Granules and Pellets PSGs

Study Types and Administration Methods

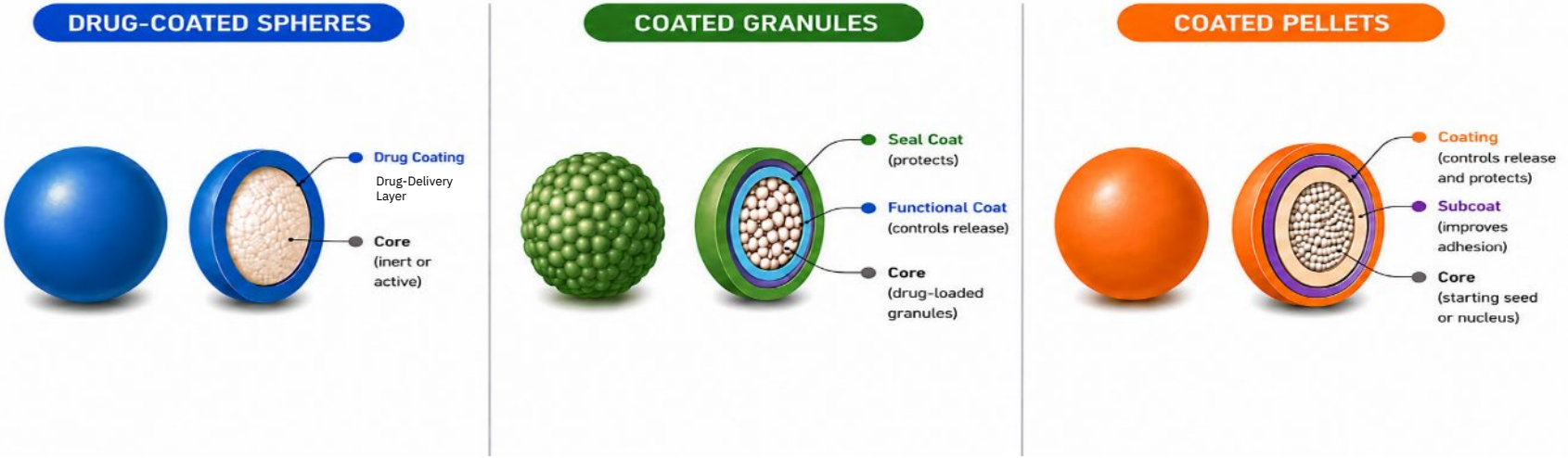
Wen Cheng Yang, Senior pharmacologist

Division of Therapeutic Performance II (DTP II),
Office of Research and Standards (ORS),
Office of Generic Drugs (OGD),
Center for Drug Evaluation and Research (CDER),
Food and Drug Administration (FDA)

Patient-Centric Oral Particulate Products

- **Immediate-Release Oral Particulate Products**
- Examples include:
  - Granules
  - Pellets
  - Microsphere based products (e.g., capsule for beads, or spheres)
  - Tablets, granules, or pellets for suspension
  - Oral suspension
- These products may offer
  - Flexible administration
  - Improved swallowability
  - Pediatric and geriatric utility
  - Better patient acceptability

Granules/Pellets



Coating function — relevant to appropriate administration vehicle and study type

Risk Based BE Approach

Potential sources of BE variability may arise from:

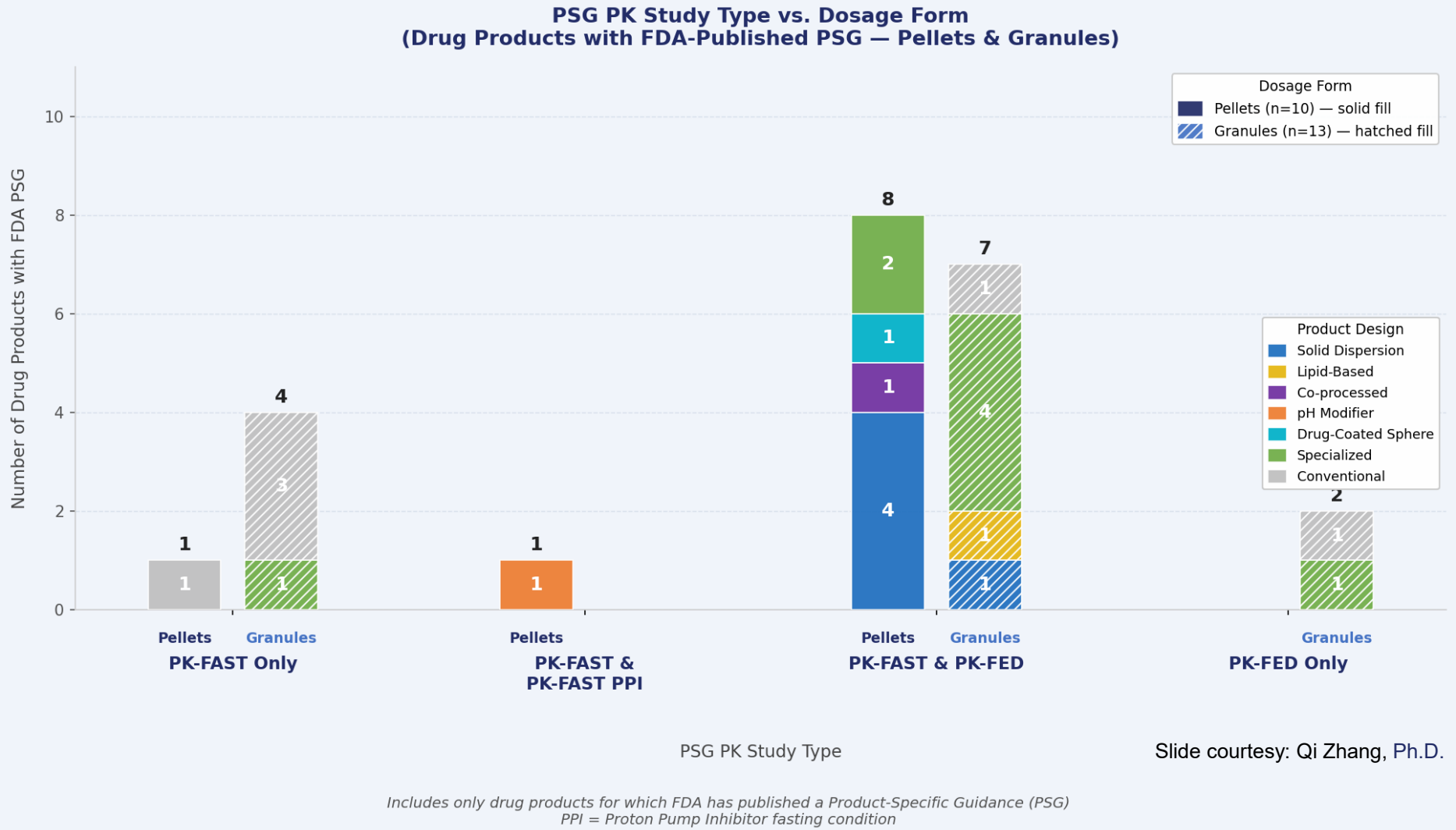
- **Formulation complexity** due to their particle characteristics, complex structure and formulation design (lipid-based, solid dispersion, nanoparticles, etc.), and the critical role of the functional coating in governing drug release
- **Functional coatings** including functional coatings, anti-enteric coatings for taste-masking, moisture/barrier coatings, drug coated polymer-based spheres, etc.
- **Gastrointestinal (GI) risk:** coatings change how drug would be release at different pH; it would lead to the variations in BE under different GI conditions (fasting versus fed)
- **Administration methods with specific preparation instruction**: including swallow with water, or directly or mixed with soft food or liquid

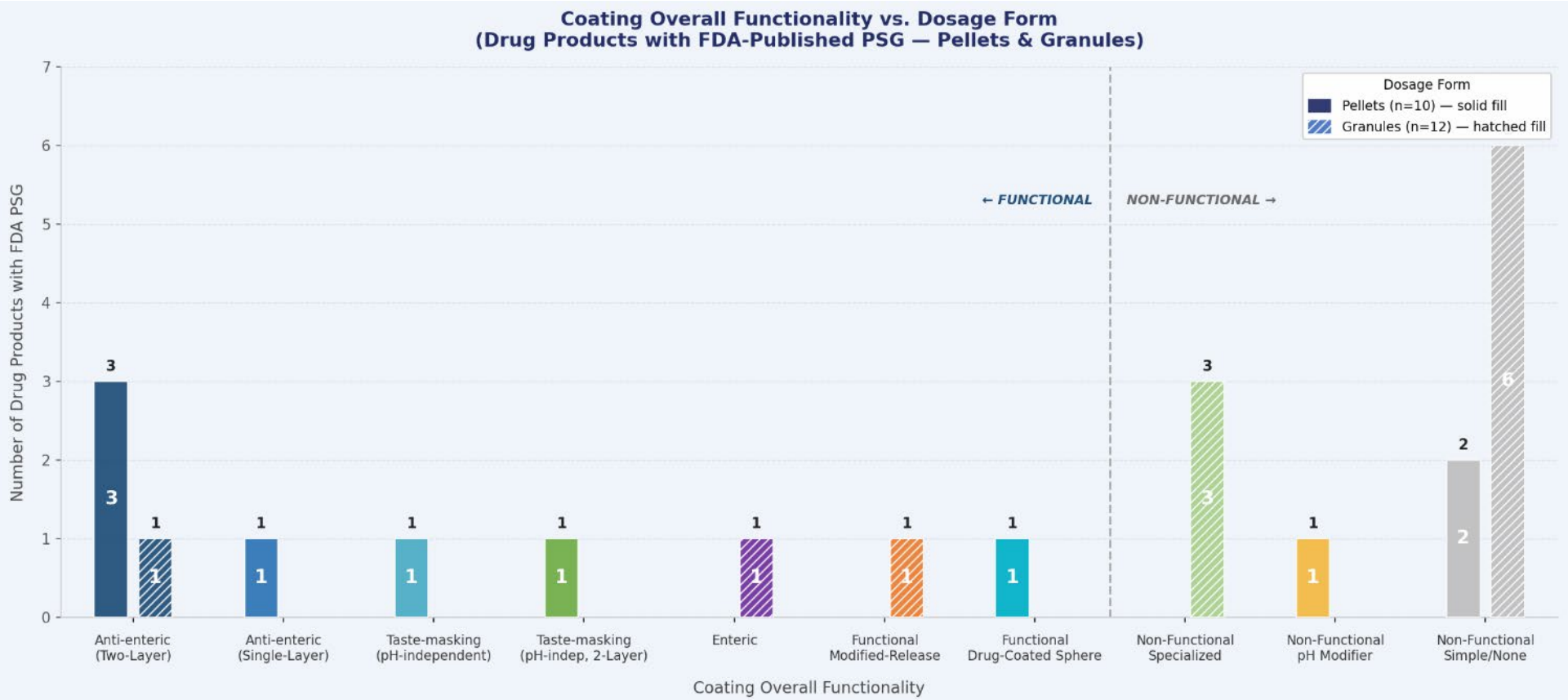
M13A-Study Types and Administration Methods

Scope	Study Type High-risk	Study Type Non-high-risk	Administration Method (Other dosage forms)
• BE based on PK endpoints for orally administered IR solid dosage • **From default two-study recommendation to a risk-based evaluation**	• **Recommends both Fasting AND Fed BE studies** • May need additional studies (e.g., PPI, different strengths)	• **Recommends Fasting OR Fed** • May need additional studies (e.g., PPI, different strengths)	• **Administered according to the comparator product labeling**: e.g., For tablets, granules, and powders labeled as being only intended to be dispersed in a liquid, BE studies should be conducted according to the comparator product label

Slide courtesy: Qi Zhang, Ph.D.

Includes only drug products for which FDA has published a Product-Specific Guidance (PSG).
Specialized = functional/two-layer coating OR specialized matrix excipient | Drug-Coated Sphere = API coated onto inert carrier

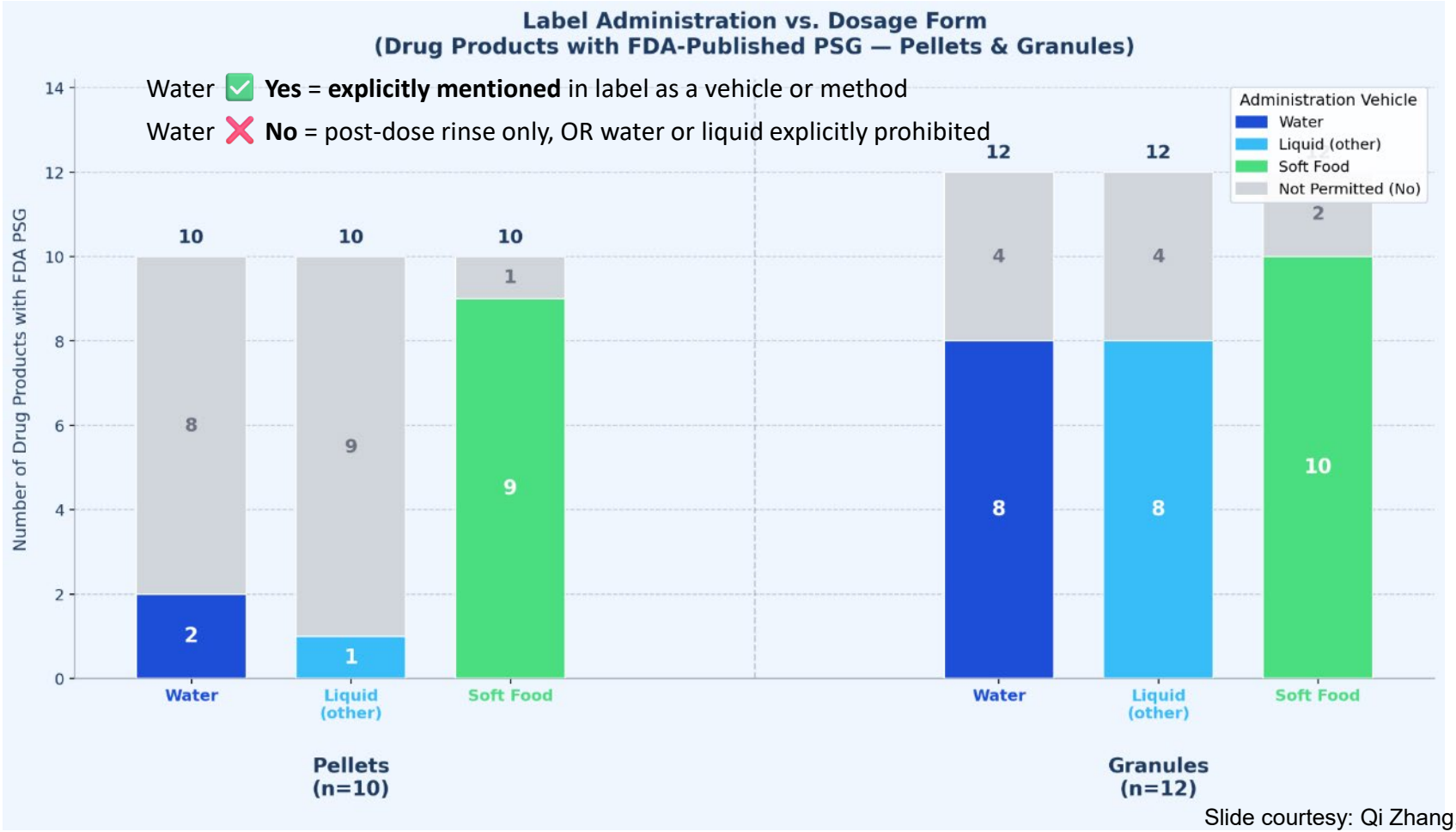

PSG PK Study Type vs. Dosage Form
(Drug Products with FDA-Published PSG — Pellets & Granules)
Dosage Form
Pellets (n=10) — solid fill
Granules (n=13) — hatched fill
Product Design
Solid Dispersion
Lipid-Based
Co-processed
pH Modifier
Drug-Coated Sphere
Specialized
Conventional
Number of Drug Products with FDA PSG
0
2
4
6
8
10
1
4
1
8
7
2
Pellets
Granules
PK-FAST Only
PK-FAST & PK-FAST PPI
PK-FAST & PK-FED
PK-FED Only
PSG PK Study Type
Slide courtesy: Qi Zhang, Ph.D.
Includes only drug products for which FDA has published a Product-Specific Guidance (PSG)
PPI = Proton Pump Inhibitor fasting condition



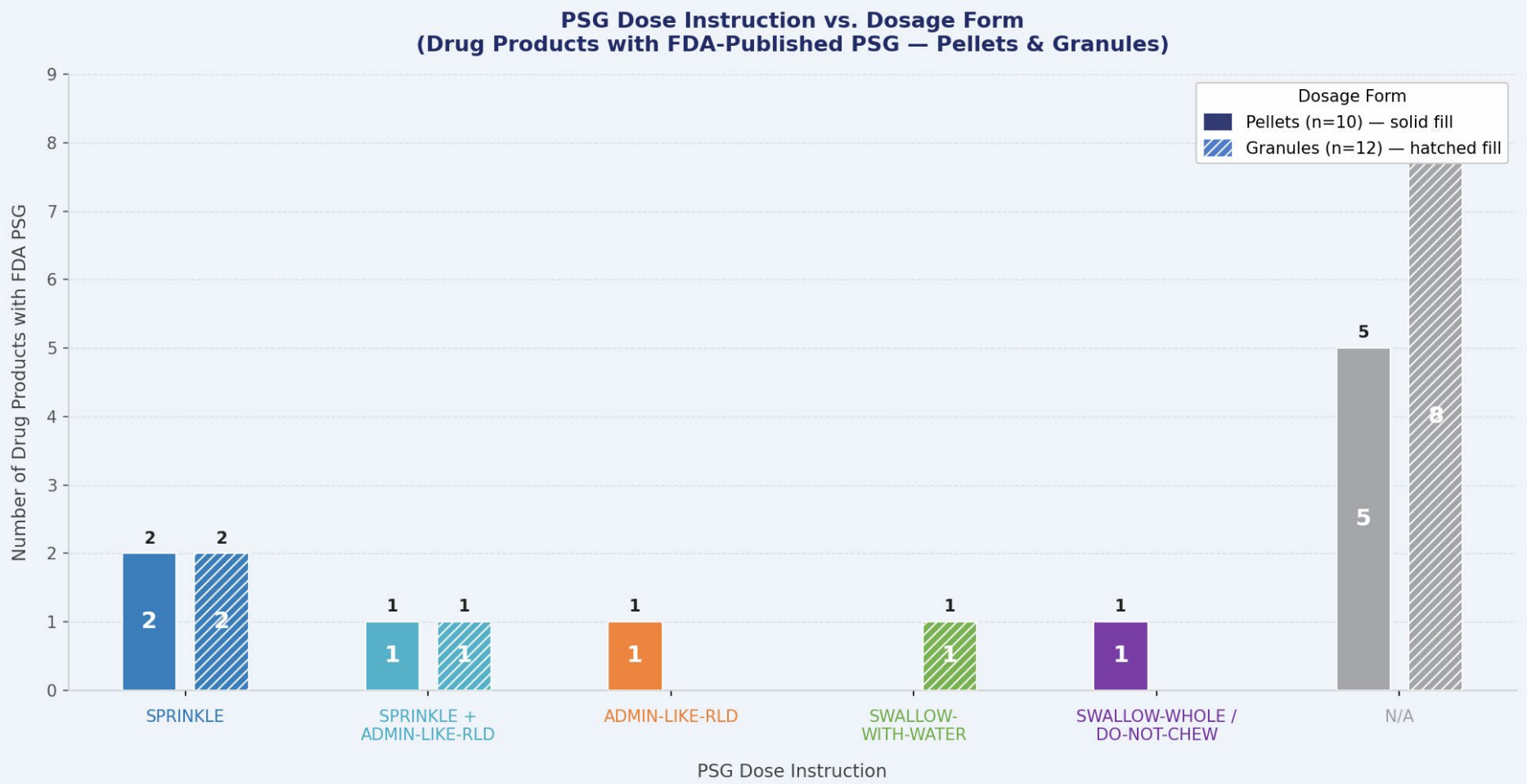
Slide courtesy: Qi Zhang, Ph.D.

Includes only drug products for which FDA has published a Product-Specific Guidance (PSG)

Anti-enteric = gastric-soluble (Eudragit E-type; dissolves pH <5) | Enteric = intestinal-soluble (HPMCAS; dissolves pH >5.5) | Drug-Coated Sphere = API coated onto inert carrier; CEBE required (Odevixibat)



Slide courtesy: Qi Zhang, Ph.D.



Slide courtesy: Qi Zhang, Ph.D.

Includes only drug products for which FDA has published a Product-Specific Guidance (PSG)
SPRINKLE = open capsule/sachet and sprinkle onto food | ADMIN-LIKE-RLD = administer as described in RLD labeling | N/A = no specific PSG dose instruction beyond standard

Case Study 1: Selumetinib Sulfate Granules

- **Indication**: For adult and pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1)
- **Recommended dose**: Based on body surface area (BSA), 25 mg/m^2 orally twice daily
- **Administration instruction**: Sprinkle granules on or mix with a small amount (about 1 to 3 teaspoons) of smooth yogurt, or fruit puree
- **BCS Class IV**
- **PK**: No clinically significant differences in selumetinib pharmacokinetics following low-fat or high-fat meals
- **Approved strengths**: EQ 5 mg Base and EQ 7.5 mg Base
- **High-risk formulation**: lipid-based multi-particulate formulation incorporating a polymer-based functional coating system

PSG Recommendation

Standard path: 2 BE studies: Fasting and fed

BE studies: High risk formulation (lipid-based)

- **Fasting Study (EQ 5 mg Base)**
  - Single-dose, two-treatment, two-period crossover in vivo at a dose of EQ 25 mg Base (5 x EQ 5 mg Base)
  - Healthy males and non-pregnant, non-lactating females
  - Prepare oral granules by carefully opening the capsule and sprinkling all of the oral granules on a small amount (about 1 to 3 teaspoons) of smooth yogurt or fruit puree.
- **Fed Study (EQ 5 mg Base)**
  - Same as above

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_213756.pdf

Case Study 2: Entrectinib Pellets

- **Indications**: Adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC), and adult and pediatric patients older than 1 month of age with NTRK gene fusion-positive solid tumors
- **Recommended dose**: 600 mg orally once daily with or without food for NSCLC; 600 mg orally once daily for adult and pediatric patients with BSA ≥ 1.51 m^2
- **Administration Method:** Sprinkle pellets on one or more spoonfuls of soft food
- **Food effect**: a high-fat, high-calorie meal did not have a significant effect on exposure of entrectinib capsules
- **Drug interactions with PPI**:
  - Coadministration of a proton pump inhibitor (PPI), lansoprazole with a single 600 mg dose of ROZLYTREK capsule reduced entrectinib AUC by 25% and Cmax by 23%.
  - Coadministration of lansoprazole, with a single 600 mg dose of ROZLYTREK capsule as oral suspension in water increased entrectinib AUC by 25% and Cmax by 17%.
- **Approved strength**: 50 mg/Packet
- **Non-high-risk formulation**

PSG Recommendation

Standard path: 2 fasting studies

BE studies: Non-high-risk formulation

- **Fasting Study (50 mg/packet)**
  - Single-dose, two-treatment, two-period crossover in vivo at the administered dose of 200 mg
  - Healthy males and non-pregnant, non-lactating females
  - Use a consistent administration method for test product and reference listed drug (RLD).
- **Fasting study, in presence of an acid-reducing agent (50 mg/packet)**
  - Single-dose, two-treatment, two-period crossover in vivo at the administered dose of 200 mg
  - Healthy males and non-pregnant, non-lactating females
  - Use a consistent administration method for test product and reference listed drug (RLD).

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_218550.pdf

Take-Home Message

- Functional polymer coatings serve to protect drug substances and control drug release at specific pH levels within the GI tract; however, they may introduce higher bioequivalence (BE) risks that warrant careful consideration during product development and regulatory assessment.
- Coated granule/pellet drug products typically carry specific administration instructions in the labels due to their unique dosing and drug release mechanisms; Product-Specific Guidances (PSGs) will consistently provide corresponding administration instructions, filling the gap in regulatory guidance for BE assessment.
- There is growing industry interest in aligning administration instructions for BE studies, and the Agency intends to ensure consistency among food instructions across the Reference Listed Drug (RLD) label, PSGs, and Abbreviated New Drug Application (ANDA) approvals to support a more standardized and predictable regulatory framework.

Acknowledgements

- Qi Zhang, Ph.D.
- Myong-Jin Kim, Pharm.D.
- Robert Lionburger, Ph.D.
- DTP II, DQMM, ORS
- Elsa 4.0