# Designing for Delivery: The Use of Mathematical Modeling

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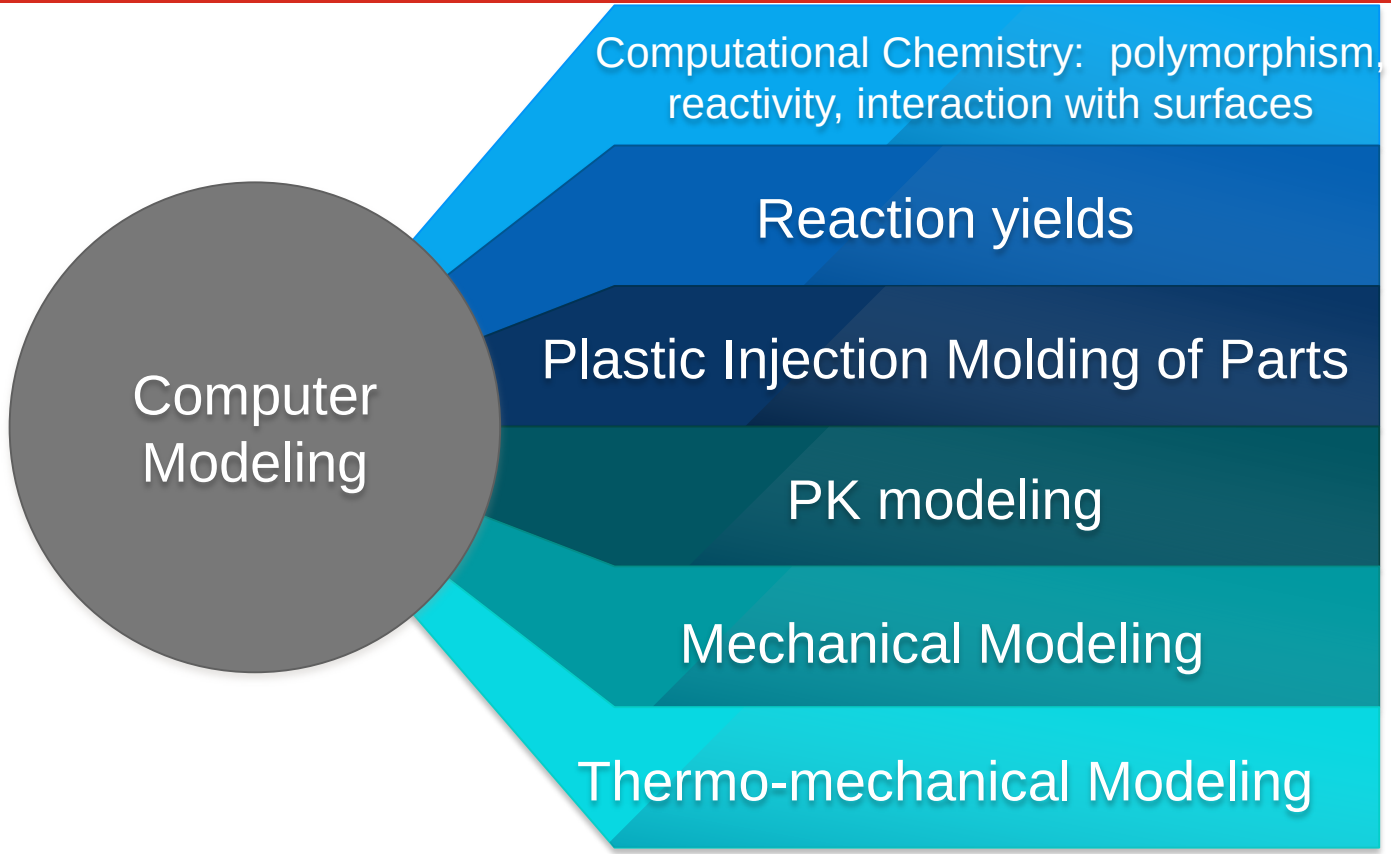
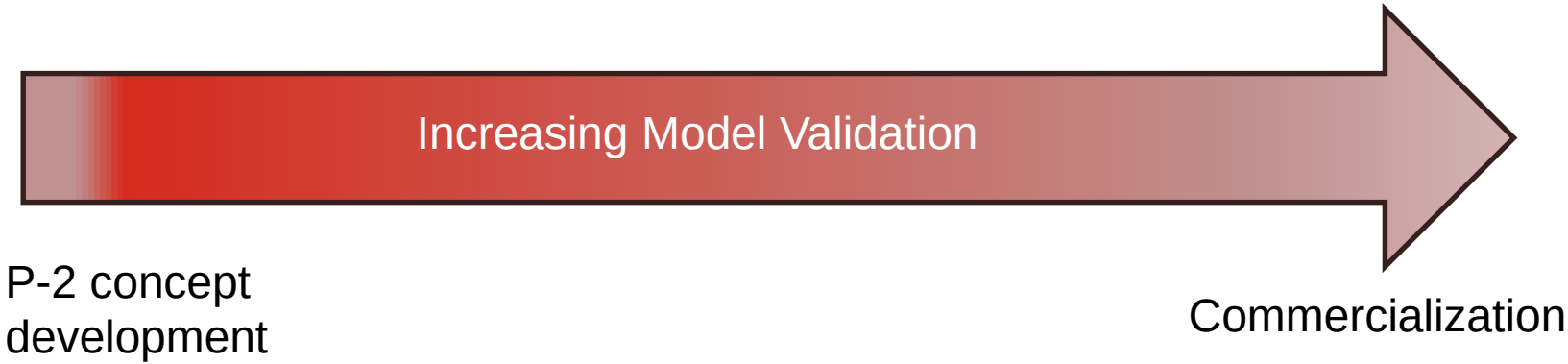
# The Use of Modeling in Drug Development



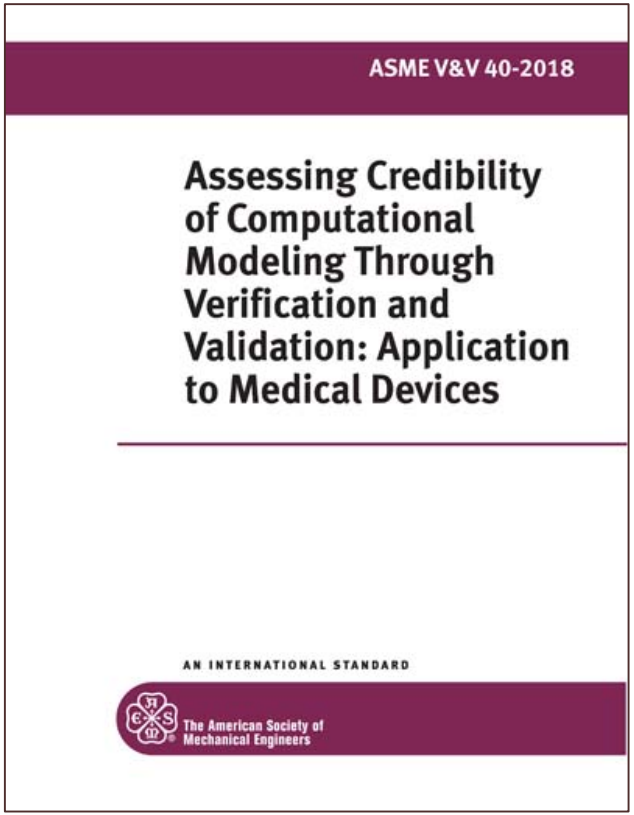
# Basic Kinds of Numerical Models

- Analytical – produces a single calculated
  - Computational chemistry
  - Reaction yields
  - PK modeling
- “Finite Approaches”
    - Computational fluid dynamics
    - Finite volume, element, difference…
- Statistical modeling

# Spectrum of Activities



# Available Resources



# Factors to Consider

- Have to understand the context of use (COU)
- Model risk
  - Model influence
  - Adverse affect resulting from an incorrect decision
- Model credibility
  - Correctness of the code and calculations
  - User error

# Model Validation

- Commercial off-the-shelf software
- Correct model inputs
  - Select the correct model
    - Linear elastic
    - Hyperelastic
  - Mechanical properties – one of the largest sources of model variability
- Independent of the model:  know your requirements and margins of safety!

# Difficulties

- Regions of interest may be too small for physical verification (dimensions do not allow)
- More accurate to do ASTM or ISO testing for model inputs than working directly with components
- Events of interest may be short-lived

# Case Study 1 – Flexible Device Containers

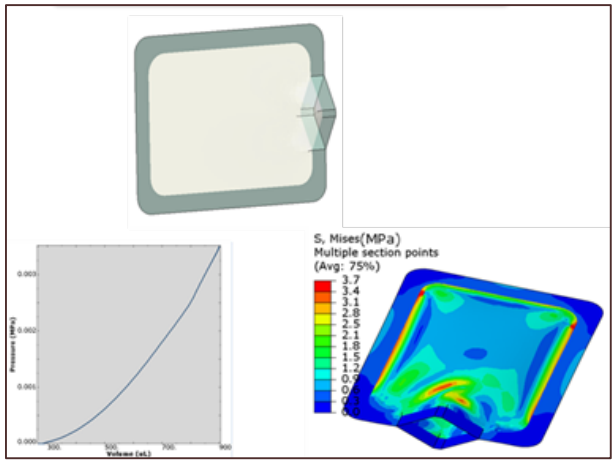
- Easy to use
- Manufacturability
- Drug compatibility
- Dose accuracy
- Residual volume
- Cost

# Case Study 1 (cont)

Applications of Modeling

- Assess mechanical design and materials of construction for stress levels
- Assess pressure as a function of fill volume

- → if the bag were heat sealed, what thermal exposure would the drug product see?



# Case Study 1 (cont)

- What temperature will the drug experience if the top of the bag is heat sealed?
  - Multiphysics analysis (temperature and stress) was performed at the top of the bag
  - Temperature would rise to approximately 44 °C for 1.5s.
- Data were used to design stability testing
  - Intent was to accelerate testing → Total thermal budget would be dominated by stability testing at 37 °C
  - Testing had to be done at 5 °C

# Case Study 1 Summary

- Validation
  - Commercial Software
  - Correct heat transfer coefficients
- Development stability testing show no impurities generated by heat sealing of the bag

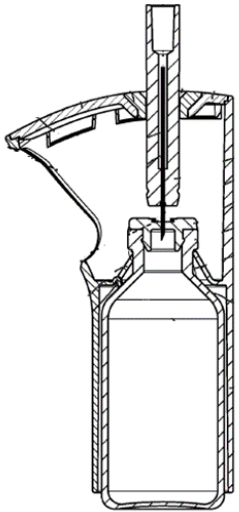
# Case Study 2 – Design of Safety Fixture for Injectable Drugs

- Injectable can be mistaken. Goal of the project was to create a safety fixture and ‘keyed’ syringe to prevent the wrong medicine from being administered.

Image provided by West Pharmaceutical Services, Inc. Copyright 2019©

- Matching colors to coordinate syringe with medicine
- Syringe is ‘keyed’

- Question: Material selection
- Robust mechanical design on locking fingers

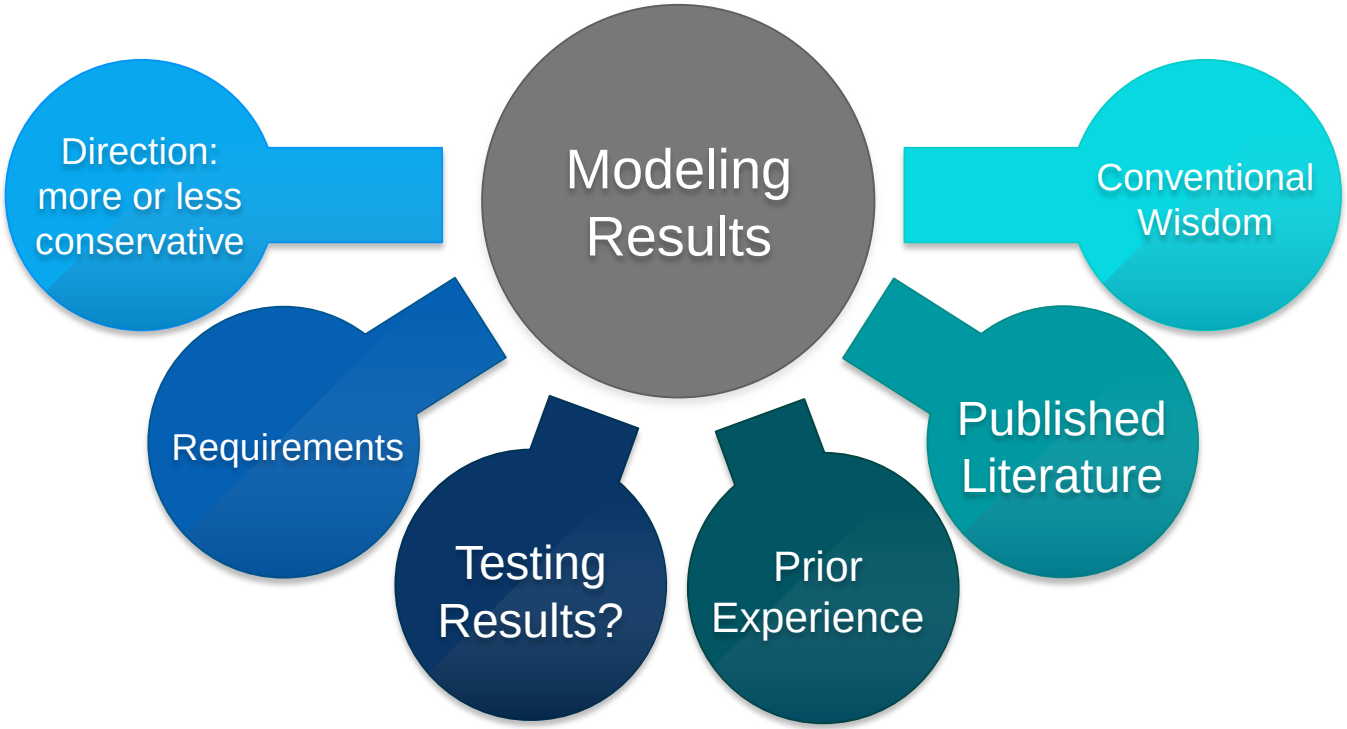


“Secured Medication Transfer System” Eli Lilly & Company, WO 2018/039065 Al

# Case Study 2

- Original thought:  use a polycarbonate for the body of the device
- Mechanical modeling:
  - Revealed that the strain on the ‘fingers’ holding the fixture on the vial exceeded 0.5%
  - Demonstrated the need for a different resin
- Fixtures were molded from both resins → Traditional PC cracked.  Modified resins didn’t
- Strength evaluation was done experimentally

# Decision Tree



# Acknowledgements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