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**#WCC2018VEGAS** 



# PHARMACEUTICS: THE KEY TO PHARMACOTHERAPEUTICS PERSONALIZATION

Ken Speidel, PharmD, RPh, FIACP, FACA

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<b>Activity Type</b>	Pharmacist	Pharmacy Technician
<b>Pharmacist UAN</b>	0864-9999-18-086-L07-P	0864-9999-18-086-L07-T
Credits	1 CPE Hours = 0.1 CEUs	1 CPE Hours = 0.1 CEUs
Release Date	October 28 <sup>th</sup> 2018	October 28 <sup>th</sup> 2018
<b>Expiration Date</b>	October 28 <sup>th</sup> 2019	October 28 <sup>th</sup> 2019



#### **ACCREDITATION**

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# KEN SPEIDEL, RPh, BS Pharm, PharmD, FIACP, FACA



- Facilitator, LP3 Network
- Consultant, MEDISCA Inc.
- Vice President, Compounding Compliance, Gates Healthcare Associates
- Surveyor and Accreditation Expert, Accreditation Commission for Health Care (ACHC/PCAB)
- Fellow, International Academy of Compounding Pharmacists (IACP)
- Fellow, American College of Apothecaries (ACA)
- Professor Pharmacy Practice (retired), University of Findlay

**Disclosure**: Surveyor, Accreditation Commission for Health Care (ACHC); Consultant, Gates Healthcare Associates; Consultant, MEDISCA Inc.



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# LEARNING OBJECTIVES

#### PHARMACISTS

- 1. Recognize the components of a certificate of analysis and safety data sheet.
- 2. Describe specific pharmaceutical principles and their relationship to relevant compounding practices.
- 3. Provide examples of the use of clinical pharmaceutics to individualize drug therapy.



# LEARNING OBJECTIVES

#### PHARMACY TECHNICIANS

- 1. Recognize the components of a certificate of analysis and safety data sheet.
- 2. Integrate components of a certificate of analysis and safety data sheet in your formulation process.
- 3. Recognize how clinical pharmaceutics can play a role in personalizing therapeutic regimens.



## OUTLINE

1

# THE NEED FOR PERSONALIZED PATIENT CARE

- Customization is key
- Opportunities for Compounding

2

#### **PHARMACEUTIC REVIEW**

- Interpreting a Certificate of Analysis (CoA) & Safety
   Data Sheet (SDS)
- Barrier/Base/Drug Relationships
- Partition, Permeability & Diffusion Coefficients

3

# CLINICAL PHARMACEUTICS FOR INDIVIDUALIZING DRUG THERAPY

- Overview
- Examples



### LET'S GET STARTED



THE NEED FOR
PERSONALIZED
PATIENT CARE

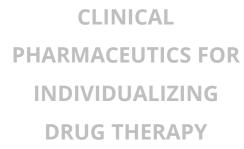
- Customization is key
- Opportunities for Compounding

2

#### PHARMACEUTIC REVIEW

- Interpreting a Certificate of Analysis (CoA) & Safety
   Data Sheet (SDS)
- Barrier/Base/Drug
  Relationships
- Partition, Permeability &
   Diffusion Coefficients
- Weight variance testing
- Beyond-use dating (BUDs)

3



- Overview
- Examples



#### CHANGES IN THE MARKET PROVIDE NEW OPPORTUNITIES

- Increasing shift of medicine from reactive to preventive
- Improved recognition for disease prevention strategies
- Customized prescription medication demand is on the rise
- Drug manufacturers do not always meet the distinct requirements of each patient
- Specialty/compounding pharmacy significant growth
- Compounding pharmacy recognized as a core competency
- Improved/unique way to set a pharmacy apart
- Identifies pharmacy as a part of the leading edge
- Effective/unique patient follow-up (compliance et al.)
- New markets continuing to open up

## THE CUSTOM IN COMPOUNDING

#### **CUSTOMIZATION OF DRUG THERAPY**

 Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create <u>customized</u> <u>medication solutions</u> for patients and animals whose healthcare needs cannot be met by manufactured medications.





#### WHEN DOES INDIVIDUALIZATION COME INTO PLAY?

There are numerous factors that can promote both personalized medicine and compounding:

- Increase in ADR's
- Genetic testing acceptance
- Increase in physician visits → increase in RXs dispensed
- Aging population with known intolerances and idiosyncrasies
- Increase in the number of exotic pets needing unique options
- Growth and understanding of Pharmacogenomics
- Increased awareness of pharmaceutical options among consumers
- Increase in drug shortages

Taken together, the rising demand for personalized medicine is evident.

## PERSONALIZATION COMPASS

- Are your BHRT doses most often the same regardless?
- Are the saliva panels you suggest often the same?
- Do you provide prescriber templates?
- Do you have go-to common APIs, sometimes same MOA?
- Do you suggest acronyms to make prescribing easy?
  - CAG/KAT/DAG etc.
  - Lidocaine, Gabapentin, Ketoprofen, Ketamine
- Do you believe that most patients with hot flashes and night sweats need estrogen?
- Do most of your patients get the same delivery system?
  - PEG Troche, O/W Cream, Liposomal Emulsion, Fatty Base Suppository
- Do you generally formulate HRT or pain with the same RODs?



### PERSONALIZED PATIENT CARE

## Compounding pharmacists must have proven competence in:

- Pharmaceutics
- Pharmacology
- Pharmacodynamics
- Pharmacogenomics
- Pharmaceutical chemistry

- Medicinal chemistry
- Physiology and pathophysiology
- Microbiology
- Non-sterile & sterile compounding
- Formulation science

## The role of the compounding pharmacist is...

The optimization of patient outcomes through individualization.



#### **COMPOUNDING PHARMACY IS A PATIENT-CENTRIC PRACTICE**

- Clinical Pharmacy Practice
- Problem Solving Centers
- Difficult cases are referred
- Off-label use potentials
- Broadened ability to provide pharm/care excellence



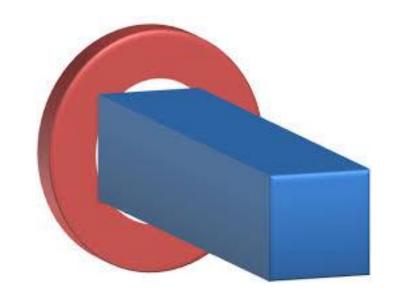


## ONE DOSE, ONE DELIVERY SYSTEM DOES NOT FIT ALL

#### PRACTITIONERS...

 Using manufactured products, are trying to match a patient to a product.

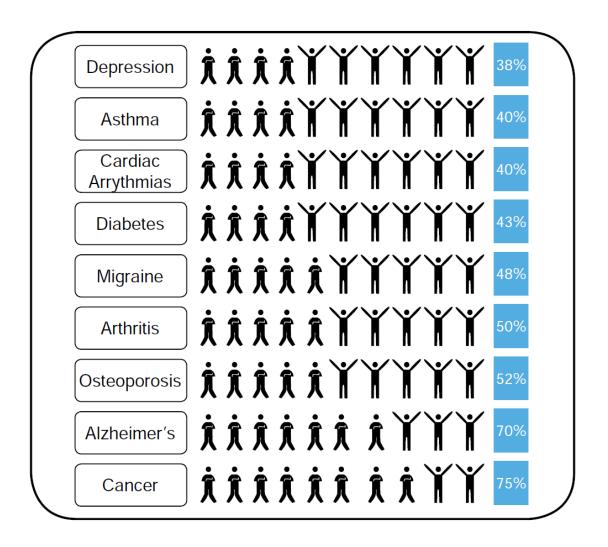
 Using compounded preparations,
 match a compounded formulation to a patient.





# ONE SIZE REALLY DOES NOT FIT ALL!

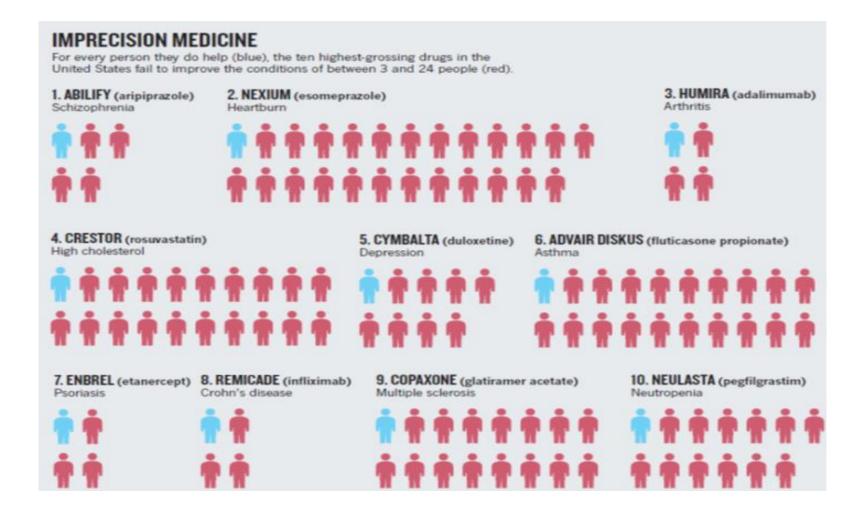
Percentage of patients for whom drugs are not effective





<sup>•</sup> Spear, B.B., Heath-Chiozzi, M., & Huff, J. (2001). Clinical application of pharmacogenetics. TRENDS in Molecular Medicine, 7(5), 201-204.

# EVIDENCE FOR THE (IN)EFFICACY OF DRUGS





## OUTLINE

1

2

3

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#### **PHARMACEUTIC REVIEW**

- Interpreting a Certificate of Analysis (CoA) & Safety
   Data Sheet (SDS)
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# CLINICAL PHARMACEUTICS FOR INDIVIDUALIZING DRUG THERAPY

- Overview
- Examples



### **PHARMACIST = CHEMIST?**

#### CHEMISTRY COMPETENCE QUIZ

- What is  $H_2O$ ?
- What is  $H_2O_2$ ?
- What is  $H_2O_4$ ?

Two men walk into a bar. One man orders  $H_2O$ . The other says, "I'll have  $H_2O$ , too."

The second man dies.



• A certificate of analysis (CoA) is a document provided by the chemical company (sometimes compounders for final products/preparations) for each bulk chemical.

• The CoA indicates the Lot number and conforms to the requirements of USP-NF (if it is a USP-NF grade chemical).

• When analyzing a CoA, it is important to compare/contrast the acceptance criteria provided in the USP-NF monograph (if available).

#### **METHIMAZOLE**

#### **METHIMAZOLE, USP**

Batch/Lot Number: 133846

Manufacturing Date: 03/01/2016

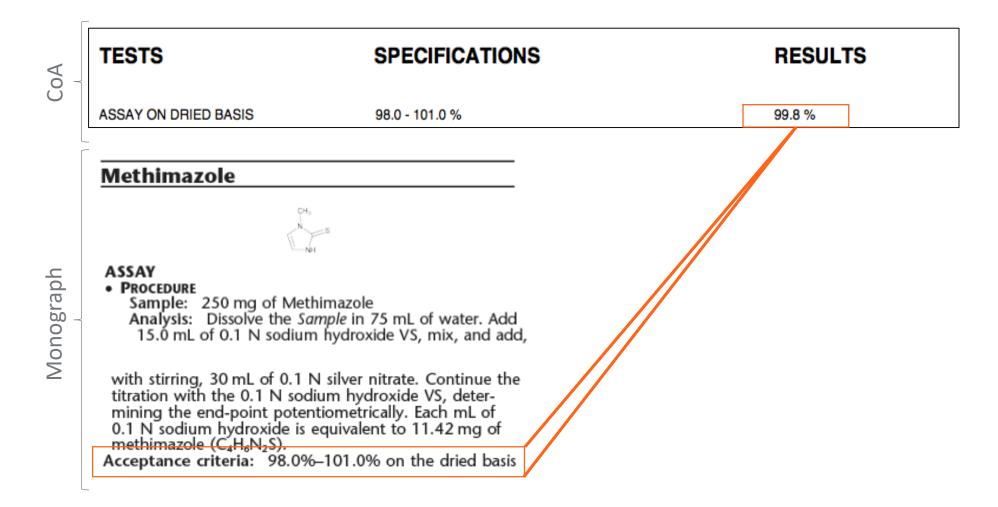
Expiration Date: 02/28/2020

Retest Date: NOT APPLICABLE

All dates in this document are in format mm/dd/yyyy unless otherwise specified

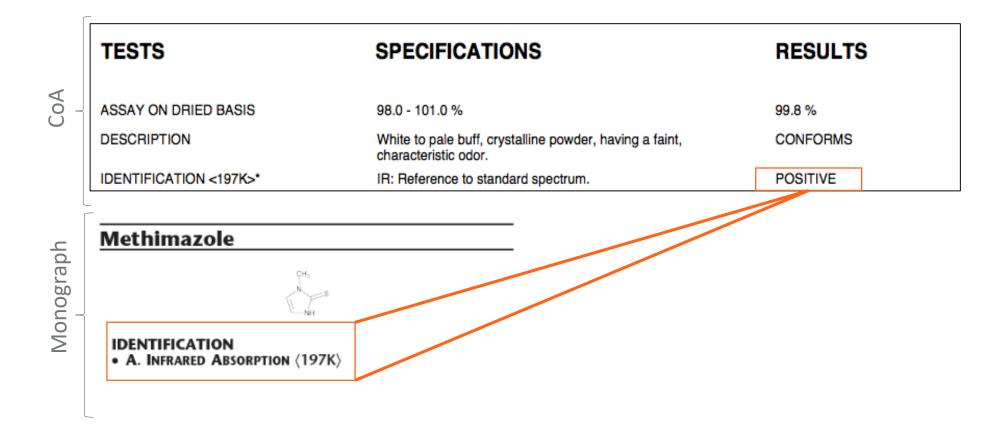


#### **METHIMAZOLE**





#### **METHIMAZOLE**





#### **METHIMAZOLE**

CoA

TESTS	SPECIFICATIONS	RESULTS
RESIDUE ON IGNITION <281>	<= 0.1 %	0.05 %
SELENIUM <291>	<= 30 ppm	<= 30 ppm

Monograph

#### Methimazole



- Residue on Ignition (281): NMT 0.1%

• SELENIUM (291)
Sample: 200 mg of Methimazole
Acceptance criteria: NMT 30 ppm



#### **METHIMAZOLE**

1	TESTS

TESTS	SPECIFICATIONS	RESULTS
ORGANIC IMPURITIES	<= 0.1 % (Methimazole related compound A)	0.071 %
	<= 0.1 % (1-Methylimidazole)	0.038 %
	<= 0.1 % (Methimazole related compound C)	0.019 %
	<= 0.1 % (Any other individual impurity)	0.082 %
	<= 0.5 % (Total impurities)	0.21 %

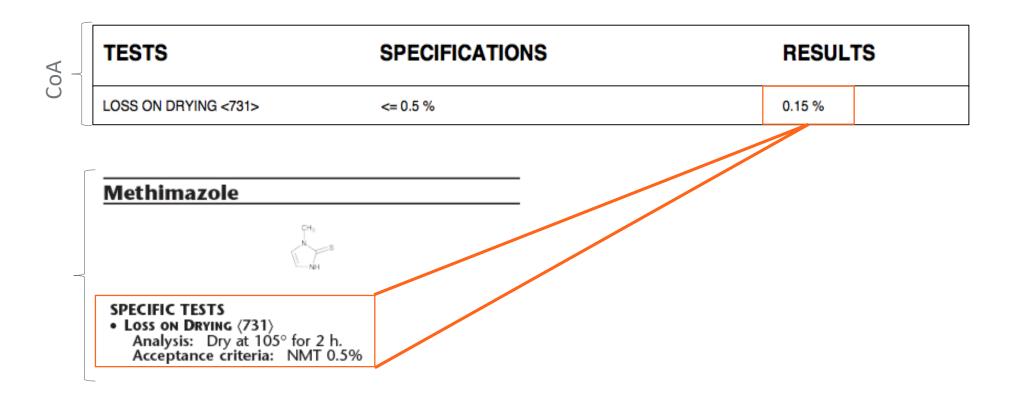
# Vlonograph

#### Methimazole

#### Table 2

Name	Relative Retention Time	Accep- tance Criteria, NMT (%)
Methimazole related compound A	0.3	0.1
1-Methylimidazole	0.4	0.1
Methimazole related compound C	0.7	0.1
Methimazole	1.0	_
Any other individual impurity	_	0.1
Total impurities	_	0.5

#### **METHIMAZOLE**





#### **METHIMAZOLE**

TESTS SPECIFICATIONS RESULTS COA \*\*PACKAGING AND STORAGE\*\* Preserve in well-closed, light-resistant containers. Methimazole Monograph ADDITIONAL REQUIREMENTS
• PACKAGING AND STORAGE: Preserve in well-closed, lightresistant containers. USP REFERENCE STANDARDS (11) USP Methimazole RS USP Methimazole Related Compound A RS 2,2-Dimethoxy-N-methylethanamine. C₅H<sub>13</sub>NO<sub>2</sub> 119.16 USP Methimazole Related Compound C RS 1-Methyl-2-(methylthio)-1*H*-imidazole.  $C_5H_8N_2S$ 128.20

 A safety data sheet (SDS) provides comprehensive information about a substance or chemical to be used in the workplace.

• It is typically written by the manufacturer or supplier on the product and details information about potential hazards, toxicity, or safety concerns.



#### A SDS SHOULD INCLUDE THE FOLLOWING ELEMENTS

- Product identification
- Hazardous identification
- Composition / info on ingredients
- First-aid measures
- Firefighting measures
- Accidental release measures
- Proper handling and storage conditions

- Exposure control guidelines
- Physical and chemical properties
- Stability and reactivity of substance
- Toxicological information
- Ecological information
- Disposal considerations
- Transport information
- Regulatory information



#### **METHIMAZOLE**

#### SECTION 1: PRODUCT IDENTIFICATION

PRODUCT NAME

PRODUCT CODE

EMERGENCY PHONE

SUPPLIER

METHIMAZOLE, USP

0360

MEDISCA Inc.

Tel.: 1.800.932.1039 | Fax.: 1.855.850.5855 661 Route 3, Unit C, Plattsburgh, NY, 12901

3955 W. Mesa Vista Ave., Unit A-10, Las Vegas, NV, 89118

6641 N. Belt Line Road, Suite 130, Irving, TX, 75063

MEDISCA Pharmaceutique Inc.

Tel.: 1.800.665.6334 | Fax.: 514.338.1693 4509 Rue Dobrin, St. Laurent, QC, H4R 2L8

21300 Gordon Way, Unit 153/158, Richmond, BC V6W 1M2

MEDISCA Australia PTY LTD

Tel.: 1.300.786.392 | Fax.: 61.2.9700.9047

Unit 7, Heritage Business Park

5-9 Ricketty Street, Mascot, NSW 2020

CHEMTREC Day or Night Within USA and Canada: 1-800-424-9300

NSW Poisons Information Centre: 131 126

Antithyroid



USES

#### **METHIMAZOLE**

#### SECTION 2: HAZARDS IDENTIFICATION

GHS CLASSIFICATION PICTOGRAM

SIGNAL WORD HAZARD STATEMENT(S)

AUSTRALIA-ONLY HAZARDS PRECAUTIONARY STATEMENT(S)

HMIS CLASSIFICATION



#### Warning

May be harmful if swallowed. May cause an allergic skin reaction. Suspected of damaging fertility or the unborn child .

Acute Toxicity - Oral (Category 5); Sensitization - Skin (Category 1); Toxic to Reproduction (Category 2)

Not Applicable.

Prevention Avoid breathing dust, fume, gas, mist, vapors, spray. Contaminated work clothing must not

be allowed out of the workplace. Wear protective gloves.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Wear protective gloves, protective clothing, eye protection, face

protection.

Response If on skin: Wash with plenty of water. If skin irritation or rash occurs: Get medical

advice/attention. Wash contaminated clothing before reuse.

If exposed or concerned: Get medical advice/attention.

Storage Store locked up.

Disposed Dispose of contents and/or container in accordance with local regulations.

Health Hazard 2 Flammability 0

Reactivity 0 Personal Protection E



#### **METHIMAZOLE**

#### SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS

CHEMICAL NAME

BOTANICAL NAME

SYNONYM

CHEMICAL FORMULA

CAS NUMBER

ALTERNATE CAS NUMBER

MOLECULAR WEIGHT

COMPOSITION

2H-Imidazole-2-thione, 1, 3-dihydro-1-methyl-

Not applicable

Not applicable

C4H6N2S

60-56-0

Not applicable

114.17

CHEMICAL NAME	CAS NUMBER	% BY WEIGHT
METHIMAZOLE, USP	60-56-0	100



#### **METHIMAZOLE**

#### **SECTION 4: FIRST-AID MEASURES**

IN CASE OF EYE CONTACT

IN CASE OF SKIN CONTACT IF SWALLOWED

IF INHALED

SYMPTOMS AND EFFECTS

Flush with copious amounts of water for 15 minutes, separating eyelids with fingers. If irritation persists seek medical aid.

Wash with soap & water for 15 minutes. If irritation persists seek medical aid.

Call a physician. Wash out mouth with water. Do not induce vomiting without medical advice.

Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician

Not expected to present a significant hazard under anticipated conditions of normal use.

#### SECTION 5: FIREFIGHTING MEASURES

SPECIFIC HAZARDS ARISING FROM THE CHEMICAL

FLAMMABLE PROPERTIES
HAZARDOUS COMBUSTION PRODUCTS
EXTINGUISHING MEDIA

PROTECTIVE EQUIPMENT AND PRECAUTIONS FOR FIREFIGHTERS Not applicable

May be combustible at high temperature

Under fire conditions, hazardous fumes will be present.

Small fire: dry chemical, CO<sub>2</sub> or water spray. Large fire: dry chemical, CO<sub>2</sub>, alcohol resistant foam or water spray. Do not get water inside containers.

Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.



#### **METHIMAZOLE**

#### SECTION 6: ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS

METHODS & MATERIAL FOR CONTAINMENT

CLEANUP PROCEDURE

Wear respiratory protection. Avoid dust formation. Avoid breathing vapours, mist or gas. Ensure adequate ventilation. Evacuate personnel to safe areas. Avoid breathing dust.

On land, sweep or shovel into suitable containers. Minimize generation of dust.

Do not touch damaged containers or spilled material unless wearing appropriate protective clothing. Wear respirator, chemical safety goggles, rubber boots and heavy rubber gloves. Stop leak if you can do it without risk. Prevent entry into waterways, sewers, basements or confined areas. Shut off all sources of ignition. Evacuate the area. If necessary, employ water fog to disperse the vapors. Absorb the matter with compatible vermiculite or other absorbing material. Place in a suitable container and retain for disposal. Ventilate and clean the affected area. Do not flush into sewerage system or to drains.

#### SECTION 7: HANDLING AND STORAGE

PRECAUTIONS FOR SAFE HANDLING

STORAGE CONDITIONS

Do not inhale. Avoid contact with eyes, skin and clothing. Avoid prolonged or repeated exposure. Wash thoroughly after handling.

Preserve in well-closed, light-resistant containers.



#### **METHIMAZOLE**

#### SECTION 8: EXPOSURE CONTROLS/ PERSONAL PROTECTION

		OSHA PEL			AIHA '	WEEL	Safe Work Australia HSIS	
Chemical Name	CAS	TWA	Celling	Skin Designation	8hr TWA	Celling	TWA	STEL
METHIMAZOLE, USP	60-56-0	N/L	N/L	N/L	N/L	N/L	N/L	N/L

N/L = Not Listed; X = Listed

**EXPOSURE GUIDELINES** 

PERSONAL PROTECTIVE EQUIPMENT

Consult local authorities for provincial or state exposure limits

Eyes: Wear appropriate protective eyeglasses or chemical safety goggles as described by WHMIS or OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166. Skin: Wear appropriate gloves to prevent skin exposure. Clothing: Wear appropriate protective clothing to minimize contact with skin. Respirators: Follow WHMIS or OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

SPECIFIC ENGINEERING CONTROLS

Adequate mechanical ventilation. Fumehood, eye wash station, and safety shower.



#### **METHIMAZOLE**

#### **SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES**

PHYSICAL STATE

Solid

DESCRIPTION

White to pale buff, crystalline powder, having a faint, characteristic odor.

SOLUBILITY

Freely soluble in water, in alcohol, and in chloroform; slightly soluble in ether.

ODOR

Faint characteristic odor

Not available

Not available

FLAMMABILITY

May be combustible at high temperature

ODOR THRESHOLD

ay be combustible at high temperatu

\_\_\_\_\_

PH

Not available

MELTING POINT

(144-147)°C, (291.2-296.6)°F

BOILING POINT

FREEZING POINT

Not available

FLASH POINT

>100 °C, >212 °F

SPECIFIC GRAVITY

Not available EVAPORATION RATE

Not available

EXPLOSIVE LIMIT

Not available

UPPER FLAMMABLE/ EXPLOSIVE LIMIT(S) Not available LOWER FLAMMABLE/ EXPLOSIVE LIMIT(S) Not available

VAPOR PRESSURE N

Not available

VAPOR DENSITY (AIR = 1) Not available RELATIVE DENSITY (WATER = 1)

Not available

LOG P (OCTANOL-WATER) Not available

AUTO-IGNITION TEMPERATURE Not available D

DECOMPOSITION TEMPERATURE Not available

VISCOSITY

Not available



#### **METHIMAZOLE**

#### SECTION 10: STABILITY AND REACTIVITY

REACTIVITY

STABILITY

MATERIALS TO AVOID

HAZARDOUS DECOMPOSITION PRODUCTS

HAZARDOUS POLYMERIZATION

POSSIBLITY OF HAZARDOUS REACTION

CONDITIONS TO AVOID

Not established

Stable under recommended storage conditions

Strong oxidants

Toxic fumes of carbon monoxide, carbon dioxide, nitrogen oxides, sulfur oxides and other gases may occur

Will not occur

Not established

Moisture, sunlight and extreme temperatures



#### **METHIMAZOLE**

#### SECTION 11: TOXICOLOGICAL INFORMATION

ACUTE TOXICITY

SKIN CORROSION/IRRITATION

SERIOUS EYE DAMAGE/EYE IRRITATION

RESPIRATORY OR SKIN SENSITIZATION

GERM CELL MUTAGENICITY

CARCINOGENICITY

REPRODUCTIVE TOXICITY

SPECIFIC TARGET ORGAN TOXICITY -SINGLE EXPOSURE

SPECIFIC TARGET ORGAN TOXICITY -REPEATED EXPOSURE

ASPIRATION HAZARDS

SIGNS AND SYMPTOMS OF EXPOSURE

POTENTIAL HEALTH EFFECTS

Oral: Rat: LD50: 2250 mg/kg

Not available

Not available

May cause allergic skin reaction.

Not available

OSHA METHIMAZOLE, USP is not listed.

NTP METHIMAZOLE, USP is not listed.

IARC METHIMAZOLE, USP is listed in group 3 (not classifiable as to its carcinogenicity to

humans).

California

This product contains the following chemical known to the State of California to cause birth

Proposition 65 defects or other reproductive harm: METHIMAZOLE, USP.

Overexposure may cause reproductive disorder(s) based on tests with laboratory animals.

May cause congenital malformation in the fetus.

Suspected human reproductive toxicant.

Not available

Not available

Not available

Not expected to present a significant hazard under anticipated conditions of normal use.

Inhalation May be harmful if inhaled. May cause respiratory tract irritation.

Incestion May be harmful if swallowed.

Skin May be harmful if absorbed through skin. May cause skin irritation

Eyes May cause eye irritation.



#### **METHIMAZOLE**

#### SECTION 12: ECOLOGICAL INFORMATION

TOXICITY

PERSISTENCE AND DEGRADABILITY

BIOACCUMULATIVE POTENTIAL

MOBILITY IN SOIL

OTHER ADVERSE EFFECTS

Not available

Not available

Not available

Not available

Not available

This product is not intended to be released into the environment

#### SECTION 13: DISPOSAL CONSIDERATIONS

WASTE DISPOSAL

Dispose of in accordance with federal / local laws and regulations. Avoid release into the environment.



#### **METHIMAZOLE**

#### SECTION 14: TRANSPORT INFORMATION

UNITED STATES & CANADA

UN PROPER SHIPPING NAME Not dangerous good

UN NUMBER Not applicable

CLASS Not applicable

PACKING GROUP Not applicable

**AUSTRALIA** 

UN PROPER SHIPPING NAME Not dangerous good

UN NUMBER Not applicable

CLASS Not applicable

PACKING GROUP Not applicable

HAZCHEM Not Applicable

ENVIRONMENTAL HAZARDS Not available

SPECIAL SHIPPING INFORMATION Not applicable



#### **METHIMAZOLE**

#### **SECTION 15: REGULATORY INFORMATION**

Chemical Name	CERCLA SARA (Title III) 40 CFR 40 CFR		EPA 40 CFR Part 355			California		
& CAS		Part 372.65	Appendix A	Appendix B	Pennsylvania	New Jersey	Massachusetts	Prop 65
METHIMAZOLE, USP 60-56-0	N/L	N/L	N/L	N/L	N/L	N/L	N/L	Х

N/L = Not Listed; X = Listed



#### PHARMACEUTICS FOR PRACTICING COMPOUNDING

#### PHARMACISTS/PHARMACEUTICS = PTSD?



#### SOME SYMPTOMS OF PTSD

- Nightmares
- Anger, rage and/or irritability
- Depression
- Loss of self-esteem
- Difficulty trusting others
- Guilt
- Trouble Sleeping
- Substance abuse
- Isolation and alienation from others
- Having thoughts and memories that will not got away
- Anxiety
- Heightened sense of danger
- Hyper alertness or startle response changes



#### WHAT IS PHARMACEUTICS?

- The art and applied science of dosage form design
  - The interface between drug and body
- Draws from a broad field including many disciplines
  - Physical chemistry (organic and inorganic)
  - Medicinal Chemistry
  - Anatomy and Physiology
  - Microbiology
  - Engineering and Physics





#### WHAT IS PHARMACEUTICS?

- A common definition of pharmaceutics → A discipline of pharmacy that utilizes scientific processes and procedures to formulate new chemical substances or commonly used and tested drugs into different therapeutic entities.
- A simpler description of pharmaceutics  $\rightarrow$  the science of dosage form design.
- Clinical pharmaceutics → is a concept that combines the principles of
  pharmacotherapy and pharmaceutics in order to treat medical conditions that may
  not have responded to traditional approaches and/or a patient has contraindications
  or intolerances to a manufactured dosage form or delivery system.



PHARMACEUTICAL VARIABLES	TO CONSIDER IN FORM	MULATION DESIGN

pH; pKa & pKb

**Phase Inversion** 

**Photosensitivity** 

Rate of Absorption

**Rectal Retention** 

**Sedimentation/Newtonian** 

**Polarity** 

Reactivity

Solubility

Sorption

**Stability** 

**Taste** 

**Texture** 

**Tonicity** 

Washability

Wettability

**Surface Area** 

Suspendability

**Temperature Sensitivity** 

**Viscosity/Stokes Law** 

I HAMMACLO HEAL VAMADLLS	10 CONSIDE	

**Ease of Administration** 

**Hydrophilic – Lipophilic Balance** 

**Eutectics** 

**Flowability** 

**Heat Labile** 

**Hydrolysis** 

Ionization

Lubricity

Odor

Lipophilicity

**Melting Point** 

**Particle Size** 

**Microbial Proliferation** 

Molecular Weight/Size

**Organoleptic Properties** 

**Oxidation - Reduction** 

**Partition Coefficient** 

**Hydrophilicity** 

**Hygroscopicity** 

Flavor

**Absorption** 

**Adsorption** 

**Bio-adhesion** 

**Buccal Retention** 

**Buffering Capacity** 

Caking/Flocculation/Brownian

**Crystalline Form / Crystallization** 

Deliquescence/Efflorescence

**Diffusion Coefficient** 

**Dispensing Container** 

Disintegration

Dispersion

Dissolution

**Coloration / Discoloration** 

**Affinity** 

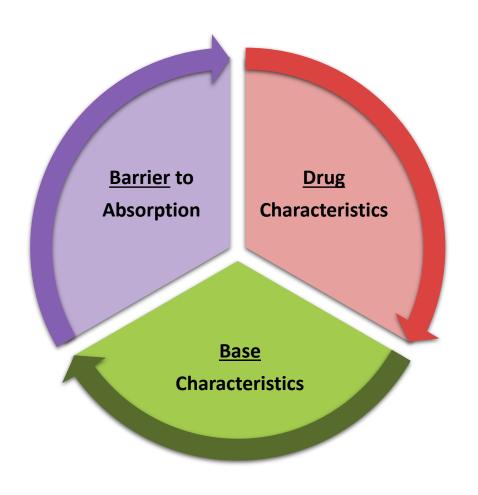
Chelation

Consistency

Creaming

**Density** 

Diffusion

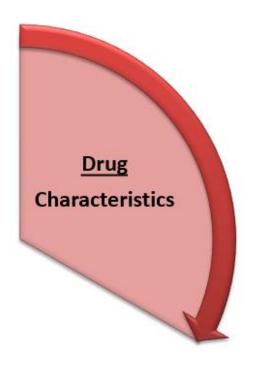


Barrier-to-Drug

Drug-to-Base

Barrier-to-Base





#### DRUG CHARACTERISTICS

- Solubility
- pKa / pKb
- pH requirement
- Hydrophilic
- Lipophilic
- Molecular size





#### BASE CHARACTERISTICS

- Composition
- State-of-matter
- Thermodynamic activity
- Occlusion
- pH
- Permeation enhancers



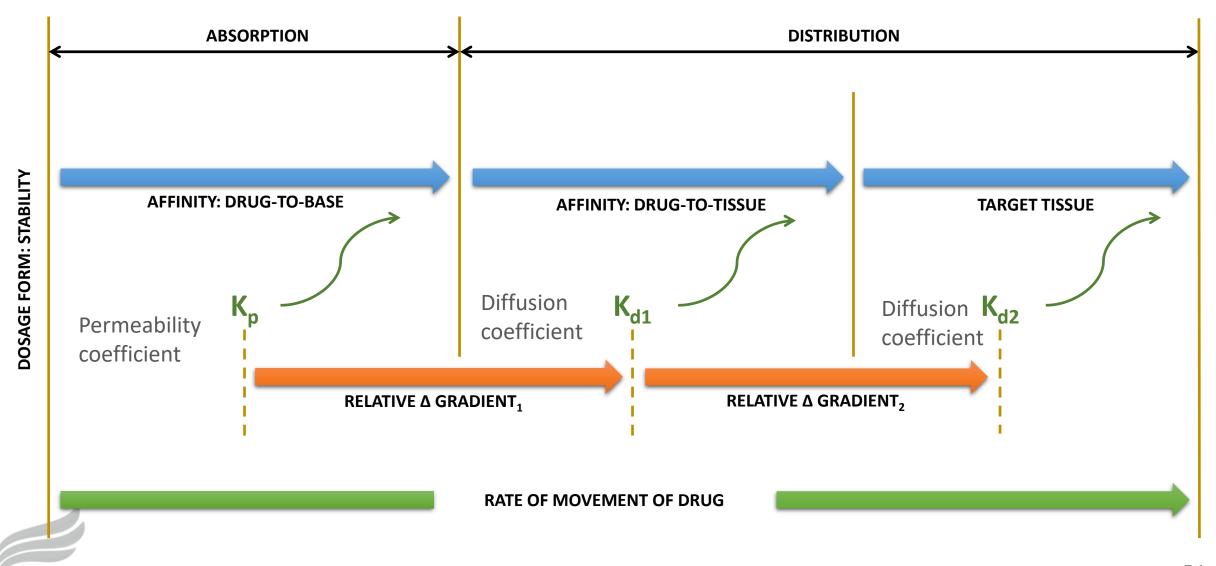


#### BARRIER CHARACTERISTICS

- Barrier mechanism
- Lipophilic layer
- Surface area
- Water content
- Other content
- Integrity / Condition



## THE GOAL OF DRUG DELIVERY



#### PARTITION COEFFICIENT

## RATIO OF DRUG CONCENTRATION IN THE OCTANOL PHASE TO THE AQUEOUS PHASE

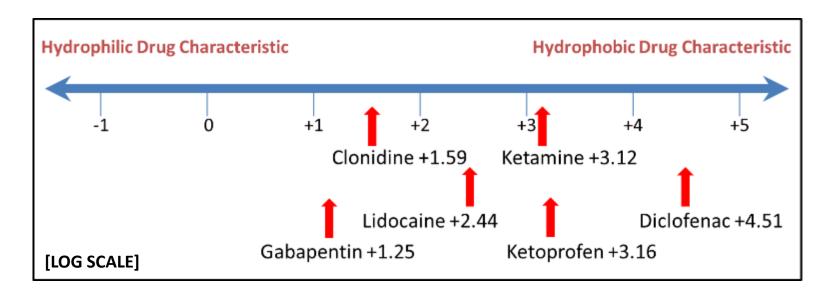
- Measures a molecule's hydrophobicity (lipophilicity)
- The partition coefficient, P, can be used to predict the behavior of compounds, such as its permeability

$$Partition\ Coefficient, P = \frac{[neutral\ species]_{Octanol}}{[neutral\ species]_{Water}}$$

- P gives us a value of the affinity of a molecule for the lipid and aqueous phases in the absence of ionization
- Often expressed as  $P_{o/w}$  or as a logarithm  $LogP = log_{10}(P)$



#### PARTITION COEFFICIENT



- Hydrophobicity affects drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of molecules, as well as their toxicity.
- Hydrophobicity of solutes are readily determined by measuring partition coefficients (log Po/w) using the shake-flask method.

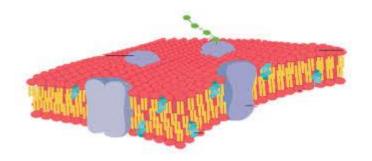


#### PERMEABILITY COEFFICIENT

#### DRUG DIFFUSION ACROSS A BARRIER

- Lipophilicity is an important parameter that can influence pharmacokinetic and pharmacodynamic behavior.
  - Strong hydrophobic interactions can result in non-specific binding with proteins (target and non-target) in the aqueous biological environment.
  - Restricting lipophilicity limits easy diffusion across biological membranes and into cells, cellular compartments and the central nervous system (CNS).
  - Some lipophilicity is required to allow a drug to enter cellular organelles.





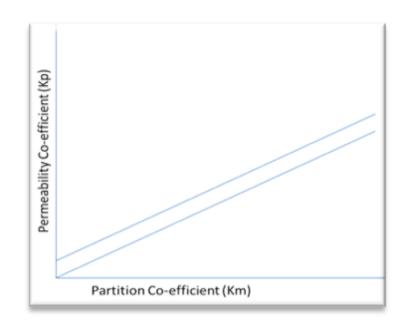
#### PERMEABILITY COEFFICIENT

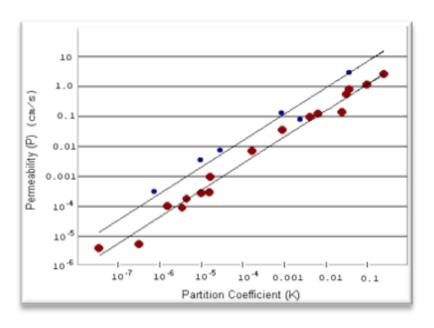
- Permeability coefficient, Kp  $-K_p = \frac{DK_m}{h}$  where Km is the partition coefficient, which can be expressed as a measure of the partitioning of drug between a lipid and aqueous phase.
- Log P as a measurement of drug partitioning, so substituting Log P for  $K_m$  we get:  $K_p = \frac{D(Log P)}{h}$
- Log P represents a measurement of the lipid solubility of the drug
  - This is the drug partition coefficient between the target tissue and formulation
  - Ideally we want the drug to partition more into the target tissue and have less affinity for the formulation



#### PERMEABILITY COEFFICIENT

Permeability is affected linearly as a molecule becomes more lipophilic





- Knowledge of the partition co-efficient coupled with the drug molecule's mechanism of action and target site helps us to optimize bioavailability
- The size of the molecules also has an effect

#### DIFFUSION COEFFICIENT

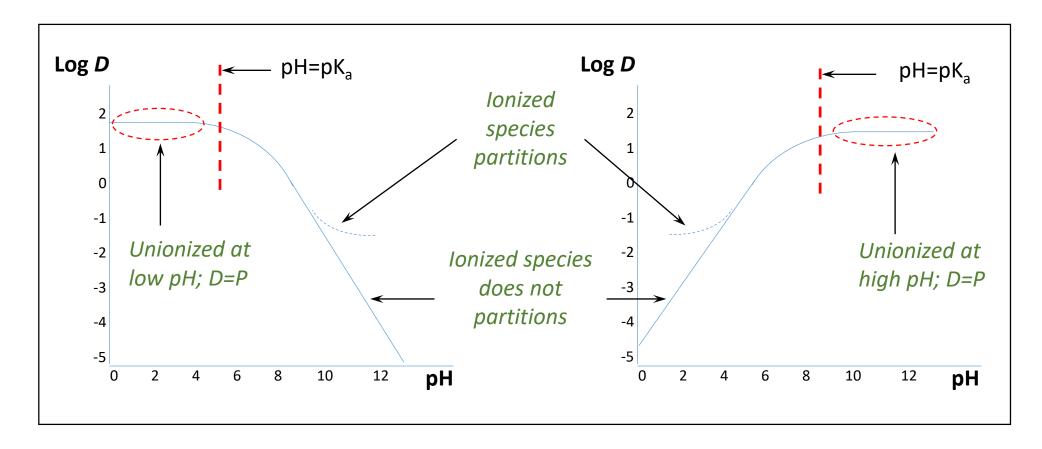
#### ALSO KNOWN AS DIFFUSIVITY, D

- Expression of the rate at which a drug molecule will pass through the depths of a tissue membrane given its tendencies/affinities toward a hydrophilic versus lipophilic environment
- Measures the mobility of a drug during diffusion
- Affected by:
  - Molecular properties
    - Smaller molecule would have greater diffusivity vs. larger one, ionization
  - Temperature
    - Application of heat to the site of administration would likely increase it



## DIFFUSION COEFFICIENT

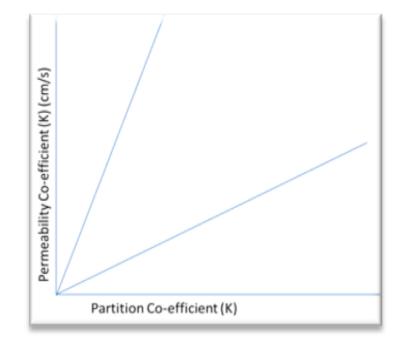
#### ALSO KNOWN AS DIFFUSIVITY, D

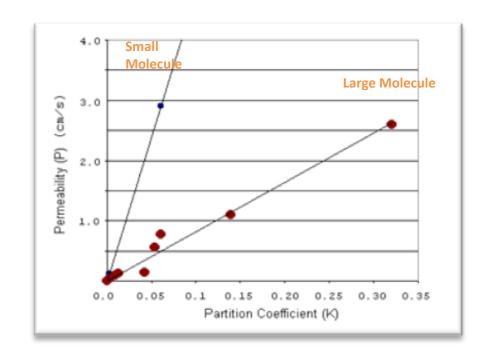




## DIFFUSION COEFFICIENT

- The slope represents the diffusion coefficient, D
  - Smaller molecules, steeper slope diffusivity increases with permeability
  - Small molecular size permits polar molecules to achieve good absorption despite low lipophilicity
  - Permeation enhancing agents can be used to alter the rate of diffusion







## **CLINICAL CASE ASSESSMENT**

DRUG	SPECIFIC DRUG CHARACTERISTICS									
Drug	MV (cm³)	Solubility	Hydrophilic Lipophilic	Log P	Log D @ pH 5.5	Log D @ pH 7.4	Polar Surface Area (Ų)	Number of Freely Rotating Bonds		
Gabapentin	161.8±3.0	H <sub>2</sub> 0: 10 mg/mL	Lipophilic	1.19±0.24	-1.36	-1.31	63.32	4		
Lidocaine HCl	Not available	H <sub>2</sub> 0: Very soluble	Hydrophilic	2.359	-0.13	1.57	23.55	5		
Ketamine	202.6±5.0	H <sub>2</sub> 0: 200 mg/mL	Hydrophilic	2.18±0.60	1.18	2.13	29.1	2		
Ketoprofen	212.2±3.0	H <sub>2</sub> 0: Poorly soluble	Lipophilic	2.81±0.33	1.53	-0.25	54.37	4		
Clonidine	153.2±7.0	H <sub>2</sub> 0: 77 mg/mL	Hydrophilic	1.41±0.58	-0.49	0.65	36.42	1		
Amitriptyline	257.8±3.0	H <sub>2</sub> 0: 1 mg/mL	Hydrophilic	4.92±0.64	1.92	3.15	3.24	3		



#### OUTLINE



2

3

## THE NEED FOR PERSONALIZED PATIENT CARE

- Customization is key
- Opportunities for Compounding

#### PHARMACEUTIC REVIEW

- Interpreting a Certificate of Analysis (CoA) & Safety
   Data Sheet (SDS)
- Barrier/Base/DrugRelationships
  - Partition, Permeability & Diffusion Coefficients

# CLINICAL PHARMACEUTICS FOR INDIVIDUALIZING DRUG THERAPY

- Overview
- Examples



#### INDIVIDUALIZE BASED ON CLINICAL PHARMACEUTICS

• Clinical pharmaceutics maintains a critical role in helping to achieve the desired outcome for a diverse patient population.

 It is a concept that combines the principles of pharmacotherapy and pharmaceutics to treat medical conditions that may not have responded to traditional approaches and/or when a patient has contraindications or intolerances to a manufactured dosage form or delivery system.



#### CLINICAL PHARMACEUTICS

- Involves the following principles (non-inclusive):
  - Adsorption/Adhesion, Buffer Capacity, Complex Organic Molecules, Crystallinity, Dosage Form Selection and Properties, Hydrates and Solvates, Melting Point, Miscibility, Organic Salts and Esters, Oxidation/Reduction, Particle Size and Surface Area, Partition Coefficient, pH, pKa/Dissociation Constant, Precipitation, Rheology/Viscosity, Sedimentation, Solubility, Surface Tension/Wetting



- Example: Nitrofurantoin → GI complications
  - Increase **particle size** to reduce absorption
    - Reduction in GI intolerance
- Example: Diazepam Suppositories → Seizures
  - Lipophilic base with lipophilic drug
    - Reduction in <u>partitioning</u> → <u>absorption</u>
    - Requires water soluble base to partition



- Example: Phenytoin intoxication (Australia)
  - Change in diluent (calcium sulfate to lactose)
  - Difference in <u>solubility</u> led to <u>rapid dissolution</u> of the phenytoin sodium, resulting in intoxication
  - Excipients are not always inert
  - Chosen for a functional attribute
  - Can be incompatible with a formulation or patient



#### SPECIFIC NICHE MARKETS

- Pain Management
  - Local anesthetics bases versus salts
  - Solubility without ionization → <u>eutectics</u>
  - Arrhythmogenic potential
    - Lidocaine/tetracaine (amide and ester)
    - Lidocaine/prilocaine
    - Must be used with caution due to high concentration



Beshay, S., et al. (2015). Efficacy and Clinical Value of Commonly Used Ingredients in Pain Management Compounds: A Literature Review. IJPC, 19(4), 295-300.

#### SPECIFIC NICHE MARKETS

- Pain Management
  - Low Dose Natrexone (LDN)
    - Immune Modulation
    - Glial Attenuator
    - Increases Endorphins/Enkephins
  - Must design as immediate release



• Beshay, S., et al. (2015). Efficacy and Clinical Value of Commonly Used Ingredients in Pain Management Compounds: A Literature Review. IJPC, 19(4), 295-300.

#### SPECIFIC NICHE MARKETS

- Hormone Restoration Therapy
  - Testosterone topical gel vs cream
    - Diffusion
    - Saliva vs serum
  - DHEA intravaginal for dyspareunia
    - Fatty base vs water soluble



• Beshay, S., et al. (2015). Efficacy and Clinical Value of Commonly Used Ingredients in Pain Management Compounds: A Literature Review. IJPC, 19(4), 295-300.

#### SPECIFIC NICHE MARKETS

- Veterinary Medicine
  - Polyoxamer for ear parasites
- Wound care/Somatitis
  - Polyoxamer powders/pastes
- ENT
  - Bio-film destruction in chronic sinus injections



Beshay, S., et al. (2015). Efficacy and Clinical Value of Commonly Used Ingredients in Pain Management Compounds: A Literature Review. IJPC, 19(4), 295-300.

#### **CONCLUDING REMARKS**

- The need for personalization is clear
- Pharmaceutics serves as a toolbox for optimizing patient outcomes
- Considering individual variation paves the way for the future





# The CUSTOM in compounding will again be CUSTOMization





