Innovating in Food Producing Animals in the New Age of “Clean Food”

Scott D. Holmstrom, PhD

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What is “Clean Food”?

- Some historical definitions:
  - As close to the earth as possible
  - If it wasn’t available to a caveman…
  - Foods free of artificial preservatives, coloring, irradiation, synthetic pesticides, fungicides, ripening agents, fumigants, drug residues and growth hormones and those that are processed, packaged, transported and stored to retain maximum nutritional value

- My definition:
  - Food that is considered to be nutritious, safe, and raised and processed **without** technology

Clean Food

Clean Food Challenge

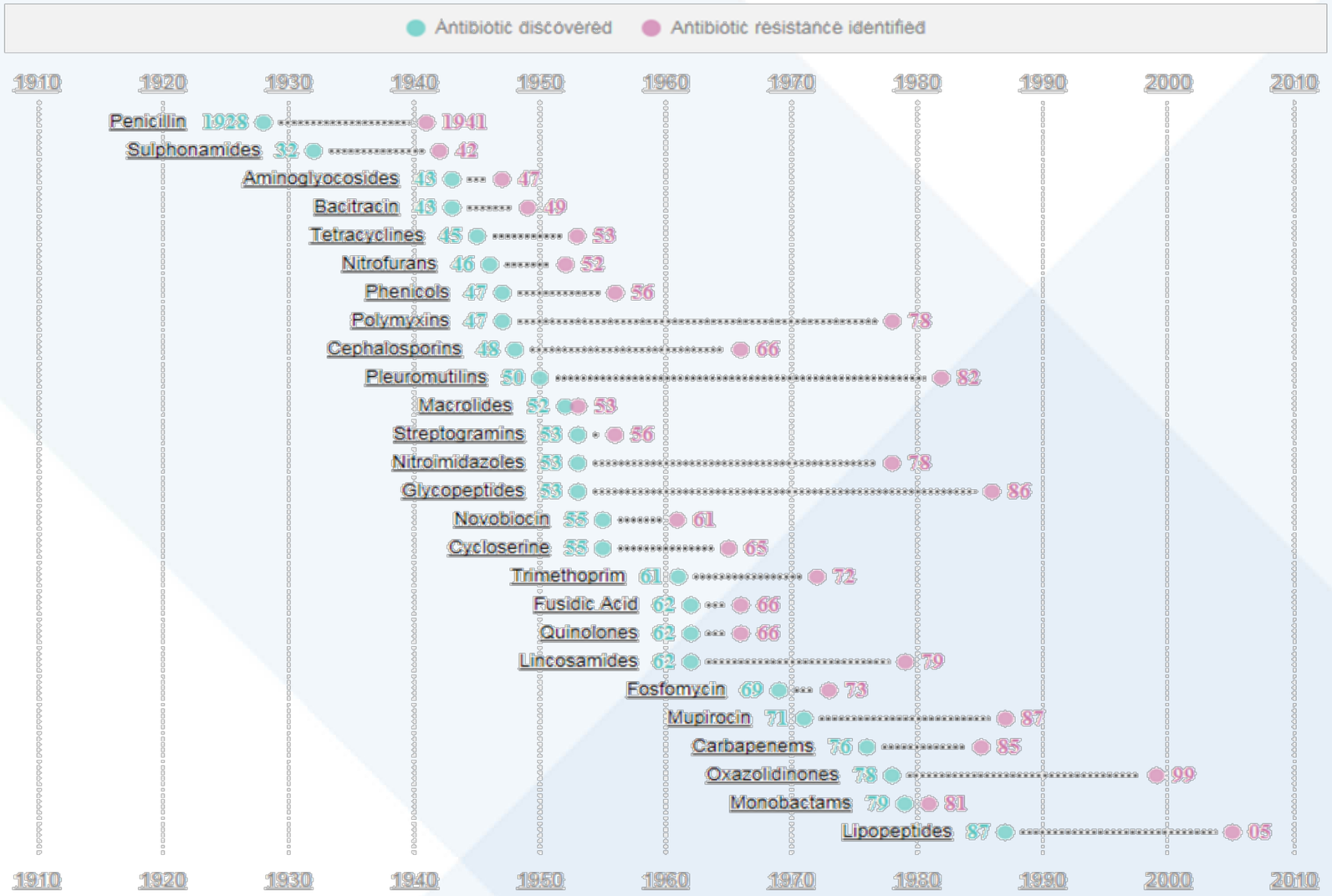
Why:
- A desire for healthy food
- Effective marketing
- Misconception, lack of understanding
- Consolidation
- Lack of segmentation
- Antibiotic resistance

Drives:
- Consumer awareness
- Aversion to corporate farming
- Sentiment against productivity drugs
- “No” labeling
- Fear

Reality:
- Increasing protein demand
- Demand for healthy food and a balanced diet
- Sustainability and productivity
- Need for healthy animals
- Animal welfare & respect for life
- Food safety

Drives a heightened need for:
- Consumer friendly productivity solutions
- Disease prevention
- Animal welfare outcomes
- Increase food safety
- Trade access
- Affordable protein

History of Antimicrobial Resistance



The Paths to Resistance

- Spontaneous Mutation

- Selective Pressure

Resistance in Animal Health?

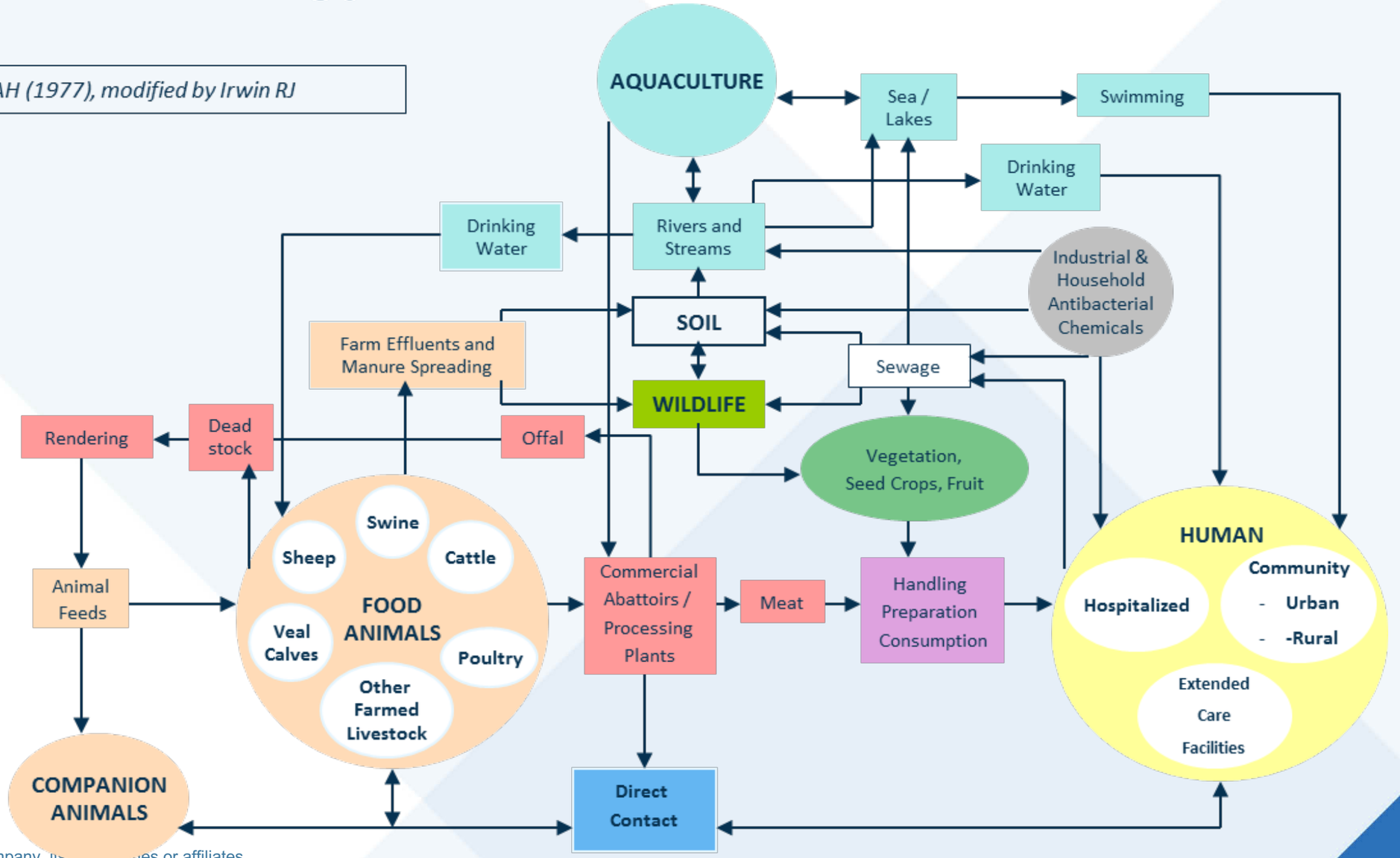
VetPath (de Jong et al):

- “Low resistance to antibiotics with defined clinical breakpoints, except for tetracycline, was observed among the major respiratory tract pathogens recovered from cattle and pigs.”

- Bacteria associated with acute clinical mastitis are susceptible to most antibiotics with the exception of penicillin G against S. aureus, and erythromycin and tetracycline against S. uberis

Epidemiology of Antimicrobial Resistance

after Linton AH (1977), modified by Irwin RJ

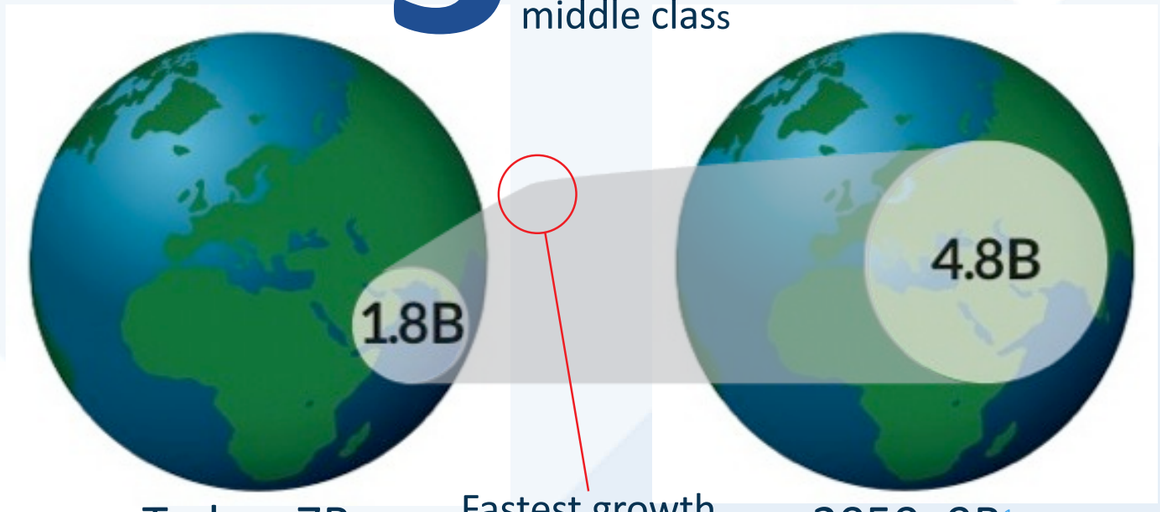


Today's Food Security Realities

GROWING MIDDLE CLASS

3 BILLION

Join the middle class



Today: 7B

Fastest growth between now and

2020[2]

2050: 9B[1]

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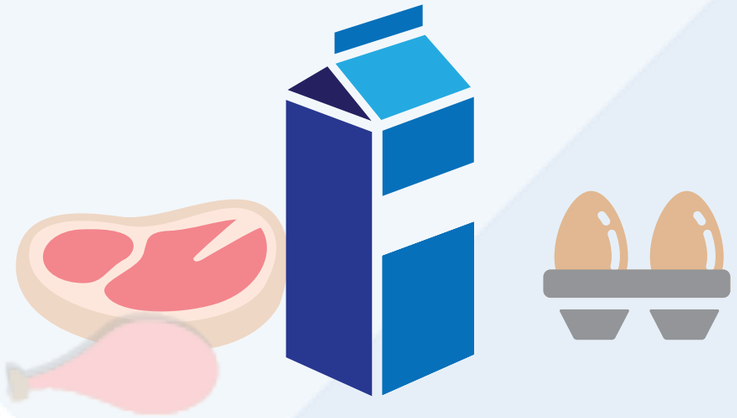
1. Kharas, Homi. OECD Development Center. Working Paper No. 285. The Emerging Middle Class in Developing Countries. Global Development Outlook. January 2010.
2. OECD-FAO Agricultural Outlook 2012-2021.

Today's Food Security Realities

INCREASING DEMAND FOR MEAT, MILK & EGGS

We will need

60% More animal-sourced foods



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Food & Agriculture Organization (FAO). "World Livestock 2011: Livestock in Food Security." Rome, 2011.

Today's Food Security Realities

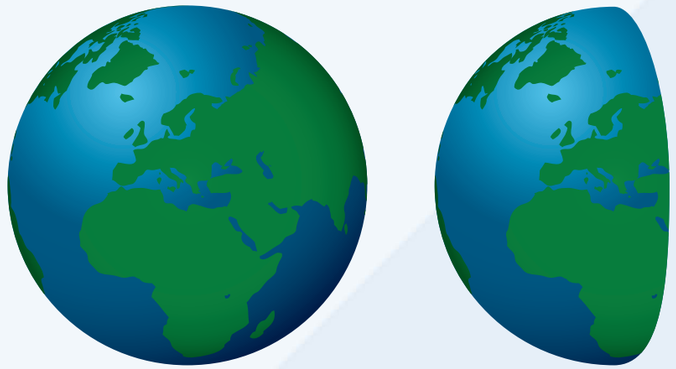
FEEDING MORE WITH LESS

By overusing our resources, it takes

1.8

Years to regenerate annual consumption

Source: WWF



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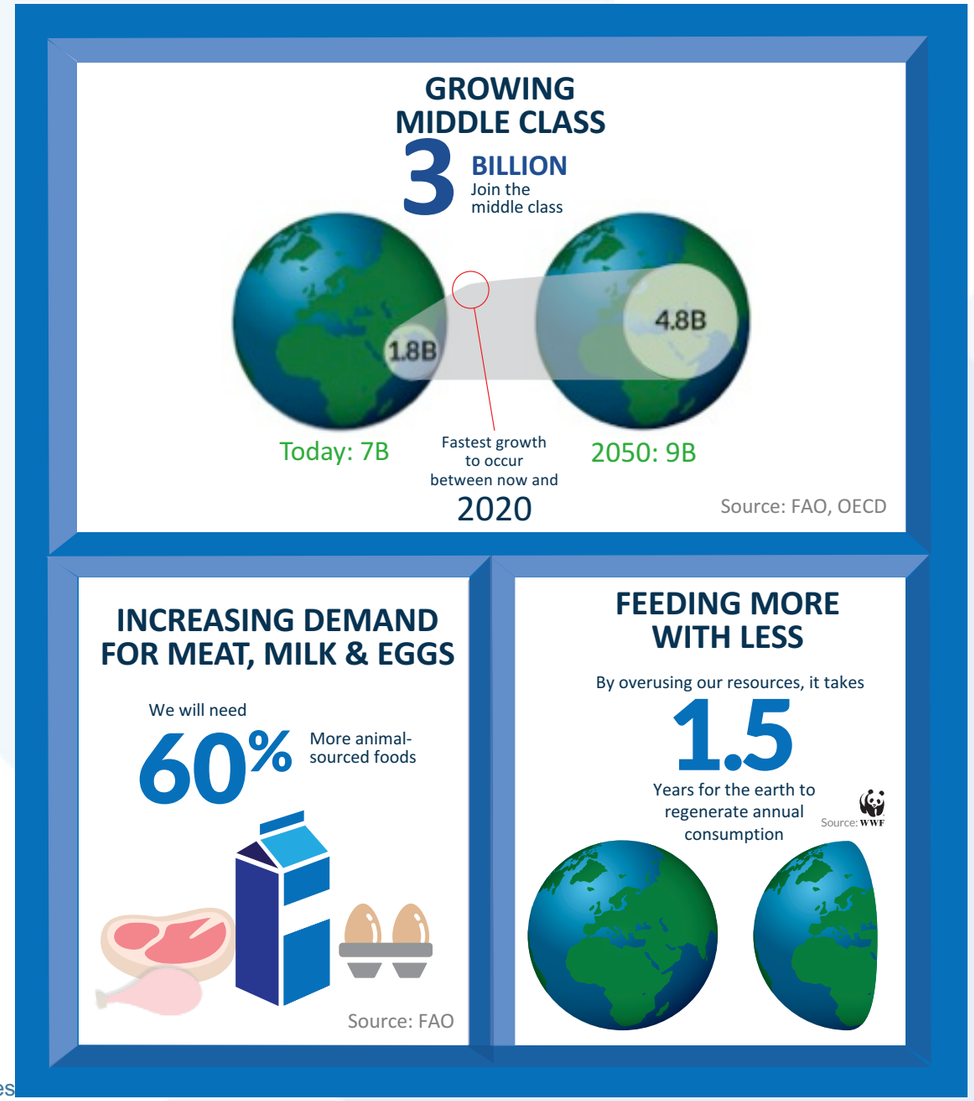
World Wildlife Fund (WWF). "Living Planet Report 2012: Biodiversity, biocapacity and better choices."

Today's 3 Food Security Realities



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An Urgent Window of Time

Considerations of Challenges and Solutions

Clean Food Challenge

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Clean Food Solutions

	Vaccines	Enzymes & Pre- Probiotics	Small Molecules	Bio-pharmaceuticals
Technologies				
Applications *(for examples)*	*Infectious diseases*	*Minimize inflammation* *Digestibility* *Microbiome enhancement*	*Many Applications*	*Targeted applications with greater specificity*

Considerations for Innovating in Food Producing Animals

- Technology Basis for Active Ingredient
- Formulation
- Cost
- Clinical Benefit and Unintended Consequences
- Clinical Complexity
- Regulatory Pathway
- Market Access (Consumer Acceptance)
- Market Access (Import/Export)

Technology Considerations for Food Animal Innovations

Technology	Benefits	Concerns
Vaccine	• Proven Technology • Viable ABX alternatives • Defined regulatory pathway • Safe, efficacious • Cost effective	• Biological diversity • Challenging to provide comprehensive solutions for bacterial, viral, and parasitic infections • Lifecycle management
Enzymes, Prebiotics	• Cost effective • Some eligible for a limited number of drug like indications	• Unintended pharmacological responses • Regulatory pathway? • Likely inconsistent indications based on geography
Small Molecules	• Target rich environment • Diverse • Cost effective	• Unintended pharmacological responses • Human food safety • Environmental safety
Biopharmaceuticals	• Additional intervention points to prevent or treat diseases • Greater specificity	• Cost of goods • Greater specificity in terms of the treatment window and dose → Complex development plan

Formulation

- Compatibility with active
- Stability
- Role of veterinarian
- User safety
- Ease of use
- Dosing compliance

Cost Considerations

Cost of protein from meat, milk, and eggs often sets the ceiling → Animal Welfare?

- Cost of development
- Cost of manufacturing
  - Existing manufacturing capabilities
  - Viable competition with CMOs
  - Price points and scale set by human pharma

- Cost of packaging
- Cost of shipment

Cost of goods often sets the floor

Clinical Benefit

- What outcomes is the product capable of providing?
- Which of these outcomes are valuable to the customer?
- Is the clinical benefit differentiated?
- Considerations for development cycle time with respect to breadth of label
- Unintended consequences

Clinical Complexity

- Should we be thinking of clinical development like a formulation?

- Novel classes and active ingredients will beget additional complexity with respect to:
  - Time with respect to disease state
  - Time with respect to production cycle (i.e., lactation)
  - Age
  - Dose
  - Prevention/Control/Treatment

Regulatory Pathway

- Is there a defined pathway for the class of technology being pursued?
- Commonality in regulatory requirements for different geographies?
- Depth of subject matter expertise – internal and external
- Background/Early Information for regulators
- Early and Often Communication with regulators
- Effectiveness of classical meeting and communication paradigms?

A Case Study: Imrestor

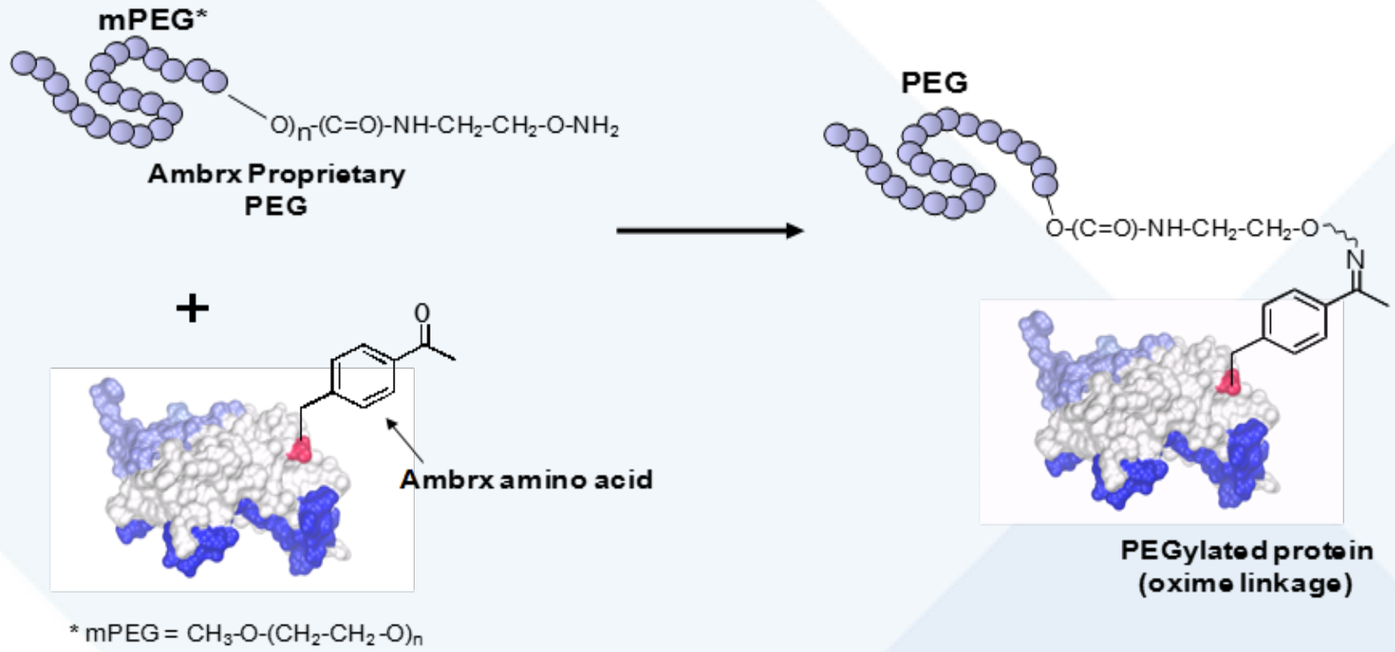
PEG bGCSF - Imrestor™

- **Proposed INN** – pegbovigrastim
- **Therapeutic classification** – Colony Stimulating Factor
- **Pharmacological classification**
  - bG-CSF is a naturally occurring 19.1 kD protein produced by fibroblasts, endothelial cells and monocytes
  - activities associated with bG-CSF are specific to cells of the neutrophilic granulocyte lineage
    - stimulates production and maturation of neutrophil precursors in bone marrow
    - activates the functional activity of mature neutrophils in the circulation, particularly during periods of immunosuppression
    - activated neutrophils exhibit enhanced antimicrobial activity

Product Description

- Wild type amino acid sequence with substitution
- Produced in recombinant *E. coli*
- 20K PEG covalently linked to pAF site
- Ready-to-Use formulation in pre-filled syringes

bG-CSF



bGCSF is conjugated with a proprietary **Polyethylene Glycol (PEG)**
This polymer is non-toxic, non-immunogenic, non-antigenic, highly soluble in water and FDA approved.

PEG-bGCSF conjugate increases product half-life and stability, reduces dosage levels and frequency of dosing.

Target Animal Safety

- A 3.5 year journey from first protocol to technical section complete
- Key learnings regarding stress contributions in pregnant animals
  - Test facility
  - Animal transport
  - Regulatory compliance

- TAS Concurred Protocol
  - Study population periparturient jerseys, moved to test facility, conducted under GLP conditions
  - Histopathology and clinical findings – abomasal ulcers, increased incidence of metritis and mastitis in Imrestor treated cows

Target Animal Safety

- Elanco strongly believe animal handling/test facility/ cow comfort contributing to the abnormal GI findings
  - CVM meeting
  - Elanco dairy experts propose a targeted GLP safety study
  - Elanco negotiates/designs/builds a facility on Lone Oak farms in Hanford CA to conduct a GLP TAS study on a commercial dairy/individual feed intakes on dairy cows
  - CVM agrees to a pilot safety study to prove GLP control on commercial dairy

Individual pens constructed on commercial dairy to maximize cow comfort, maintain GLP regs

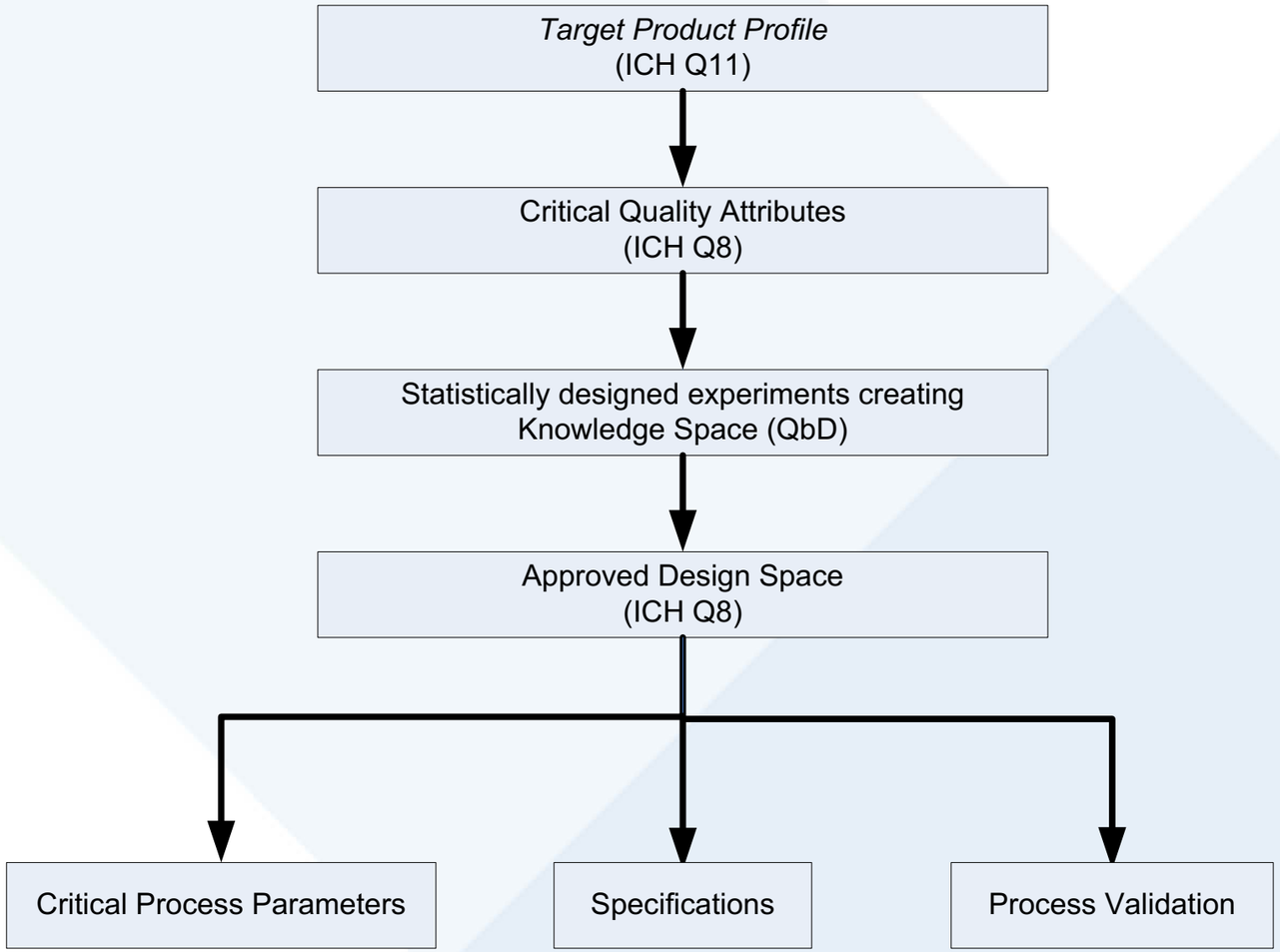
- Margin of safety established

Key Imrestor™ US Efficacy Results

- Mastitis Incidence

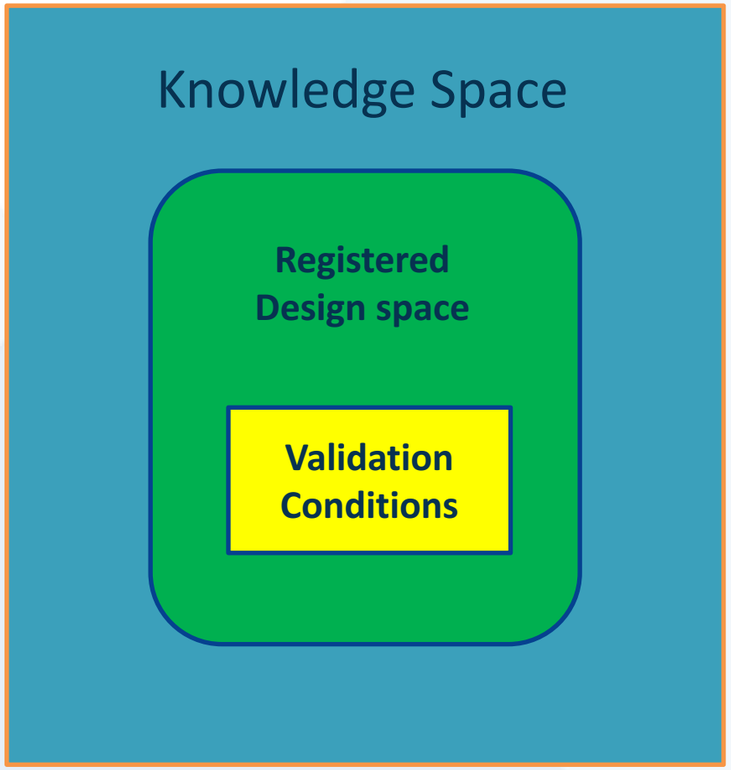
Treatment	WA	CA	WI	CO	Combined
Saline	12 (15%)	20 (25%)	26 (33%)	14 (18%)	72 (23%)
PEG bG-CSF	7	14	20	7	48
% reduction	23%	30%	23%	50%	33%
				p-value	0.016

Design Space

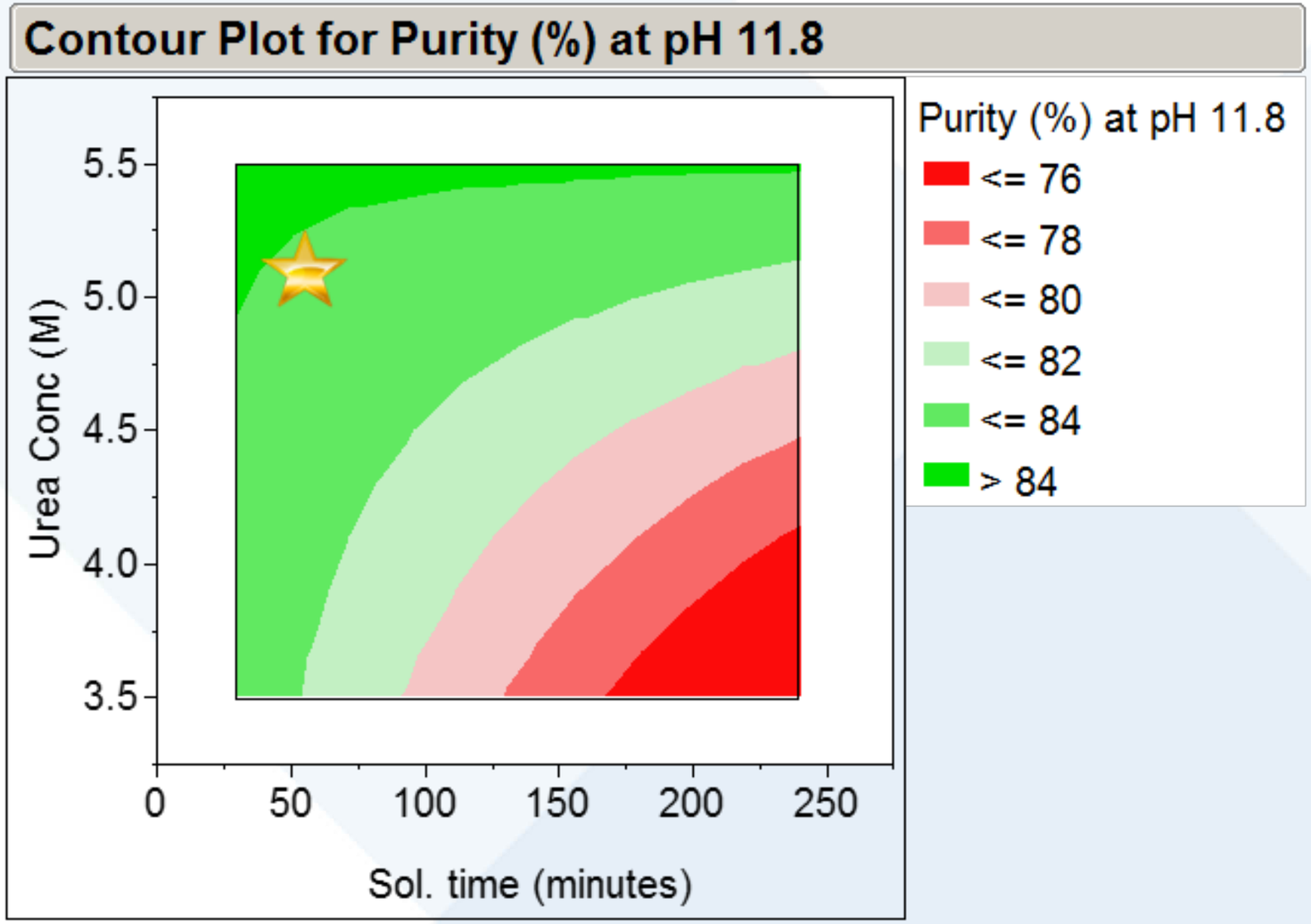


Design Space

- QbD development work demonstrates design space
- All areas of multi-dimensional design space produce product of acceptable quality judged by Critical Quality Attributes
- Sponsor chooses to register the process with a sub-set of conditions where the process will be performed routinely within the registered design space
- Validation of the process is carried out within this space by sponsor
- Movement within registered design space does not require prior notification
- Elanco proposed to revalidate after movement within the approved design space and notify in the annual report



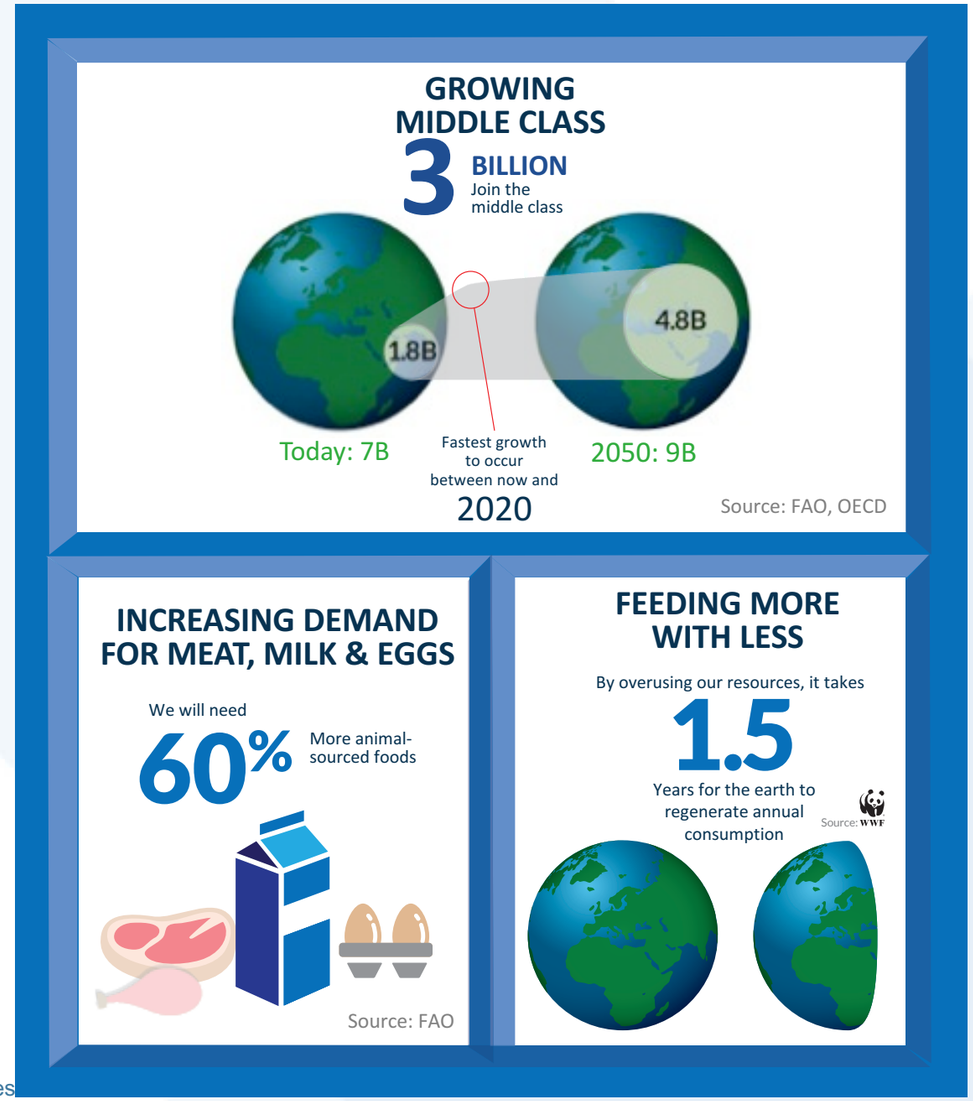
Example from Solubilisation Studies



QbD Realized

Critical Process Parameters			
Parameter	Target	Design Space	Knowledge Space§
Solubilization pH	11.6-12.0	11.6-12.5	11.2-12.5
Solubilization time, min	30-60	30-120	30-240
Refold reaction pH	9.0-9.4	8.3-10.6	8.3-11.0

Today's 3 Food Security Realities



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An Urgent Window of Time

Conclusions

- Innovating in food producing animals is challenging!
- It is worthwhile
- We are just beginning