Introduction: Richard Coulter

- Veterinarian
  - University of Melbourne (Australia)

- Poultry Industry (Australia)
  - veterinarian,
  - livestock management

- Global Animal Health (Rhone-Poulenc)
  - Technical & Regulatory Affairs

- Animal Feed Industry (Ridley AgriProducts)

- RA Consulting: biotech, animal health,

- Phibro Animal Health Corporation (US)
  - Global Scientific & Regulatory Affairs
## Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABX</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>AMR</td>
<td>Antimicrobial Resistance</td>
</tr>
<tr>
<td>CDC</td>
<td>US Centers for Disease Control &amp; Prevention</td>
</tr>
<tr>
<td>CVM</td>
<td>US FDA Center for Veterinary Medicine</td>
</tr>
<tr>
<td>FFD&amp;CA</td>
<td>US Federal Food, drugs and Cosmetics Act</td>
</tr>
<tr>
<td>GFI</td>
<td>Guidance For Industry</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi Drug Resistant (DR = Drug Resistant)</td>
</tr>
<tr>
<td>SPS</td>
<td>Sanitary and Phytosanitary</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin Resistant Enterococci</td>
</tr>
</tbody>
</table>
Presentation Overview

- **AMR – What is the policy issue?**

- **Brief historical background:**
  - What is driving the process & what role does science play
  - Global regulation of animal use MFA antibiotics.
  - DO OTHER COUNTRIES HAVE SIMILAR REQUIREMENTS TO THE USA? (Asks Dr. Hickam)

- **What can we learn from the international experience?**

- **What is on the horizon re AMR policy?**
  - What should agriculture and animal health be concerned about?
  - What should we hope for in agriculture and animal health?

- **Discussion**
USA – AMR concern vs Action?

**US CDC data (2013)**
- 2,000,000 people/year acquire AMR infections.
- 23,000 people/year die of, or with(?), AMR infections

**Specific resistance concerns (CDC)**
- **Drugs**: Carbapenem & other ESβ-lactams, Macrolides, FQs, Fluconazole, Vancomycin, 3/4G cephalosporins.

- No AGP use of these classes
- Little animal overlap; little/no AGP role
WHO & CDC: Good alignment at the top

Ref: WHO. Critically Important Antimicrobials in Human Medicine. 3rd ed.
Antibiotics and resistance

- Antimicrobials are one of the oldest drug classes of the modern pharmaceutical age.
- AMR and its negative effect on efficacy was identified ~1940. With the discovery of each new class, subsequent resistance was rapidly identified.
- AMR: naturally occurring phenomenon. ABX Resistance genes date back to pre-historic times & pre-date ABX discovery.
- Rapid observation of resistance should be expected....
- ...Bacteria are ready to go with resistance genes for the ABX we have not yet discovered.

“...authenticated ancient DNA from 30,000-year-old Beringian permafrost.... highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics.

...show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use....


Source: US Centers for Disease Control and Prevention
The ‘modern’ AMR debate

- In-feed use in animals quickly followed human use. Mechanistic studies rare. Development = administer then observe effects on health and growth

- 1969: The Swann Report postulated the use of ABX in animals could compromise the effectiveness of ABX therapy in humans


1997-9: Europe bans production uses of ABX:
- Political compromise to accommodate Swedish accession to EC.
  - Mandatory harmonized regulations across all Member States.
- Regulation promoted as science but EU scan panel disagreed
  - The “Precautionary Principle” supports social concern based decision making. Does not require evidence/science basis.

- EU action
  - Directed at production uses.
  - Policy NOT directed based on Medical Importance.

Claims
- Therapeutic
- Production

Do bacteria know or care what the label claim says regarding AMR selection?
First... what has happened globally?

International policy & standards

Short overview of various country actions on animal use ABX
- Did the actions actually consider likely benefit to human health?
  - What did they do?

- Australia
- Canada
- Japan
- USA (more detail and current policy actions)

- EU:

- Short review of the what has followed various policy actions
  - What benefits have accrued to AMR in human health
  - What is being reported
  - Unintended consequences
International policy actions

- **All countries are entitled to set their own domestic food standards / safety policies**
  - Sovereign rights for all governments confer both a right and a responsibility to take measures to protect the human health within their country.
  - Science/evidence based policies are more likely to produce science based outcomes, but national law-making does not have to be science based, nor do domestic standards.
  - Control of use of veterinary drugs is a matter for each sovereign government to determine.
    - The OIE is the international body charged with encouraging solidarity in the control of animal diseases including the control of use of animal drugs.

- **Member countries of the WTO are bound by SPS measures regarding traded foods**
  - Technical food standards applicable to trade between members must be evidence based.
  - Where agreed international standards exist (eg Codex), they must be followed unless the departure is supported by a valid risk assessment. The ultimately dispute resolution is the WTO.
  - SPS standards should be quantitative, measurable and relate to the traded food commodity.
Australia

- **JETACAR report of 1999.**
  - Prioritized ABX according to human importance (1999)
  - Mandatory vet / dentist / physician control over use.
    - ALL ANIMAL USES MOVED TO VET CONTROL.

- **APVMA review of compounds (started 2001)**
  - RA's have not shown significant animal causality for human health AMR.
  - Production uses of ABX* discontinued. Vet control of use of antimicrobials*.
    - **Streptogramins (virginiamycin) prioritized**
      - Considered importance of use in each animal species.
        - If not used, importance to be established by sponsor.
        - Risk Assessment affirmed existing therapeutic uses in broilers, sheep, beef and dairy cattle.
        - Production uses discontinued. All uses under veterinary control (VFD) in 2003.
    - **Macrolides (kitasamycin, oleandomycin and tylosin)**
      - Kitasamycin, Oleandomycin discontinued as previous claims were all production.
      - Tylosin re-scheduled to “vet only” in June 2014.

[* Ionophores remain OTC and may be used for production.]
Canada

- **PUMA (Prudent Use of Medically Important antimicrobials in Animals)**
  - **Categorization of Medical Importance**

<table>
<thead>
<tr>
<th>Category</th>
<th>Preferred option for treatment of serious human infections</th>
<th>No or limited alternatives available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – Very High Importance</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>II – High Importance</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>III – Medium Importance</td>
<td>No</td>
<td>No/Yes</td>
</tr>
<tr>
<td>IV – Low Importance</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

- Low importance includes: Flavophospholipols & Ionophores only

- Deletion of production claim uses of MIAs
  - Potential for sponsors to provide adequate data to seek new therapeutic claims.

- All MIAs require veterinary prescription. Schedule F (= Prescription Drug List)

- Regulation promulgated February 1st, 2018. 10mo phase in period for labelling.

- From December 1, 2018 all MIAs will be sold by prescription only.
Review process for Feed Additives
- Feed Additives permitted under a non-proprietary, positive list system.
- Veterinary Drugs may only be added to feed ‘on farm’.

Initial plan (c2001)
- Deletion of ABX classes. Plan ‘arbitrary’ / not aligned with human health objectives.
- Plan abandoned following expert technical consultations

Revised plan (c2008)
- Science based consideration of all feed additive classes, including non-ABX’s.
- Dual purpose: AMR review + safety (tox) review older drugs
- Initial intent to review higher priority first
  • Actually worked through the “easy ones” first
    • Ionophores, anticoccidials, anthelmintics
    • Deleted if no sponsor support / perceived need.
- Despite Risk Assessment process, outcomes seem strongly aligned with WHO CIA list

Risk assessment outcomes determined by “Food Safety Committee”
- Possible determinations: High / Moderate / Low / Negligible
- Vet oversight not being expressly considered.

Risk management determined by MAFF.
- All classes determined High, Moderate or Low to be delisted. Negligible classes retained.
FFD&CA requires FDA to initiate formal action to withdraw the approval of any drug it believes to be unsafe.
- Historically, this has occurred: Human & Animal drugs
- 2005: Enrofloxacin withdrawn from poultry use.
  • Use was therapeutic, not production (“AGP”)

Current ABX policy objectives outlined GFI-209
1. Medical Importance determined by GFI-152 appendix (2003)
2. Medically Important ABX to be used under vet control.
3. Production claims defined as ‘not judicious’.
   - Implementation described in GFI-213. Effective 01/01/2017.
   - CVM have announced plan to review GFI-152 MIA determinations
     • Original list determined qualitatively.
     • Opportunity to ACTIVELY support vet use of lower risk classes, not just indiscriminant volumetric use reduction.

Summary
- Withdrawal of Production uses of MIA’s
- Prevention, Control & Treatment uses retained.
- All MIA use under vet control (VFD or Rx).

Non-judicious” does not mean unsafe.
Like “Precautionary Principle” it is a way of presenting unsupported opinion as fact.
USA – AMR concern vs Action?

**US CDC data (2013)**
- 2,000,000 people/year acquire AMR infections.
- 23,000 people/year die of, or with(?), AMR infections

**Specific resistance concerns (CDC)**
- Drugs: Carbapenem & other ESβ-lactams, Macrolides, FQs, Fluconazole, Vancomycin, 3/4G cephalosporins.

**Analysis:**
- CVM approach is very similar to that of other western jurisdictions and the EU actions of 1999.
  - Policy action directed at old gen AGPs - impact on Human AMR ??
  - Are we even attempting to measure the impact of these policies
  - Alignment with the public AMR threat ??
  - Mandatory veterinary control of use (Rx / VFD)

No AGP use of these classes
Little animal overlap; little/no AGP role
Back to Europe – did it work?

- Brief overview as the data are well known.

- The original driver was the political situation (Sweden), but the lightening rod issue was VRE, the assertion was it was driven by Avoparocin use in animals.
  - Avoparocin banned.
    - Glyco-R in poultry/pigs decreased
    - VRE in human continues to rise as it does worldwide.

- Avoparocin never used in the US. VRE is one of the leading AMR concerns highlighted by the CDC.

- Unintended consequence was the rise in use of broad-spectrum “treatment” ABX.
  - Newer data available, reinforces the earlier data.
  - NL “2009, 5 year plan”: Reduce animal ABX use by 50% in 5 years
    - Exceeded goal: 55% by 2012. Mostly Tetracycline reduction.
    - Increased use of newer higher biopotency ABX cephalosporins, FQs.

- Beneficial impact on human health?
What is on the horizon for AMR policy?

- Western countries have discontinued ABX production uses & implemented Rx/VFD. What is next?

What should agriculture and animal health be concerned about?

1. Monitoring: Almost all countries have/are introducing volumetric monitoring of ABX use.
   - Outlook: Monitoring of volume will almost certainly drive volume reduction, with little if any linkage to health outcomes in animals or humans. Reductions may target low MIA, old class ABX.

   - Preferred: The objective of policies to combat AMR, is to mitigate the loss of critical human therapies.
     - Particularly CDC/WHO identified critical ABX (Carbapenems & other ESβ-lactams, Macrolides, FQs, Vancomycin, 3G & 4G cephalosporins).
     - Therefore: measure rates of resistance to these key ABX in human medicine and analyse trends. Measure frequency of bacterial species resistant to these CDC/WHO critical ABX in food commodities/food animals. Take actions as appropriate
What is on the horizon for AMR policy?

2. The EU will try to impose/transmit its domestic policy regulations on other countries.

- **History:** The EU has seen the adoption of most of its 1999 antimicrobial restrictions in most developed countries and many developing countries.

- **Mechanism:** The EU is positioning its detailed domestic regulations as food safety standards, and is attempting to impose these on trading partners, then to extend to all other countries.
  - “**Reciprocity Policy**” drafted in 2015, finalization expected June 2018.
  - The EU “Reciprocity Policy” asserts that to ensure safe imported food for its citizens, trading partners must reciprocate the EU domestic standards.
    - EU would ban importation of foods raised in countries where vet drugs (esp. ABX) are authorised with use conditions different to those within the EU. This policy is not supported by a suitable risk assessment and is inconsistent with the SPS provisions of the WTO.

- **Forum:** Initial pressure on weaker international supply countries. Also likely the EU will try to formalize/ratify using the Codex-TFAMR. Arguably a policy document published by Codex could be valid at WTO.
What is on the horizon for AMR policy?

3. The WHO is attempting to expand its scope of pre-eminence to include the OIE’s role of control of use, in particular targeting ‘prevention of disease’ uses:

  - **November 2017:** WHO publishes “WHO GUIDELINES ON USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS”

  - **Four recommendation areas:**
    - Overall antimicrobial use [Strong recommendation, low quality evidence]
    - Growth promotion use [Strong recommendation, low quality evidence]
    - Prevention use (in the absence of disease) [Strong recommendation, low quality evidence]
    - Control and treatment use (in the presence of disease) [Conditional recommendation, very low quality evidence]

  - WHO is positioning that AMR risk associated with antimicrobial use in food animals impacts human health and therefore WHO must engage in the OIE area of recommending control of use of antimicrobials in food animals.
    - This is a significant stretch based on (WHO’s own words) “low quality evidence” or “very low quality evidence”.
    - WHO’s own publication Critically Important Antimicrobials aligns quite well with other sources (eg CDC) but is based on an opaque process of expert opinion, rather than being transparent and based on an evidentiary process.
What is on the horizon for AMR policy?

- What should we hope for in agriculture and animal health?

- The CVM has announced it will revise GFI-152 (The MIA classification).
  - This is an opportunity for the USA to provide leadership in the practical guidelines for Control of Use of antimicrobials in food animal medicine.
  - Positive opportunities:
    1. **Work on both ends of the classification.** Typically policies focus solely on restricting.
    2. A useful guidance should identify and support antimicrobials of low to negligible importance to human medicine (and this list should include a meaningful scope, not just ionophores).
    3. These antimicrobials need to be clearly classified as “NOT MEDICALLY IMPORTANT”
    4. The CVM needs to ACTIVELY communicate that it is “ok to use these N-MIA’s”, in fact it is the right thing to do when animal health/welfare would suffer if treatment/prevention was denied.
      - Farmers / Vets should feel conflicted when they take action to support animal health using N-MIA compounds.
    5. CVM can then differentiate by supporting the CDC and discouraging the most important MIA’s.

CVM has done a good job supporting the Concept of Treatment, Prevention and Control. A similar support for an expanded N-MIA list would help farmers and vets in their job of caring for their animals.
What does global experience tell us?

- **You will likely get the expected:**
  - Restricting ABX with negligible impact human health will not likely improve the AMR outlook in human health.

- **Every country SAYS its food animal ABX policy is science based and the objective is to reduce Resistance in Human Health, but:**
  - Underlying policy rarely aligns with the statements
  - Policies: soft option to be seen “doing something”
  - Reduced use of low importance ABX increases use of broad spectrum ABX of higher medical importance.

- **Appropriate antibiotic use in animals does not only mean reduced use, or no use.**
Discussion time
Chronology: ABX use / resistance

Source: United States Centers for Disease Control and Prevention