FDA, XCA, RXE:

What Does the Alphabet Soup of Drug Approval Mean for Vets

Brennen McKenzie, MA, MSc, VMD

Key Points

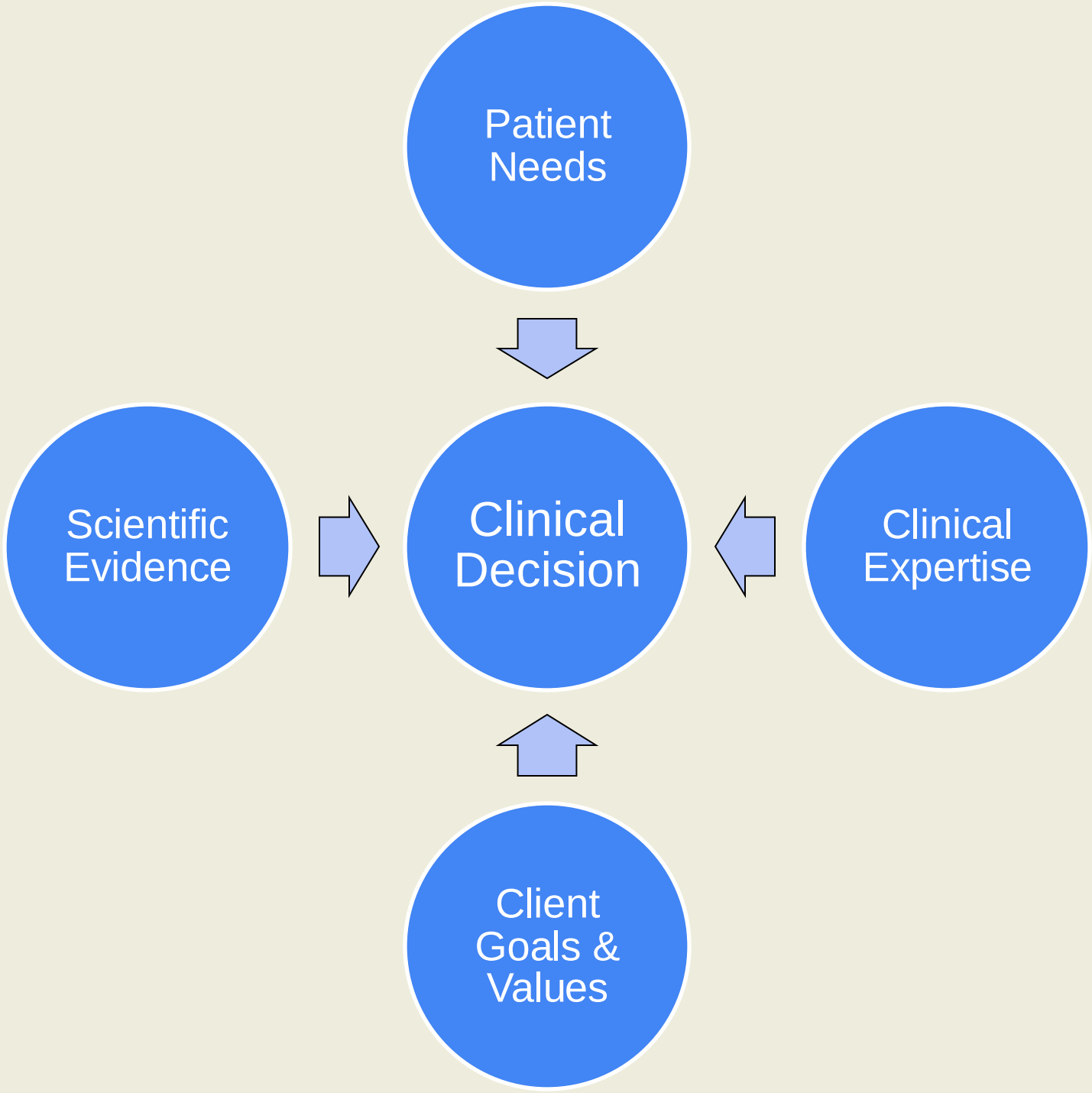
- Evidence-based Treatment Choices
  - Can regulatory criteria help?

- Drug Categories
  - Approved Rx drugs
  - Conditionally approved Rx drugs
  - Off-label drug use
  - Supplements, OTC meds, etc.

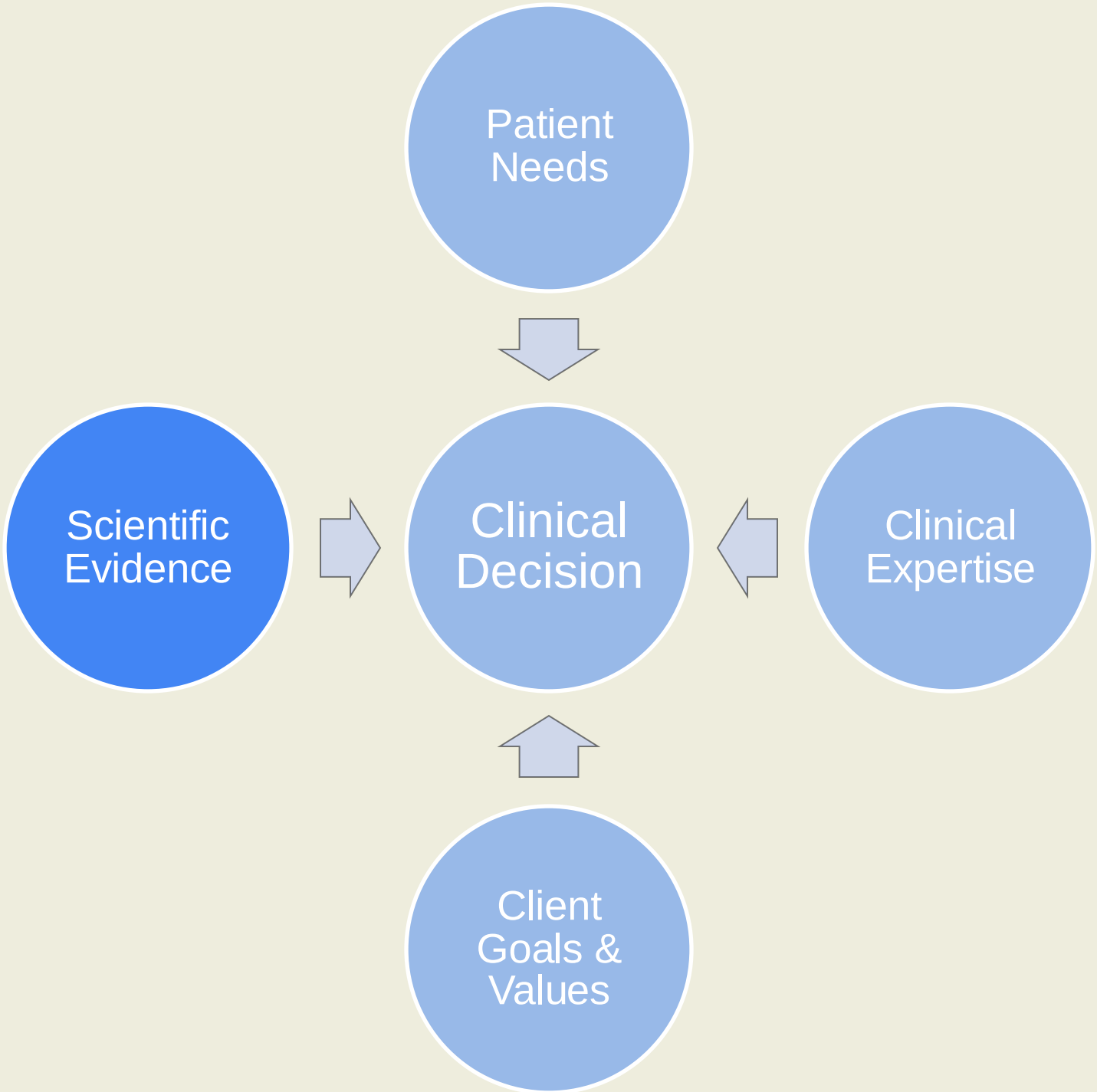
Making Evidence-based

Treatment Choices

What is EBVM?


Patient Needs
Scientific Evidence
Clinical Decision
Clinical Expertise
Client Goals & Values

What is EBVM?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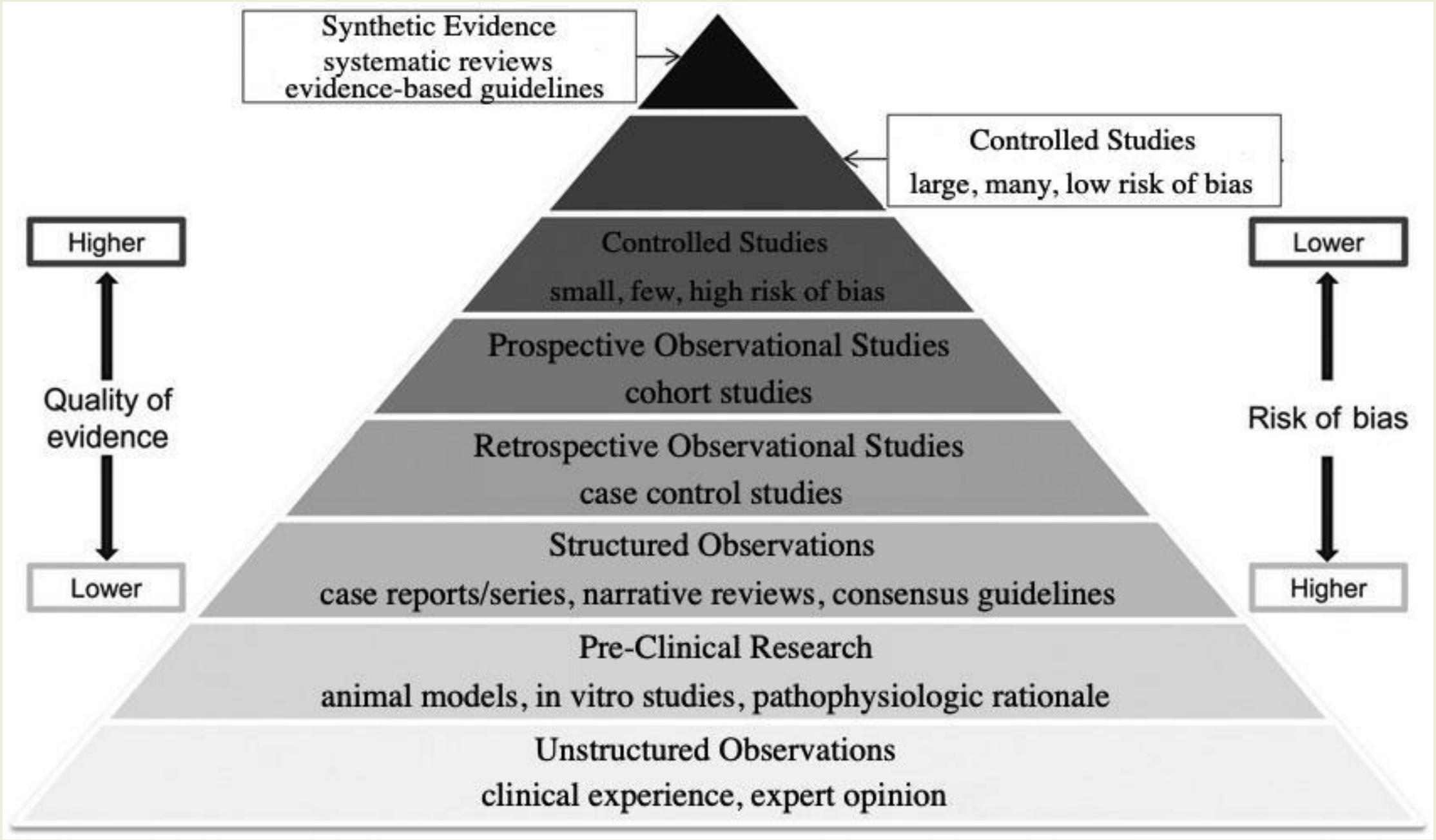
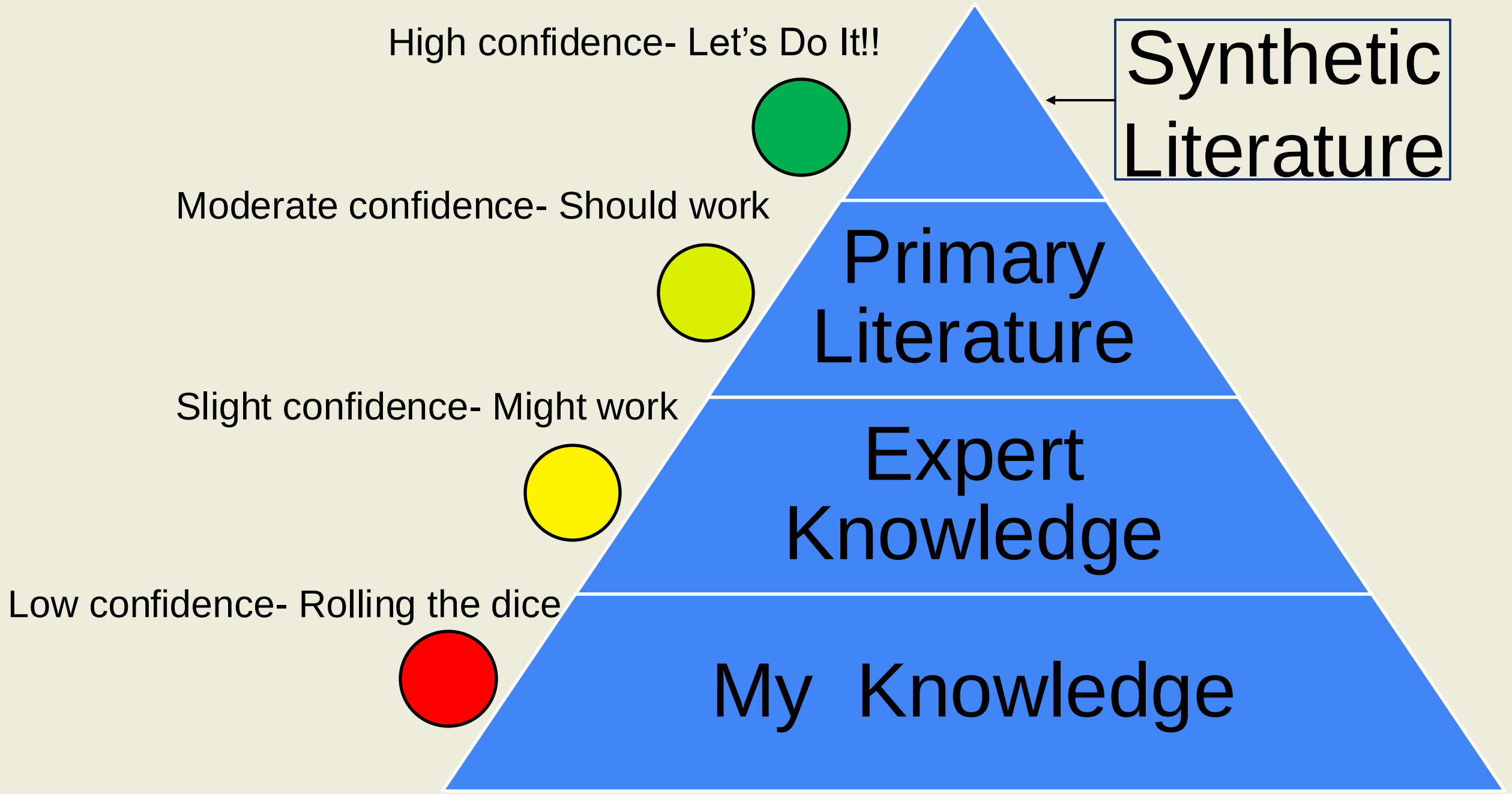
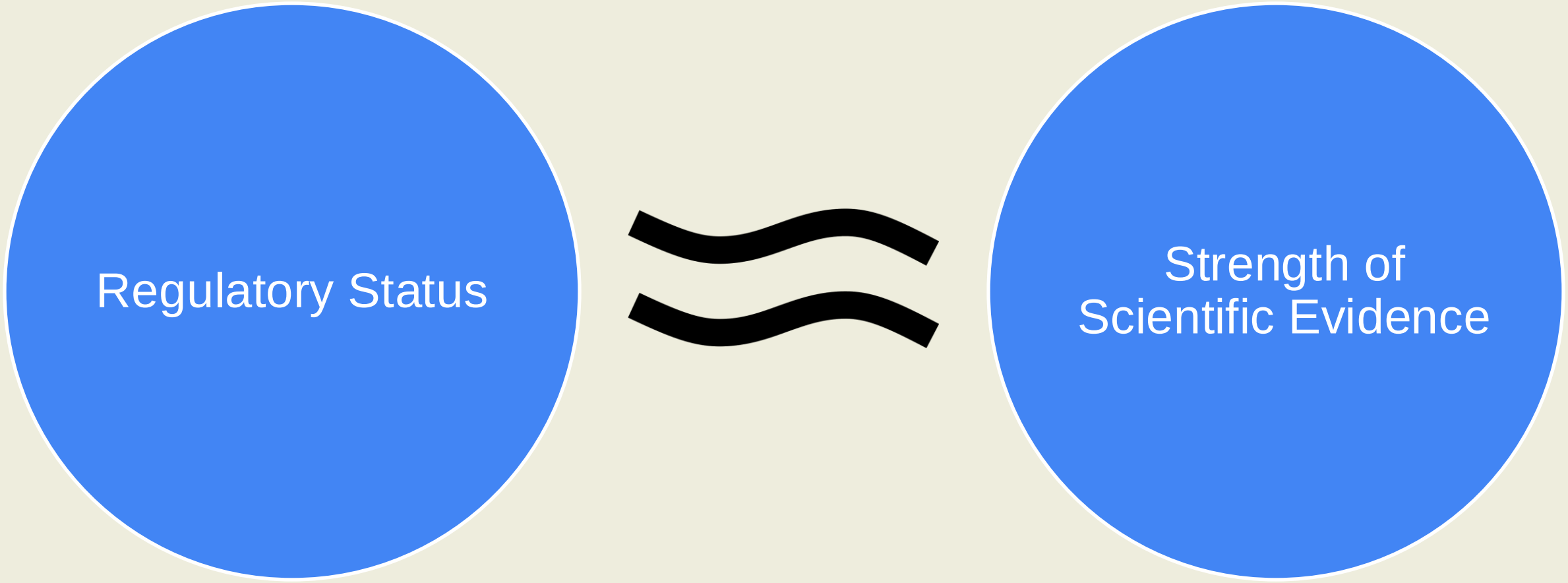
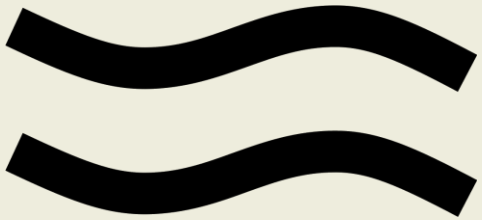

Synthetic Evidence
systematic reviews
evidence-based guidelines
Controlled Studies
large, many, low risk of bias
Higher
Quality of evidence
Lower
Controlled Studies
small, few, high risk of bias
Prospective Observational Studies
cohort studies
Retrospective Observational Studies
case control studies
Structured Observations
case reports/series, narrative reviews, consensus guidelines
Pre-Clinical Research
animal models, in vitro studies, pathophysiologic rationale
Unstructured Observations
clinical experience, expert opinion
Lower
Risk of bias
Higher


High confidence- Let's Do It!!
Moderate confidence- Should work
Slight confidence- Might work
Low confidence- Rolling the dice
Synthetic Literature
Primary Literature
Expert Knowledge
My Knowledge


Regulatory Status
≈
Strength of
Scientific Evidence

Regulatory Status



High confidence- Let's Do It!!

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Drug Approval Categories

Drug Approval Categories

- Approved Prescription Drugs
- Conditionally Approved Prescription Drugs
- Off-label Drug Use
  - Approved for humans
  - Approved for other vet species or idications
- Other
  - OTC drugs
  - Supplements
  - Therapeutic Diets

Approved Prescription Drugs

Approved Rx Drugs

- Highest standard of evidence
- Components (Technical Sections)
  - Target Animal Safety
  - Effectiveness
  - Human Food Safety
  - Chemistry, Manufacturing and Controls (CMC)
  - Environmental Impact

Approved Rx Drugs

- Highest standard of evidence
- Evidence available
  - FOI Summary

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-732

Carprofen Tablets

Caplets

Dogs

Carprofen Tablets are indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

Sponsored by:

Approved Rx Drugs

- Highest standard of evidence
- Evidence available
  - FOI Summary
  - Drug insert

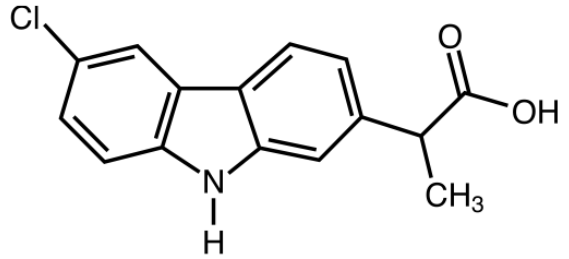
RIMADYL®

(carprofen)

Caplets/Chewable Tablets
For oral use in dogs only

Sterile Injectable Solution 50 mg/mL
For subcutaneous use in dogs only

Non-steroidal, anti-inflammatory drug



CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Rimadyl (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the nonproprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight 273.72. The chemical structure of carprofen is shown above. Carprofen is a white, crystalline compound. It is freely soluble in ethanol, but practically insoluble in water at 25°C.

Approved Rx Drugs

- Highest standard of evidence
- Evidence available
  - FOI Summary
  - Drug insert

EFFECTIVENESS: Confirmation of the effectiveness of Rimadyl for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries, was demonstrated in placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of Rimadyl chewable tablets, caplets and injectable in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of Rimadyl caplets when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily. In these two field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered Rimadyl at labeled doses.

Based upon the blood level comparison between subcutaneous and oral administration, Rimadyl effectiveness for osteoarthritis after dorsoscapular subcutaneous and oral administration should be similar, although there may be a slight delay in the onset of relief after subcutaneous injection.

Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of Rimadyl caplets and injectable for the control of postoperative pain when dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered Rimadyl preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered Rimadyl showed statistically significant reduction in pain scores compared to controls.

ANIMAL SAFETY: Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that Rimadyl is well tolerated in dogs after oral administration.

Approved Rx Drugs

- Highest standard of evidence
- Evidence available
  - FOI Summary
  - Drug insert
  - Journal publications
  - CE presentations
  - Company reps and info

Approved Rx Drugs

- Target Animal Safety (TAS)
  - Healthy individuals of target species
  - Route, formulation
  - Dose multiples
  - Duration depends on intended use
  - Study design standards
  - Monitoring, evaluation, analysis

Approved Rx Drugs

- Substantial Evidence of Effectiveness
  - "Adequate, well-controlled studies”
  - Field trials (GCP)
  - Lab studies (GLP)
  - Real-world data
  - Previously published evidence

Approved Rx Drugs

- Quality of Evidence
  - Not perfect
  - Potential funding bias
  - Oversight and standards
  - Independent evaluation of data collected

High confidence- Let's Do It!!

Moderate confidence- Should work

Approved Rx Drugs

- carprofen
  - Approval evidence
  - Extensive post-approval research
  - Frequent positive comparator

High confidence- Let's Do It!!

Approved Rx Drugs

- selegiline
  - Approval evidence
  - Scant post-approval research
  - Not recommended in analogous human disease

Slight confidence- Might work

Conditionally Approved Prescription Drugs

Conditionally Approved Rx Drugs

- Similar standard of evidence
- Major species, if….

address a serious or life-threatening condition

complex or particularly difficult studies

OR

address an unmet medical need

complex or particularly difficult studies







Conditionally Approved Rx Drugs

- Components (Technical Sections)
  - Target Animal Safety
  - Effectiveness
  - Human Food Safety
  - Chemistry, Manufacturing and Controls (CMC)
  - Environmental Impact

Conditionally Approved Rx Drugs

- Components (Technical Sections)
  - Target Animal Safety
  - Effectiveness
  - Human Food Safety
  - Chemistry, Manufacturing and Controls (CMC)
  - Environmental Impact


Effectiveness
(reasonable)
Is the drug reasonably expected to be effective?
Chemistry, Manufacturing, and Controls
Are the drug's manufacturing processes and quality standards consistent and scalable?
Target Animal Safety
Is the drug safe? Are the side effects well-documented?
Effectiveness
(substantial)
Has the drug been shown to be effective in clinical trials?
Conditional FDA Approval
Full FDA Approval

Conditionally Approved Rx Drugs

- Reasonable Expectation of Effectiveness
  - Pilot studies in target species
  - Previously published studies
  - Foreign studies
  - Extrapolation from
    - imilar species
    - elated diseases
    - elated dosage forms

Conditionally Approved Rx Drugs

- Restrictions
  - No off-label use

Conditionally Approved Rx Drugs

- Restrictions
  - Time limit on approval
    - 1-year
    - Renewable up to 5 years total
  - Making progress towards substantial evidence

Conditionally Approved Rx Drugs

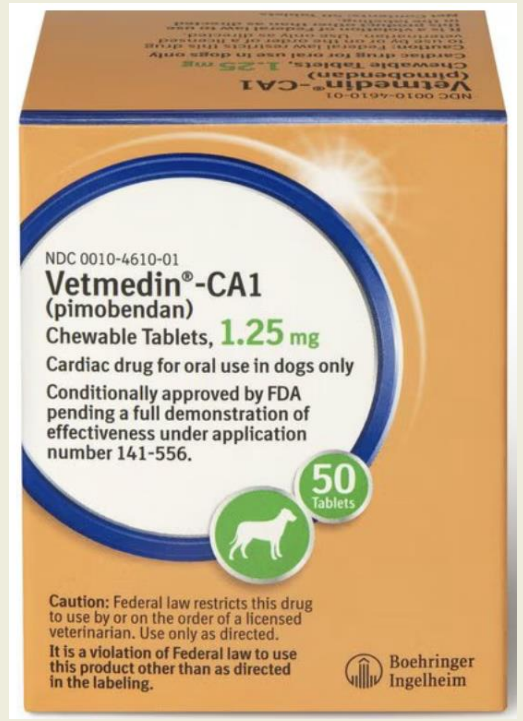
- Quality of Evidence
  - Nearly the same as approved drugs
  - Less evidence for effectiveness

High confidence- Let's Do It!!

Moderate confidence- Should work

Conditionally Approved Rx Drugs

- pimobendan
  - Fully approved for CHF in 2007
  - Conditionally approved for Stage B2 MMVD
  - Approval evidence- large clinical trial
    - >350 dogs
    - 1 years
    - Blinded, placebo-controlled
    - Large difference in CHF, survival



High confidence- Let's Do It!!

Conditionally Approved Rx Drugs

- Laverdia (verdinexor)
  - No prior approval, clinical use
  - Pilot studies
    - small studies (17 and 58 dogs)
    - open-label
    - no control group
    - variable treatment protocols
    - highly variable response

Moderate confidence- Should work

Off-label Drug Use

Off-label Drug Use

- No approved animal drug is available for the intended use.
- An approved animal drug is available for the intended use, but:
  - That drug does not contain the needed active ingredient.
  - That drug is unavailable in the needed dosage form
  - That drug is unavailable in the required concentration.
  - The veterinarian has found, within the context of a valid VCPR, that the drug is clinically ineffective when used as labeled.

→ Technically “Extra-label”

→ Conditions

- Drug is approved for some human or animal use
- Not unapproved, conditionally approved or indexed
- Patient’s health is threatened, may suffer or die
- Valid VCPR
- No approved drug you could use

- Records and labeling
- Specific prohibitions for food animals
- Compounding restrictions

Off-label Drug Use

- Examples
  - morphine, methadone
  - ondansetron, famotidine, omeprazole
  - zonisamide and levetiracetam (Keppra)
  - gabapentin, tramadol, lidocaine
  - antihistamines

Off-label Drug Use

- Quality of Evidence
  - Less evidence than approved drugs
  - Evidence quantity and quality variable

High confidence- Let's Do It!!

Moderate confidence- Should work

Slight confidence- Might work

Low confidence- Rolling the dice

Off-label Drug Use

- Morphine
  - Well-established physiologic rationale
  - Widely used in many species
  - Extensive research evidence in humans and veterinary species

High confidence- Let’s Do It!!

Off-label Drug Use

- gabapentin
  - Few, unrelated validated uses in humans
    - post-herpetic neuralgia
    - partial seizures
    - restless leg syndrome
  - Little research evidence in veterinary species

Slight confidence- Might work

Low confidence- Rolling the dice

Supplements

Supplements

- No Such Thing!

“there is no ‘dietary supplement’ regulatory classification for animal food substances and products.”

U.S. Department of Health and Human Services Food and Drug Administration Center for Veterinary Medicine (CVM). Product Regulation. Accessed July 18, 2024. Available at: https://www.fda.gov/animal-veterinary/animal-food-feeds/product-regulation#:~:text=Thus%2C%20there%20is%20no%20%22dietary,intended%20use%20(see%20below)

Supplements

- No Such Thing!

“[these products] are considered either ‘foods’ or ‘new animal drugs’ depending on the intended use”

U.S. Department of Health and Human Services Food and Drug Administration Center for Veterinary Medicine (CVM). Product Regulation. Accessed July 18, 2024. Available at: https://www.fda.gov/animal-veterinary/animal-food-feeds/product-regulation#:~:text=Thus%2C%20there%20is%20no%20%22dietary,intended%20use%20(see%20below)

Supplements

- No Such Thing!
- 1994 Dietary Supplement Health and Education Act (DSHEA)
- 1996 FDA CVM decided DSHEA doesn’t apply to veterinary species

Supplements

- It is a **drug** if it is intended to
  - Cure disease
  - Treat disease
  - Prevent disease

- But…
  - Previous policy of enforcement discretion if
    - no clear risk
    - no inaccurate or explicit drug claims
  - Policy withdrawn in 2020
  - Current policy not entirely clear

Supplements

- Variable, Usually Limited Evidence
  - Typically only pre-clinical lab studies
  - Often extrapolated from rodents, humans
  - Rarely clinical trials
  - No independent oversight to reduce bias

Moderate confidence- Should work

Slight confidence- Might work

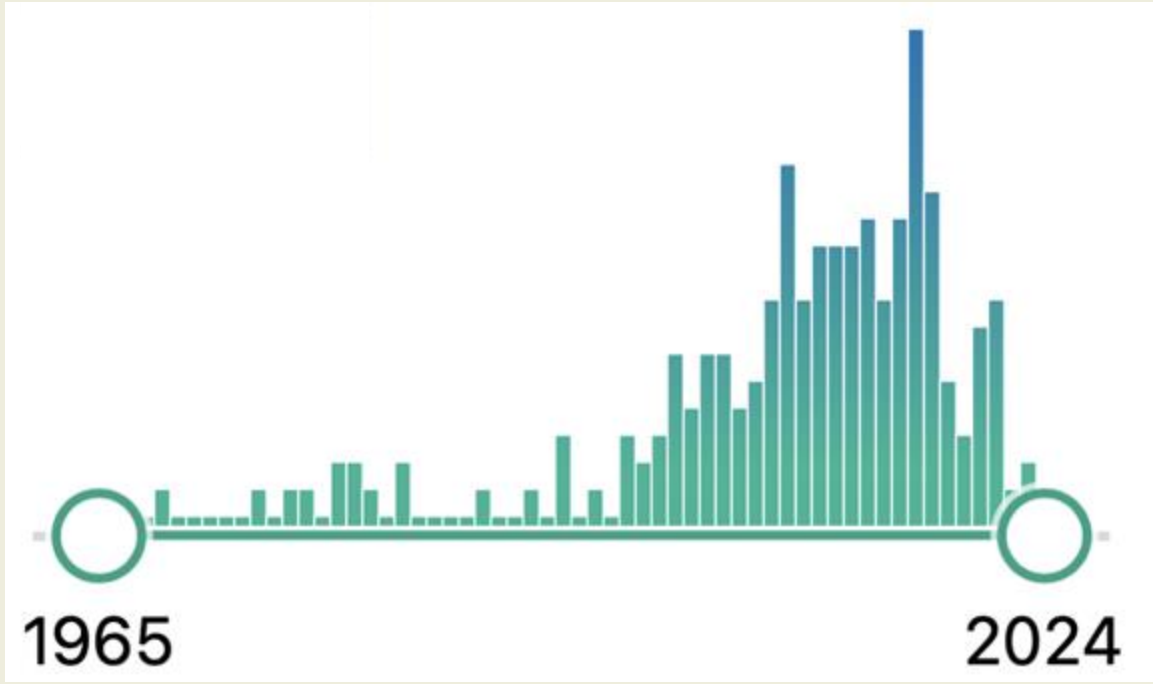
Low confidence- Rolling the dice

Supplements

- glucosamine
  - Lots of studies
  - Inconsistent findings
  - Significant risk of bias

Glucosamine

- *Osteoarthritis*
  - *Pubmed- 163 RCTs*
  - *Pubmed- 50 systematic reviews*
    - *60% some effect, 40% no effect*



Glucosamine

- *Osteoarthritis*
  - *Seems to provide chondroprotective effects and less inflammatory biochemical response in approximately half of the evaluations.*
  - *However, these effects are inconsistent between the clinical and the preclinical studies*
  - *A possible caregiver placebo effect may explain some of the beneficial responses observed in clinical trials with dogs.*

Barbeau-Grégoire M, Otis C, Cournoyer A, et al. Systematic Review and Meta-Analysis of Enriched Therapeutic Diets and Nutraceuticals in Canine and Feline Osteoarthritis. *Int J Mol Sci*. 2022;23(18):10384.

Glucosamine

- *Osteoarthritis*

American College of Rheumatology and the Arthritis Foundation

- *Recommends against glucosamine alone or with chondroitin because treatment does not improve knee and hip OA in studies without industry funding*

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res. 2020;72(2):149-162.

Glucosamine

- *Osteoarthritis*

  American Academy of Orthopedic Surgeons

  - *May be helpful in reducing pain and improving function…however, the research is inconsistent/limited*

Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. JAAOS - J Am Acad Orthop Surg. 2022;30(9):e721.

Glucosamine

- *Osteoarthritis*
  - *“Lack of evidence” to draw a definitive conclusion*

Mosley C, Edwards T, Romano L, et al. Proposed Canadian Consensus Guidelines on Osteoarthritis Treatment Based on OA-COAST Stages 1–4. Front Vet Sci. 2022;9.

Glucosamine

- *Osteoarthritis*
  - *3-4 of 9 panel members sometimes recommend glucosamine*

Cachon T, Frykman O, Innes JF, et al. COAST Development Group's international consensus guidelines for the treatment of canine osteoarthritis. Front Vet Sci. 2023;10:1137888.

Supplements

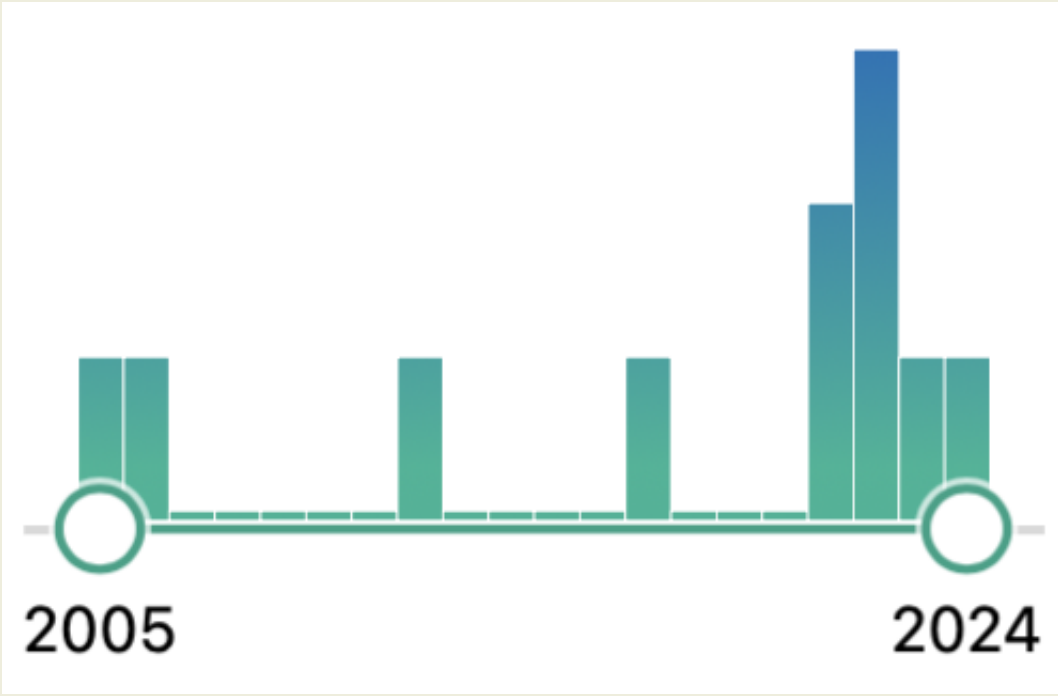
- glucosamine
  - Lots of studies
  - Inconsistent findings
  - Significant risk of bias

Slight confidence- Might work

Low confidence- Rolling the dice

Omega-3 fatty acids

- *Osteoarthritis*
  - *Pubmed- 20 RCTs*
  - *Pubmed- 10 systematic reviews/meta-analyses*
    - *8/10 showed a benefit*



Omega-3 fatty acids

- *Osteoarthritis*
  - *In general terms, there is sufficient evidence to consider the benefit of long-chain omega-3 fatty acids, such as EPA and DHA, as adjunctive therapy in canine and feline patients diagnosed with osteoarthritis.*

Magalhães TR, Lourenço AL, Gregório H, Queiroga FL. Therapeutic Effect of EPA/DHA Supplementation in Neoplastic and Non-neoplastic Companion Animal Diseases: A Systematic Review. In Vivo. 2021 May-Jun;35(3):1419-1436.

Omega-3 Fatty Acids

- *Osteoarthritis*

  American College of Rheumatology and Arthritis Foundation

  - *Conditionally recommends against…insufficient benefit to consider their use*

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res. 2020;72(2):149-162.

Omega-3 Fatty Acids

- *Osteoarthritis*
  - *9 of 9 panel members recommend omega-3 fatty acids*

Cachon T, Frykman O, Innes JF, et al. COAST Development Group's international consensus guidelines for the treatment of canine osteoarthritis. Front Vet Sci. 2023;10:1137888.

Supplements

- omega-3 fatty acids
  - Moderate number of studies
  - Inconsistent but generally positive findings
  - Significant risk of bias

Moderate confidence- Should work

Slight confidence- Might work

Supplements

- Quality control
  - No FDA guidelines for QC
  - No post-market monitoring/reporting
  - *Inconsistent QC, mislabeling*
    - *glucosamine*
    - *probiotics*
  - *Industry voluntary self-regulation*

Finno CJ. Veterinary Pet Supplements and Nutraceuticals. Nutr Today. 2020 Mar-Apr;55(2):97-101.

Weese JS. Evaluation of deficiencies in labeling of commercial probiotics. Can Vet J. 2003 Dec;44(12):982-3.

Adebowale AO, Cox DS, Liang Z, Eddington ND. Analysis of glucosamine and chrondrotin sulfate content in marketed products and the caco-2 permeability of chondrotin sulfate raw materials. *J Am Nutraceutical Assoc*. 2000;3(1):37–44.

Over-the-Counter Drugs

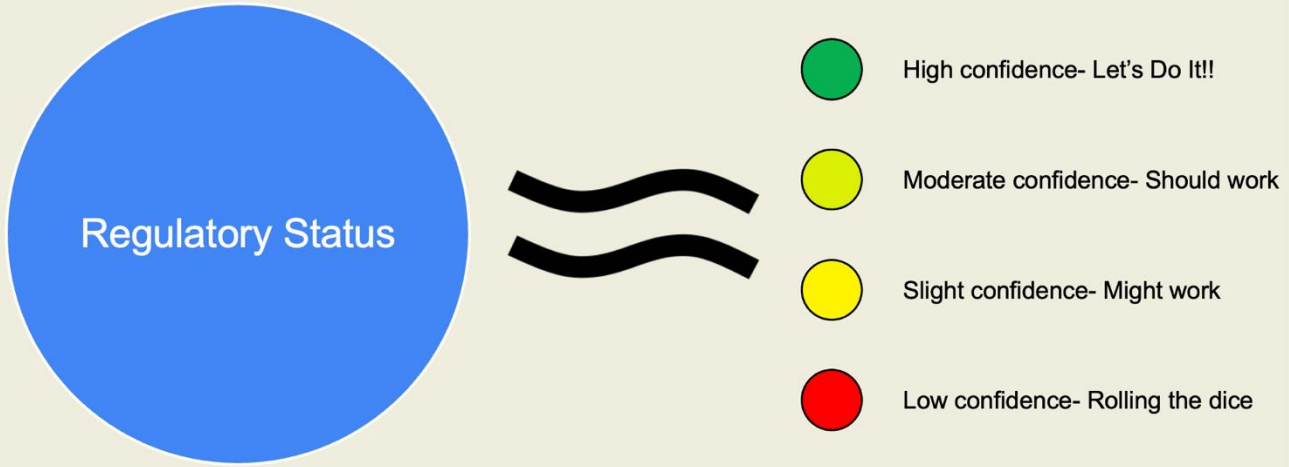
OTC Drugs

- OTC drugs are approved drugs

“If adequate ‘directions for use’ can be written on the drug’s label in such a way that a non-veterinarian can use the drug safely and effectively, then the drug company can market the animal drug as over-the-counter (OTC)”

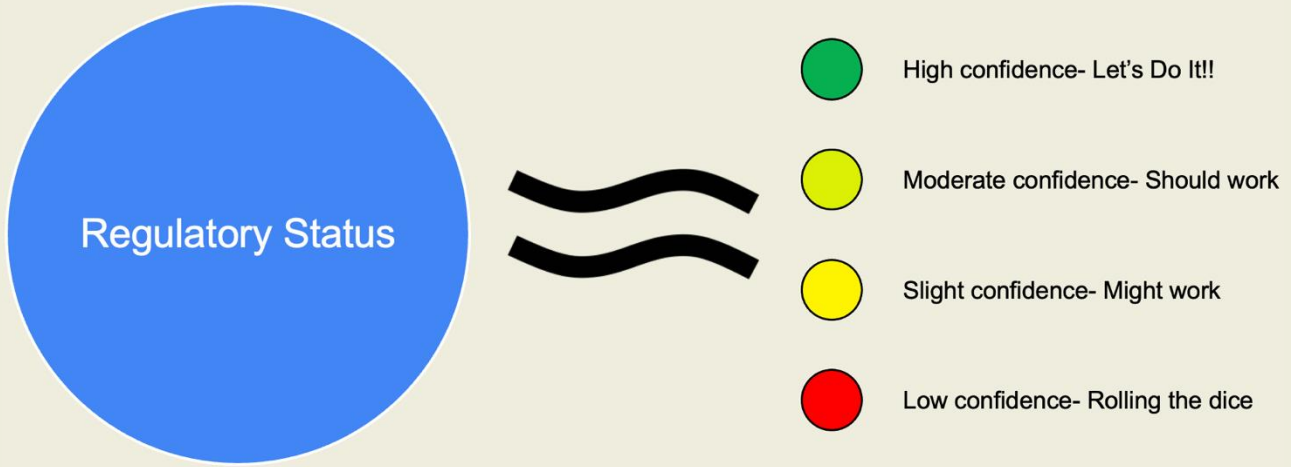
Key Points

- Regulatory Status & Evidence
  - Status corresponds loosely to level of evidence
  - Variable evidence even within categories
- More Oversight ~~Better~~ Evidence
  - Fully Approved Rx drugs
  - Conditionally approved Rx drugs
  - OTC drugs
  - Off-label drug use
  - Supplements



Key Points

- Regulatory Status & Evidence
  - Does not replace critical evaluation of all evidence!!
  - Practical and financial barriers to approval



Key Points

- Regulatory Status & Treatment
  - *Follow label instructions*
    - *indication*
    - *population*
    - *contraindications*
  - *Use approved products first if possible*
  - *Use drugs off-label only when appropriate*
    - *No appropriate approved drug*
    - *Good evidence to justify*
  - *Disclose uncertainty and evidence to clients*