8.33 µg/kg bw caused tremors, with the NOEL being 1.7 µg/kg bw.
- FDA – most sensitive effect was bronchodilation in people with asthma, with the NOEL being 0.83 ug/kg bw; ADI was set at 0.083 µg/kg bw. Bronchodilation was described as slight, transitory and reversible at the next highest dose (1.7 µg/kg bw)

FDA U.S. FOOD & DRUG ADMINISTRATION

EFSA - 2016

- JECFA derived an Acute Reference Dose and an Acceptable Daily Intake of 0.04 µg/kg body weight (per day) based on neurological effects seen in humans (tremors) and, after carrying out an exposure assessment, has recommended maximum residue limits (MRLs) for zilpaterol in cattle of 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.
- The LOAEL and UF used by JECFA are “reasonable” except EFSA may have conducted DR modeling
- The approach followed by JECFA for setting MRLs for zilpaterol appears to be scientifically robust*
- Only a withdrawal period of more than 3 days would result in residue levels leading to acute dietary exposure estimates below the ARfD
- The available literature investigating the effects of zilpaterol on animal health and welfare is limited but indicates** a potential increase in mortality, heart rate, respiration rate and agonistic behaviour in cattle.

efsa
European Food Safety Authority


thank you
merci
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
obrigado
dziękuję
bedankt
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