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Incentives for R&D of New Antibiotics for Use in Food Animals

Presidential Advisory Council on Combating Antibiotic Resistant Bacteria
Public meeting, 21 June 2016, Washington DC

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- **global representative body of companies and associations**
- **R&D, manufacturing and commercialisation**
- **veterinary medicines, vaccines, other animal health products**

10 largest global companies

Bayer HealthCare
zoetis
Elanco
Boehringer Ingelheim
MERCK Animal Health
Vétoquinol Signe de Passion
MERIAL
Virbac
ceva
Phibro Animal Health Corporation

80+% global animal health sector

29 regional associations

NORTH AMERICA
Canada
Mexico
United States

EUROPE and AFRICA
Europe
Belgium
Denmark
France
Germany
Ireland
Italy
Netherlands
Portugal
Spain
Sweden
Switzerland
United Kingdom
South Africa

CENTRAL/SOUTH AMERICA
Argentina
Brazil
Chile
Paraguay

ASIA/PACIFIC
India
Australia
Indonesia
Japan
Korea
New Zealand
South-East Asia
Thailand

The associations represent the larger companies as well as hundreds of medium-sized and smaller companies.

The human-animal industry connection

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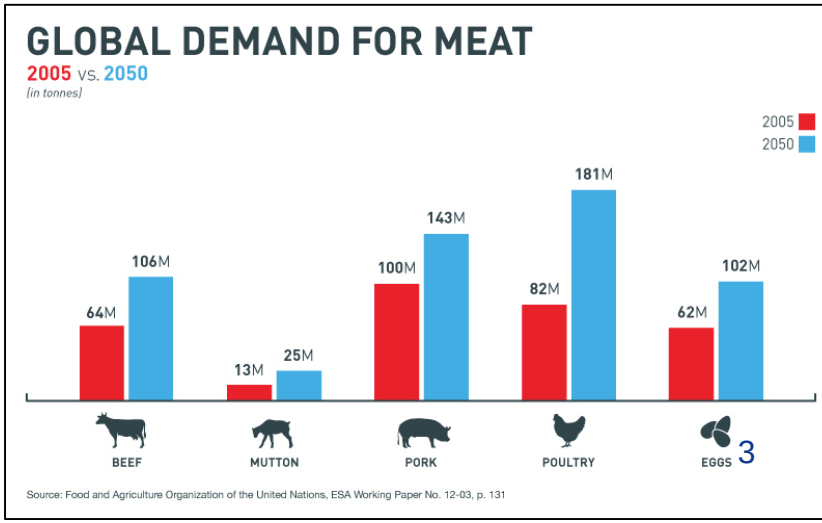
- Discovery - many basic molecules reviewed in last 20 years
- Human health provided much discovery of antibiotics – AH "*discovery*" not well resourced, only "development"
- AH using molecules "*discovered*" in human R&D: 1) animal analogues 2) antibiotics unsuited to human use
- Food animal antibiotics - low margin commodity model, profitability based on volume
- Animal protein demand increased = increased research and business incentives

….but changing

- Development time/investment needed increased
- Magnified antibiotic resistance discussions
- Animal/human health R&D became less connected = AH pipeline smaller



Where are we today?

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- No "*low hanging fruits*" left – they were "plucked" a long time ago…..
- Divergence: human health R&D focussed on different diseases, applications, pathogens
- Additional hurdles for veterinary antibiotics
  - Offer an ROI in a much smaller market
  - Not be on a potential list of antibiotic classes reserved for human-only use
  - Have international food/consumer safety standards set for trade (Codex Alimentarius)
- Investment in animal antibiotics jeopardized by up-take in human use (e.g. pleuromutilins)
- Societal and retail pressures = business risk for animal health companies
- Increasing cost for farmer in commodity businesses = business risk

Result

- Antibiotic volume restrictions discouraged investment
- Traditional antibiotic R&D funding diverted to:
  - prevention
  - alternatives
  - maintaining existing products ("defensive" R&D)
  - other products (pet antiparasitics, anti-inflamatories, generics, cardiac, skin/dental care, nutritionals)

What incentives have been tried?

- In human health, hundreds of millions are being allocated:
  - IMI's New Drugs for Bad Bugs programme: €700 million project
  - UK Longitude prize: £10 million for a point–of–care diagnostic test
  - Fleming Fund: €300 million
  - Current talks of billions to incentivize human pharma companies

In veterinary medicines:

- Few financial incentives have been offered
- No tradition of getting (or wanting) government financial support

What has worked?

In the veterinary health world, the market works:

- there are no "*distorting*" incentives (subsidies, etc.)
- AMR challenges not as significant in animals as in humans (yet)
- but, some diseases without adequate treatments

Incentives:
10 recommendations that might work

Recommendation 1:
"Make the most sensible use of what we have"

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- Conventional antimicrobial strategies = low risk potential to human medicine
- Preferential encouragement of classes which have low relevance to human medicine
- Need equal willingness to downgrade importance rankings as to upgrade, in accordance with true medical utility
- Too easy for regulators to say "*they are all important*" - a reasonable number of antibiotics must be available in animal health to avoid overdependence
- Untreated animals are a risk to human health - unethical
- There are many with a mindset of pretending non-use in animals is a viable option…
- Assumes animal diseases will eradicate themselves…
  <u>They won't - they will get worse.</u>

Recommendation 2:
"Increase the odds of a reasonable ROI"

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- Market valuations determine ROI for any discovery/development programme:
  1) *Is this likely to have a profitable outcome?*
  2) *Is this within current R&D and commercial competencies?*
  3) *What is the level of risk? Is it technically achievable?*
  4) *What is chance/cost of regulatory approval?*
  5) *Is this sufficiently attractive vs. other R&D opportunities?*

Using the ROI approach, there is no market sufficiently large or interesting enough to warrant a full new antibiotic programme.

To change this, need to change market dynamics. Consider:

- Counterintuitive to invest in a new antibiotic and then hold until last resort
- Future markets will be more generic, meaning with reduced value
- Increased risk due to reduced leverage opportunities from human health side
- Increased challenges due to '*humans first*' approach

Recommendations 3 + 4:
"Regulatory improvements"

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3. Improving regulatory environment

- More regulatory predictability helps reduce development risk
- Cost of generating regulatory data is upwards of 70% of cost of bringing to market
- Need to reduce regulatory burden that disincentivizes, delays or restricts progress
- Regulatory agencies can help by:
  - Setting and sticking to timelines
  - Early hazard / risk assessment for new development candidates
  - At proof of concept stage before entry into full development
  - Challenge will be to define the right (early) data sets

4. Better global convergence of regulatory processes

- Companies have global approach – R&D ROI decisions based on multiple markets
- Need a much greater drive to get regulatory requirements more aligned globally, resulting in lower costs ➡ a more attractive market to invest in

Recommendations 5 + 6:
"Support vaccines and alternatives"

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5. Support vaccines

- Vaccines are intuitively attractive, but discovery and development are not easy
- Increased financial incentives may be helpful
- Increased regulatory incentives will help drive investment:
  - Expedited approval options
  - Earlier proprietary protection for novel solutions

6. Support alternatives

- Have a panel including private sector companies assessing which have merit
- Financial incentives that support development/lower barriers to bring these to market
- Expedited regulatory assessment, where product safety is the primary goal, would allow increased speed to market. Efficacy could be fully demonstrated in market.

Recommendations 7 + 8: *"Improve data protection" "Define better performance metrics"*

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7. Improve data protection

- Big disincentive is that animal health generics are treated the same as human health

- In human health it makes sense to have generics after the patent period to drive down prices/costs. This makes no sense in animal health, because the cost of antibiotic is an important main driver of use.
- When generics come to market, antibiotic use increases - the opposite of what's wanted
- Solution: increase patent periods/ data protection for antibiotics
- Opportunities to explore /update existing "old" portfolio to "new" products

8. Define better performance metrics

- Performance metrics to be constructed to reflect anticipated benefit to human medicine
- Discipline of defining what improvement is expected in human health is lacking from almost all AMR initiatives

UK Department of Health
"…*clinical issues with AMR in human medicine are primarily the result of antibiotic use in people, rather than the use of antibiotics in animals."*

- Most plans fail to produce true benefit and threat of AMR to human health increases
- Be aware of unintended consequences: e.g. if a use limit is set on weight, large reductions will be achieved by switching to more potent products (often CIAs)

Recommendation 9: *"Political leadership "*

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9. Show stronger (and smarter) political leadership

- Policymakers approach is: "*political reduction targets*" + "*1st choice vs reserve for veterinary classes"* – this increases commercial risk – reduces new investment
- Need directional messages how new veterinary antibiotics will be viewed
- Political leadership to set straight myths propagated in the AMR debate
- Ensure decisions are backed by sound science (in Codex, EU re biotech, etc.)
- To promote closer global regulatory cooperation

Recommendation 10:
"Develop smarter financial incentives"

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Ideas that won't work

- Financing AH companies to develop new antibiotics - politically not realistic
- Organise research in consortia: challenging to agree terms/costs, many don't want this
- Guaranteeing prices or volumes: politically difficult, maybe ok on human side
- Prizes: won't work for larger companies (finance isn't the issue), maybe smaller ones

How to spend public money wisely

- Invest to ease regulatory burden: lighter, smarter regulation that maintains standards
- Fund promotion of benefits of vaccination (food chain, societal, etc.)
- Research AMR transfer pathways: which are the most significant?
- Research into diagnostics: the "holy grail": cheap, reliable, pen/bedside diagnostic
- Finance promising SME/academic R&D, but target funds to realistic prospects only (*no big investment in many alternatives – need to ask why not…)*
- Use tax tools to ease investment – if new antibiotics/vaccination/alternatives really are a public good, governments should support them fiscally

Conclusions

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1. Business model for investment in existing or new antimicrobials is unattractive
2. Need more joined-up approach between: political - regulatory - business
3. Need a comprehensive approach: can't just do one recommendation
4. Get the scientific analysis right – the top priority should be AMR transfer pathways: *"If we don't have a better analysis of AMR transfer pathways, we will apply solutions that will likely make the AMR problem worse."* (private comment Professor after UK AMR Review)
5. Political support for sound science – rejection of non-scientific analyses
6. Support vaccination and alternatives – regulatory, politically, financially, educationally
7. Use public money in a smart, targeted way