An Industry Perspective on Import MRLs in APEC and Beyond

Audrey Chen, PhD
FMC Ag Solutions, Global Regulatory Sciences, Ewing, NJ USA

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Outline

- Food safety and MRLs
- MRL setting challenges
- Global MRL harmonization directions
- Import MRLs in APEC
- Additional challenges

Food Safety and MRLs

- Food safety analysis begins with MRLs, but not ends with MRLs
- Risk assessment should always be performed to evaluate food safety at proposed MRLs

Why are MRLs different?

- Different application rate and timing
- Different residue definition
- Different residue method
- Different MRL calculation
- Different crop groups for extrapolation
  - Leek (bulb veg. in US/Codex; stem veg. in EU; leafy veg. w small leaves in TW)
  - Cotton seed (oilseed in US/Codex/EU; dry beans in TW)
  - Peanut (legume oilseed in Codex; oilseed in EU; dry beans in TW; misc. in US)

MRL Setting Challenges (1)

Example: Analysis of parent + 2 conjugated major metabolites (>50% TRR in crop metabolism studies)

- US EPA guidelines
  - Acid hydrolysis for >10% TRR (or >0.05 ppm) conjugated metabolites (deconjugation, ~1N HCl pH < stomach acid pH 1.5-3.5)
  - Radiovalidation (deconjugation w ~1N HCl)
- EU guidelines
  - Deconjugation (bioavailability, digestive tract) should be considered for >25% TRR (or >0.05 ppm) conjugated metabolites
  - Extraction efficiency (deconjugation may not occur)
  - Apply conversion factors (conjugated vs. free metabolite) w/ o deconjugation
- JMPR guidelines
  - Radiovalidation with rigorous extraction
  - or use commonly used solvents for extraction efficacy

Residue Definitions

Example: Parent + 2 conjugated major metabolites

- EPA guidelines

  MRL ↔ parent + 2 major metabolites

- EU guidelines

  MRL ↔ parent w or w/o conversion factor

- JMPR guidelines

  MRL ↔ parent only

- MRLs from national registrations may not be the same
- New harmonized test guidelines may not be harmonized

MRL Setting Challenges (2)

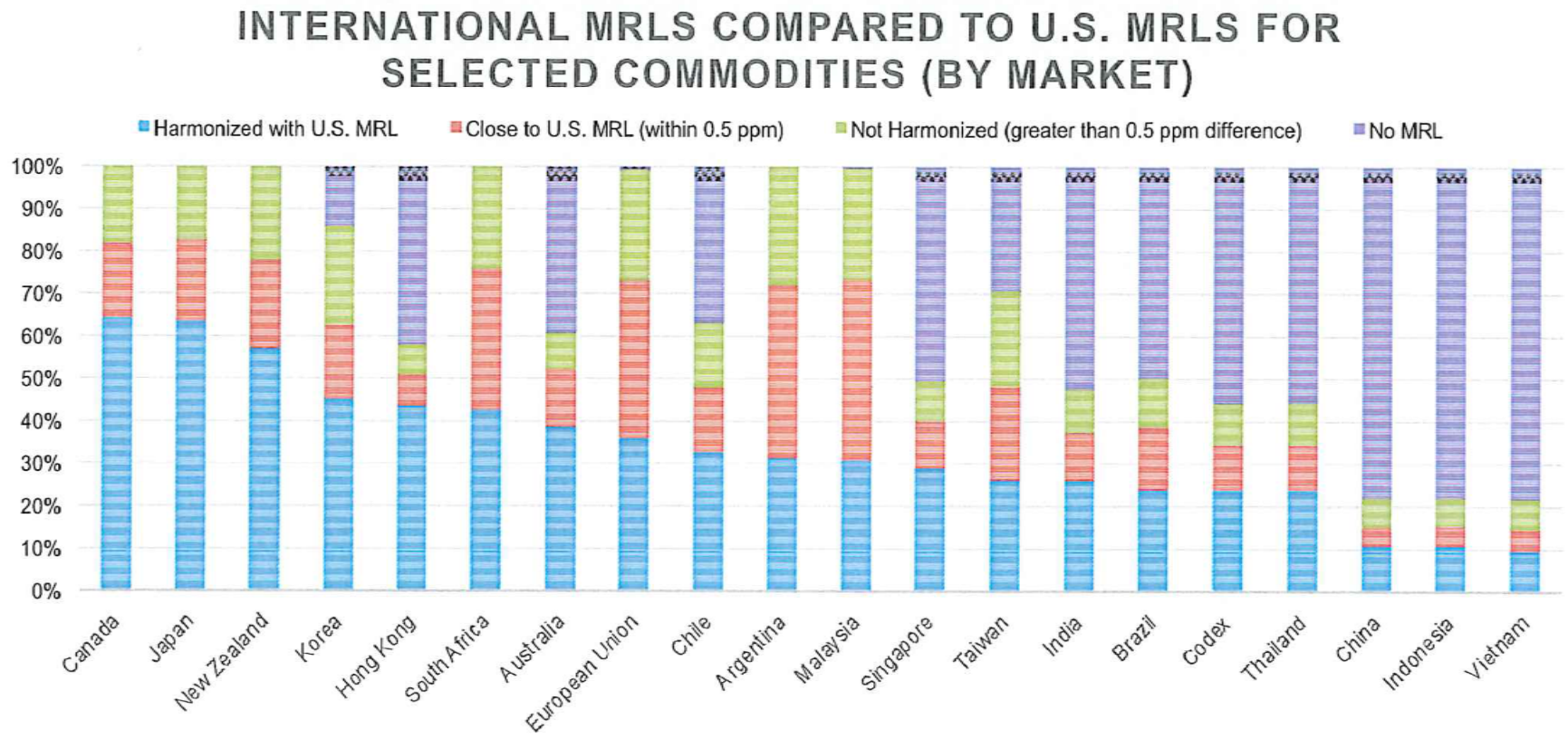
Current Status (EPA):

- Monitoring methods (solvent extraction, e.g. QuEChERS) → MRLs used for harmonization
- Enforcement methods (acid hydrolysis) → MRLs used for risk assessment

- Global joint review (new ais) may resolve the issue?

MRLs – International vs. US

BRYANT CHRISTIE INC.



Based on 389 AIs and 779 commodities

Import MRLs (IT)

- Allow importing of foods/feeds containing MRLs not set nationally
- Import MRL application requires less data review (no e-fate and ecotox impact)
- Not all countries have IT application system (China)
- IT Regulations vary by countries
- Some countries set separate IT (S. Korea, Japan, Australia, US, Canada)
- Some countries combine IT and national MRLs [more regulations; Taiwan, China (maybe, no policy yet)]

- Allow or accept highest IT already established in other regions, if risk to local consumers is acceptable

IT - APEC

- Japan – Positive List (2006), IT (2.5-3 yrs)
- S. Korea – Positive List (2010), IT (1.5 yrs)
- Taiwan – Priority List (2014), IT (1-2 yrs)
- Hong Kong – Positive (2008) and Priority Lists (2013), IT ?
- China – IT (estimated 3-5 yrs), may consider CXLs
- Australia – IT (1 yrs)
- New Zealand – IT (CXLs)
- NAFTA (USA, Canada, Mexico) – IT (~2 yrs)
- ASEAN (Indonesia, Singapore, Thailand, Philippine, Malaysia, Viet Nam, Brunei) – IT (national MRL list + CXLs)
- Peru, Chile - IT (CXLs, EU, US)
- New Guinea, Russia – IT (?)

IT - S. Korea (1)

- New AI doesn't need product registration prior to IT, submit tox and residue data only (~1.5 yrs)
- Accept Crop group MRLs
- Provisional MRLs - lowest MRLs (e.g. from monitoring program) or 0.01 ppm will replace CXLs w/o valid residue data, no more provisional MRLs after 2021 (extended 3 yrs from 2018)
- GAPs in US MRLs usually remained the same
- GAPs in CXLs may be changed (e.g. banana or mango export from Philippine to Korea, previous (>20 yrs) residue reports and CXLs can't support the current use)

IT - S. Korea (2)

- New local (e.g. Philippine) residue trials (3 per crop) are needed when GAPs have been changed
- Local residue GAP trials are risky to conduct by inexperienced personnel
- Local residue labs do not fully understand what constitutes in a valid residue method
- Cost is too high to bring in experts to do the GLP or GAP residue studies

- USDA-MFDS MRL workshop (Feb. 8-9) for further harmonization?
- APEC IT approach?

IT - Taiwan (1)

- Registered AI needs efficacy and residue data for IT application (~1 yr, cost is free)
- Need at least 3 efficacy trials including 2 complete trials (≥3 plots) for each crop
- Need efficacy and residue data for major crops for IT, some major crops in TW are minor crops in US (e.g. papaya MRL extrapolated from crop group MRL)
- No crop group MRLs
- New AI needs product registration + local residue trial prior to IT (~2 yrs)
- TACTRI – application/harvest/analysis (GLP) and dossier review
- Registrants – crop trial location and in-life phase (ITs are usually US projects, work with inexperienced local farmers and colleagues)

IT - Taiwan (2)

- Crop trial set up may be compromised (e.g. w or w/o scaffolding for pea trial)
- Communication errors (e.g. rate on ai or fp)
- TACTRI should also take care of the crop trial location and in-life phase
- Some property reports accepted by EPA are inadequate; more QC reports/certificates are needed

Taiwan Priority List Update (1)

- Priority list for 116 import MRLs (2014) - USDA/ FAS/Grower Associations/TFDA
- In Oct. 2016,
  - 23 MRLs established
  - 3 under review
  - 4 rejected
  - 86 applications not received
- FMC received 8 MRLs (registered ai) in Jul. 2016, papaya MRL rejected w/o residue data (papaya MRL extrapolated from tropical fruits inedible peel in US)

Taiwan Priority List Update (2)

- Dossier submitted for 5 MRLs (a new ai) in Nov. 2016 (MRLs expected in 2018)
- TACTRI completed analysis in Apr. and residue report in May, residues were <LOQ (0.01 ppm),
- LOQ was 0.05 ppm when MRLs were set ~20 yrs ago in US (before LC-MS/MS)
- MRL harmonization must be considered

- USDA-TFDA MRL workshop (Feb. 13-14)?
- APEC IT approach?

IT - US EPA (1)

- After two APEC IT harmonization workshops (2015), EPA said "US has one of the least flexible system for establishing IT"
- 4 pilot projects in 2016-17 – evaluate an approach to establish IT w/o US registration
- Determine acceptance of JMPR/National Authority residue chemistry GLP data review
- Determine IT based on harmonization

IT - US EPA (2)

- US companies – Registrations usually start from EPA, followed by EU, and then Codex
- EU companies – Registrations usually start from EFSA, followed by US, and then Codex
- Codex MRLs established after US/EU MRLs, ITs to US usually unnecessary
- Most likely EU MRLs are to be accepted as ITs, if MRLs not set in US
- PRIA fee required

IT - US EPA (3)

EPA has established ITs based on the foreign data set when MRLs not set in US (case-by-case):

- Bifenthrin on tea - IR-4 submitted residue data from China, Japan and India as minor crop
- Kyralaxyl on grapes - based on EU data
- Mancozeb on mandarins - based on Korean data

Carfentrazone-ethyl - Registration Review

US EPA

- Registered 1998, RR 2011-2017 (MRLs for all crop groups)
- Highest chronic consumer exposure 78% of ADI (0.03 mg/kg bw/day, Tier 1)
- May 2016 conclusion - remain as reduced risk product

EU EFSA

- Registered 1998-2003, RR 2011-2017 (3 crops, same MRLs and ADI)
- Highest chronic consumer exposure ~1% of ADI
- Aug. 2016 conclusion – potential carcinogenic (relevance of metabolites in groundwater? Need more tox studies.)
- Jan. 2017 – EC concluded it fulfills safety requirement, pending on decision by ECHA

- >10x additional study time and cost spent for EU RR
- Reviews based on same set of tox reports

Other Regulations to be Harmonized

- Regulatory Test Guidelines
- Toxicity end-points and classifications
- Risk assessment procedures

Thank You