Novel therapeutic approaches for treating bacterial infections in cattle

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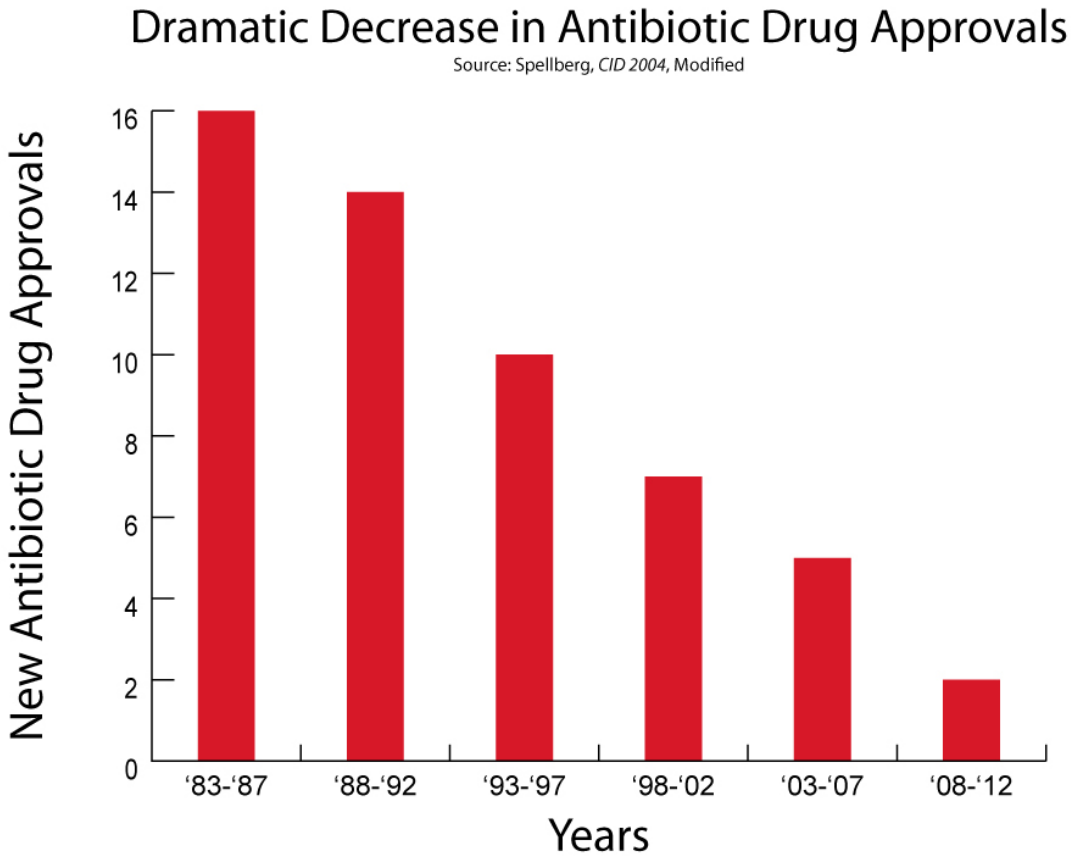
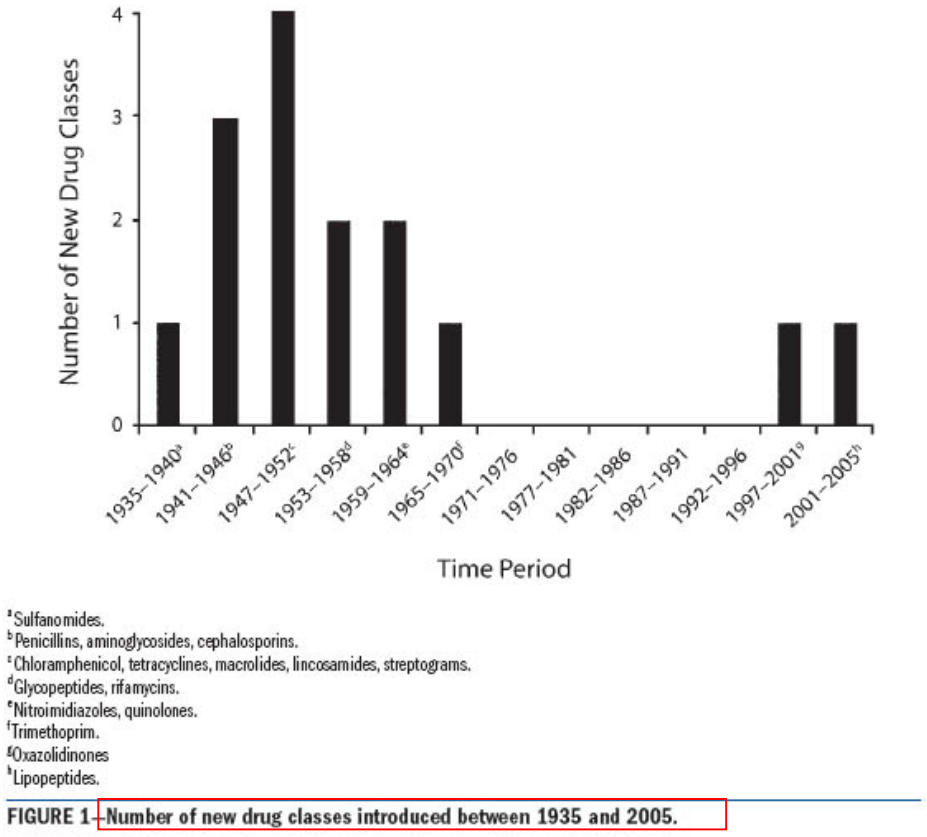
Current scenario
Decline in antibacterial approvals



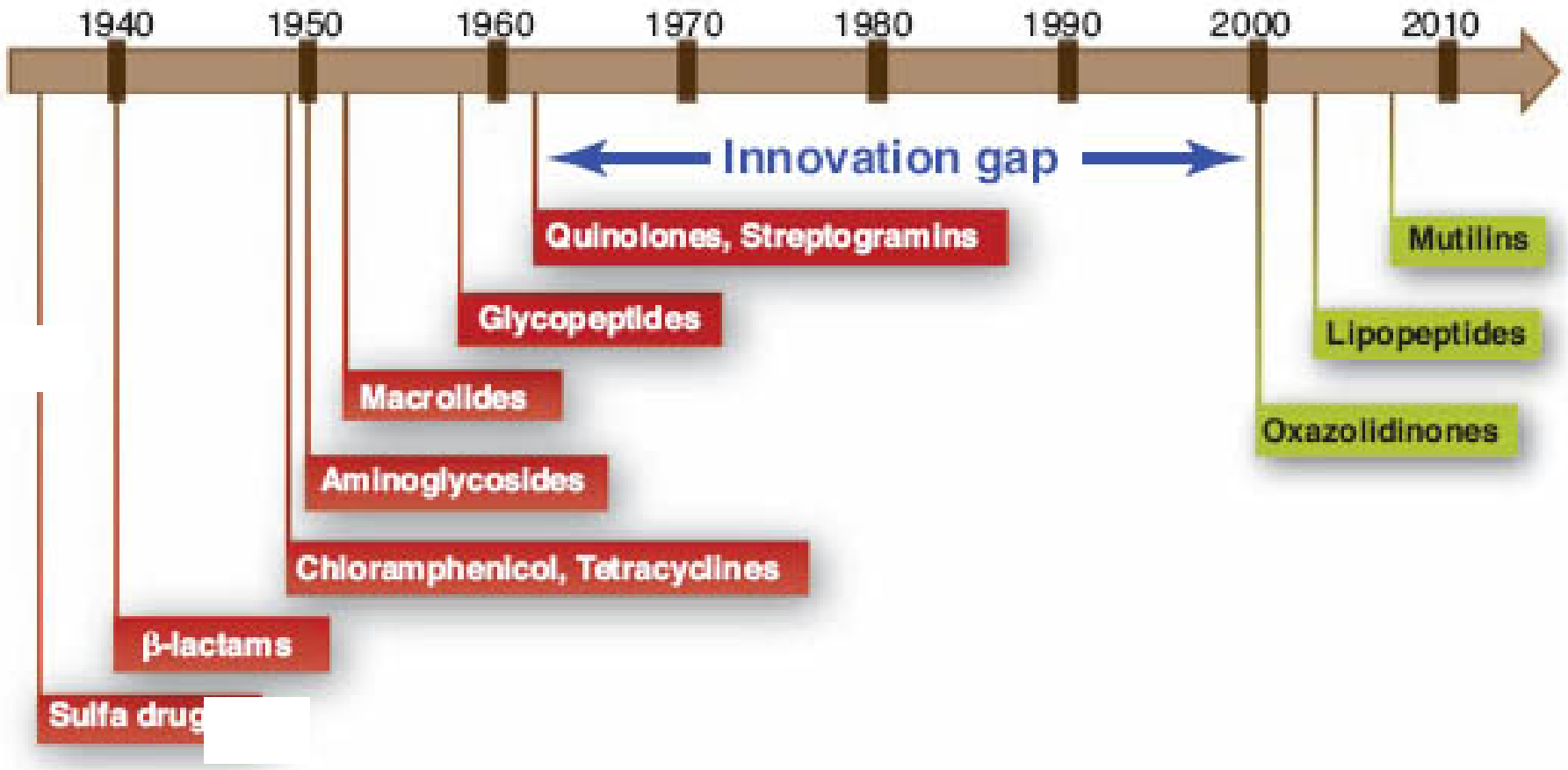


[a] Sulfanomides.
[b] Penicillins, aminoglycosides, cephalosporins.
[c] Chloramphenicol, tetracyclines, macrolides, lincosamides, streptograms.
[d] Glycopeptides, rifamycins.
[e] Nitroimidiazoles, quinolones.
[f] Trimethoprim.
[g] Oxazolidinones
[h] Lipopeptides.

FIGURE 1—Number of new drug classes introduced between 1935 and 2005.

The Infectious Diseases Society of America (IDSA)

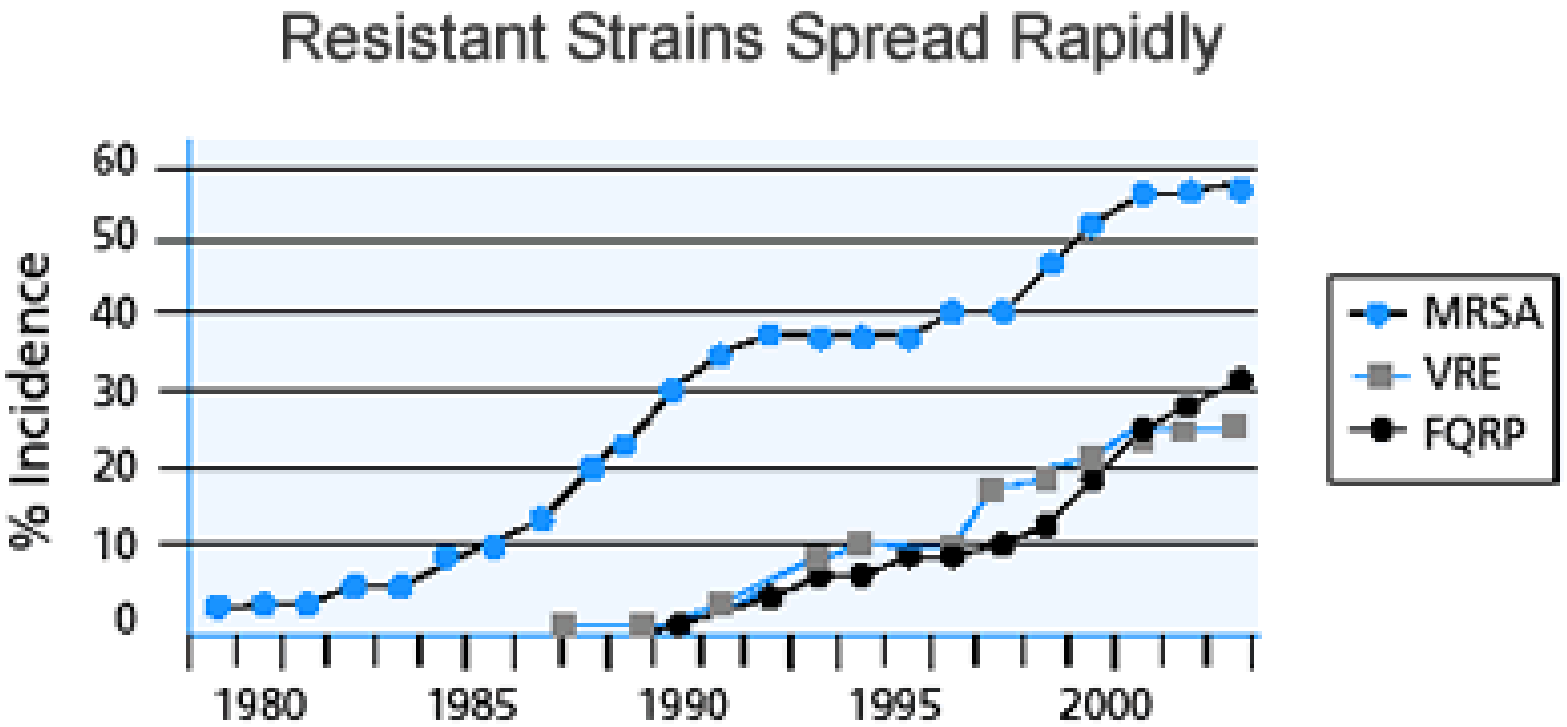
Current scenario



Between 1962 and 2000, no major classes of antibiotics were introduced.

Current scenario

Resistance to drugs on the rise



Source: Centers for Disease Control and Prevention

MRSA = Methicillin-resistant *Staphylococcus Aureus*
VRE = Vancomycin-resistantant Enterococci
FQRP = Floroquinolone-resistant *Pseudomonas aeruginosa*

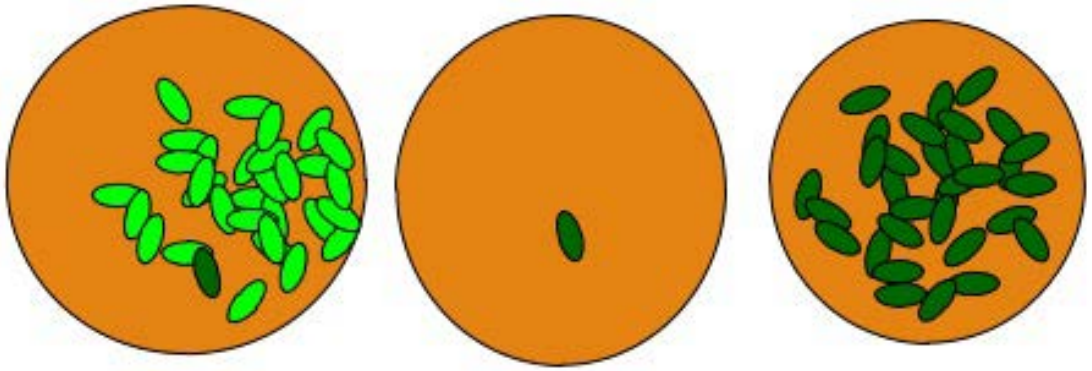
The Infectious Diseases Society of America (IDSA)

Current scenario

Resistance to drugs on the rise

Survival of the fittest

- Resistant bacteria survive, susceptible ones die



Mutant emerges slowly

Sensitive cells killed by antibiotic

Mutant's progeny overrun

Dr.T.V.Rao MD

Trend

The Pipeline of New Antibiotics Is Drying Up

In spite of the pressing need for new drugs to treat resistant infections, there simply are not enough new antibiotics in the pharmaceutical pipeline to keep pace. Major pharmaceutical companies with the R&D "muscle" to make progress are losing interest in the antibiotics market, even as they increase their overall R&D budgets. Of greatest concern is the dearth of resources being invested in drug discovery.

IDSA

A growing number of drug companies appear to be withdrawing from new antibiotic research and development.

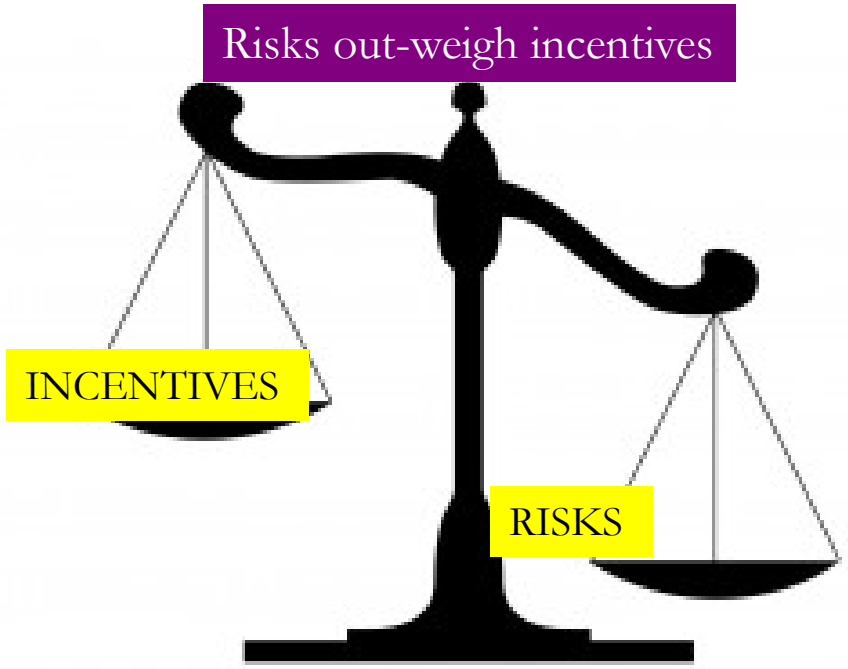
ELSEVIER

Why is big Pharma getting out of antibacterial drug discovery?

Steven J Projan

Current Opinion in Microbiology 2003, 6:427–430

1. **Curtail the 'unnecessary use'** of antibacterial agents **Increasing pressure** by the health care community
2. Most antibacterial use is for **short courses of therapy**. Unlike '**life-style drugs**'.
3. **Anti-infective drugs** are considered 'life-saving' medications and, are under **aggressive price controls**.
4. **Liability claims for adverse events**.
5. Finally, **new antibiotics run the risk of rapid obsolescence** (resistance)



Answers!

1. Rational **use of antimicrobials** in clinical and community settings.
2. Development and **use of alternative therapies** (e.g., vaccinations, probiotics, and phytomedicines) for prevention/delay of bacterial infections **and possible evolution of resistance.**

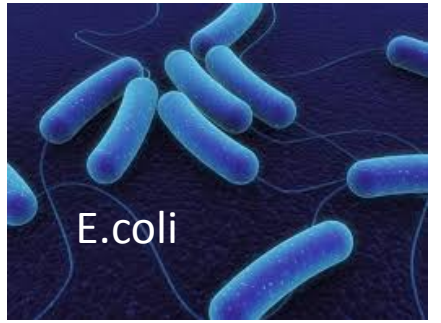
3. New Drugs.

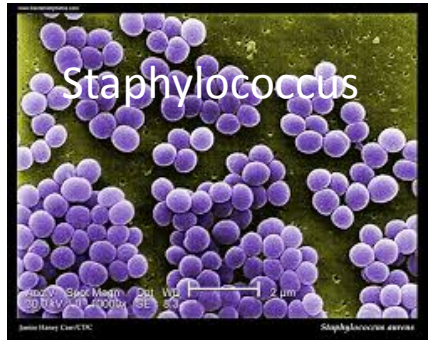
1. Identifying novel treatments and drug targets.
2. **Drug repositioning**.

Problems – decrease in efficacy of antibiotics for mastitis therapy

- The development of **resistance to monotherapy** (single antibiotic) lead to dual antimicrobial coverage (two antibiotics) for several pathogens involved in mastitis.

- Extensive usage of antimicrobial agents and the evolutionary antimicrobial resistance strategies of mastitis bacteria has resulted in **emergence of multi-drug resistant bacteria**.





Combination drugs in cattle for infections

Hybrid drugs in market

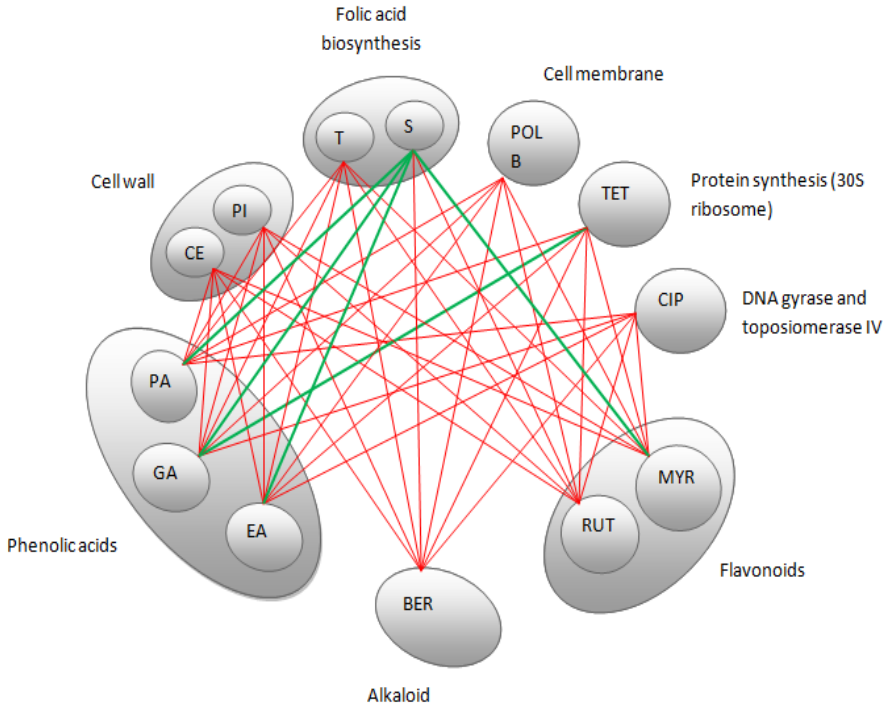
- Trimethoprim (benzyl pyrimidine) linked fluoroquinolone (BP-4Q- 002) hybrid compounds (Labischinski et al., 2010b)

- Aminoglycoside-fluoroquinolone(Pokrovskaya et al., 2009a).

- Peptide-aminoglycosides hybrids (Bera et al., 2010a)

  - have been shown to be potent antimicrobial agents against both Gram-negative and Gram-positive bacteria.

Drug-Phytochemical combinations



Drug-phytochemical combination assay

→ **Synergistic interaction**

Phytochemicals (PA, GA, QUER & MYR)

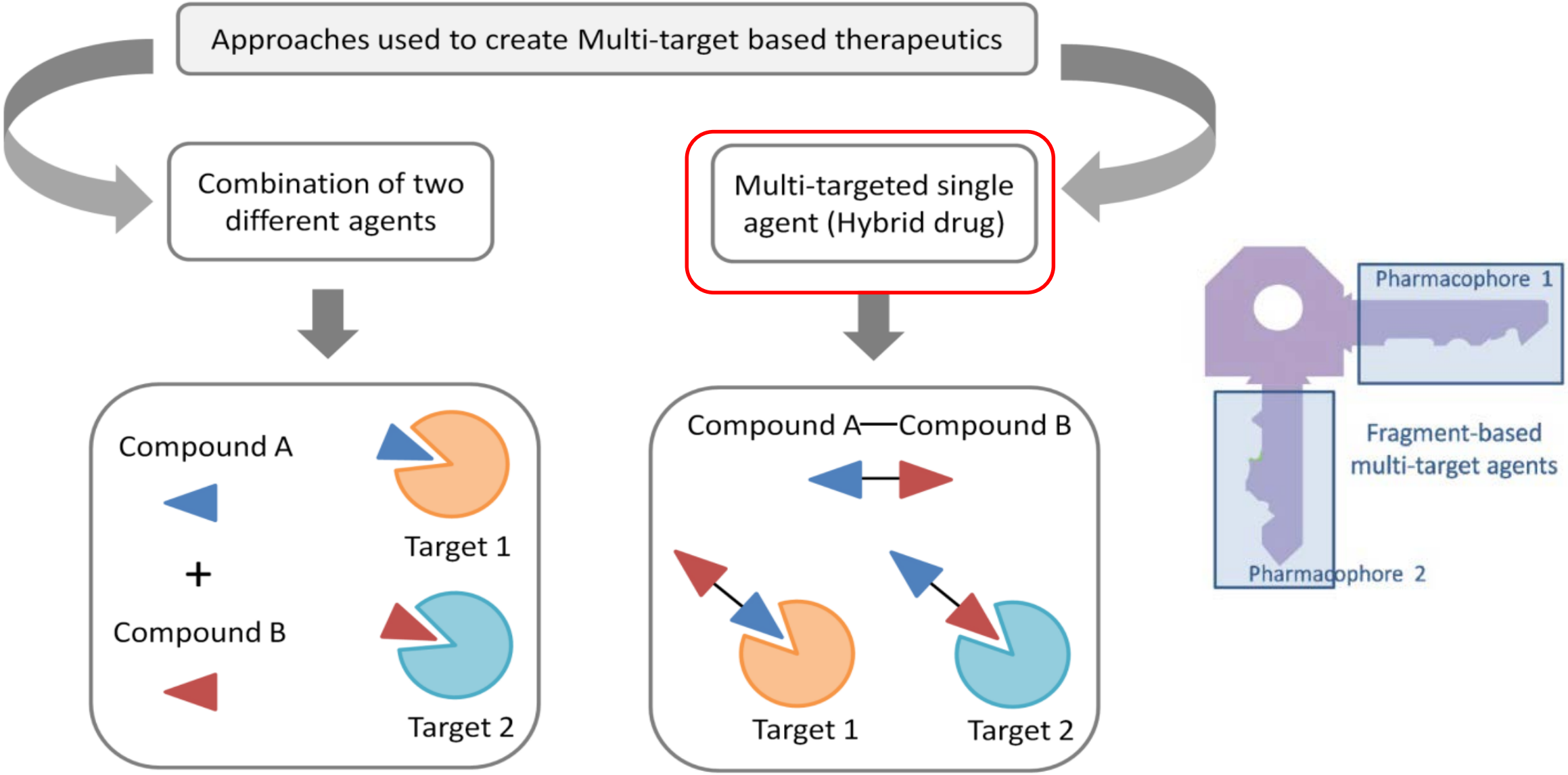
+

Sulfonamides (SMX and SUD)

DHFR

DHPS

Hybrid combination drug



Advantages of a single multi-target drug

- Greater predictable pharmacokinetic and pharmacodynamic relationships due to the administration of a single drug.
- Increased penetration capacity due to the additional pharmacophore.
- Lower toxicity.
- Delay the onset of resistance.
- Overcome the existing bacterial resistance mechanisms due to activity at multiple sites.

Benefits of Results to Saskatchewan

- Development of a **novel broad-spectrum antimicrobial agent**.
- The research will produce new **patents** and help Saskatchewan dairy farms economically.
- Help to **decrease the development of drug resistance** in mastitis infections.
- Product will have positive environmental foot prints.
- **Ecotax** benefits.
- **Increase in demand for natural products** and **benefits for farms that grow these plants**.
- The hybrid drug has potential to be used against:
  - mastitis in other livestock
  - mastitis in humans
  - other inflammatory diseases

Technology Transfer Plan

- Saskmilk for technology transfer.
- Field testing with the help of Saskatchewan cattle farms and beef cattle farms.

Down the road…

- Approvals for commercialisation and marketing of the drug can be got.

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