Bristol Myers Squibb®

Shaping the Future of Pediatric Formulation Development

Minitablets and Drug Product Nomenclature

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24th June, 2026

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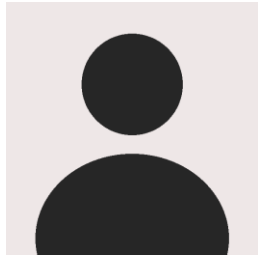
- Pharmacist & Formulator
- Over 21 years at BMS with 14 years dedicated to paediatric drug product development
- Member of the BMS Pediatric Centre of Excellence
- Member of the IQ Pediatric Working Group

IQ Minitablet Nomenclature Team

- Cheryl English
  - Senior Director, Regulatory CMC
  - Pfizer

- Jole Rodriguez
  - Regulatory Affairs CMC
  - Eli Lilly



- Peter Kuehl
  - Roche

- Joanna Koziara, PhD
  - Head of Technical Development Business Strategy and Operations
  - Gilead Sciences

- Matt Santangelo
  - Senior Scientist - Drug Product Design
  - Pfizer

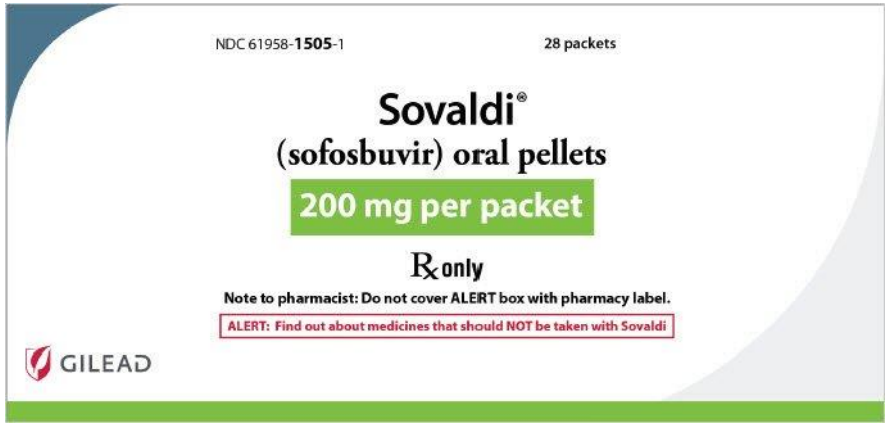
- Bhanu Bejgum, PhD
  - Senior Principal Scientist, Drug Product Technologies
  - Amgen

Evolving paediatric dosage forms

- Moving beyond conventional liquids, tablets and capsules
- Increasing use of novel / flexible dosage forms, including minitablets
- Growing need for global alignment in terminology

Lack of harmonisation in dosage form terminology

- No globally harmonised nomenclature exists for oral multiparticulate solid dosage forms
  - The term “minitablets” is not formally recognised by Health Authorities
- USP and Ph. Eur./EDQM frameworks are misaligned
- Terminology used in development is not consistently recognised by Health Authorities
- Sponsors must adapt regulatory filings, labels and lifecycle management across different health authorities
- What should we call minitablets?



US patient information leaflet

SOVALDI® (sofosbuvir) tablets, for oral use
SOVALDI® (sofosbuvir) oral pellets
Initial U.S. Approval: 2013

UK patient information leaflet

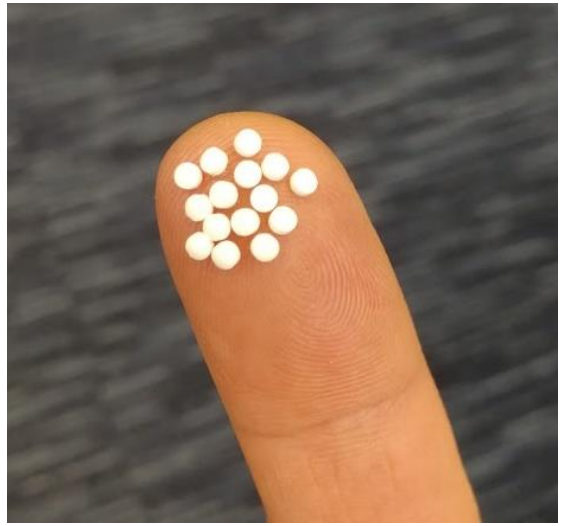
Package leaflet: Information for the user

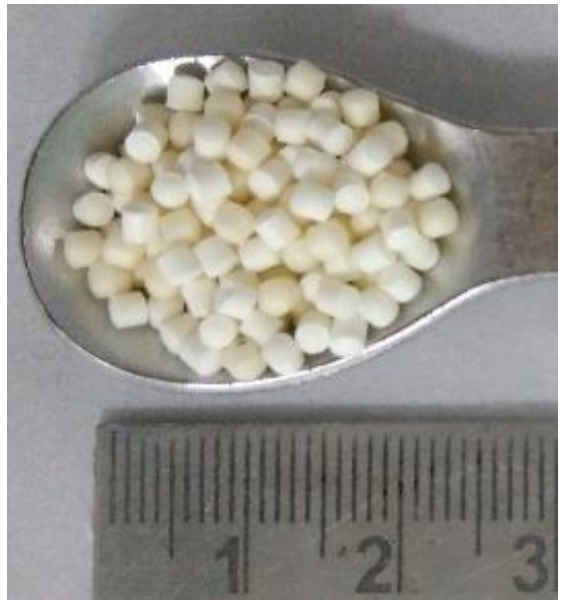
Sovaldi 150 mg coated granules in sachet
sofosbuvir

What is a minitablet?

What are minitablets and why do we like them?

- Tablets ≤ 2.5mm diameter (typically 2.0mm)
  - FDA Guidance for Industry "Size of Beads in Drug Products Labeled for Sprinkle Rev.1", May 2012
- Use adult tablet formulation
  - Leverage experience and reduce development work
- Solid dosage form better for stability and dose accuracy
  - A priority for developing countries (WHO)
- High dose-flexibility by adjusting minitablet number
- Can mix with food for administration
  - Best suited for patients aged 6 months and older
  - Typical to ween children on to semi-solid foods at this age
- Can easily be coated for taste masking
- Package into sachets to present as a single unit dose





Nomenclature

What should we call them?

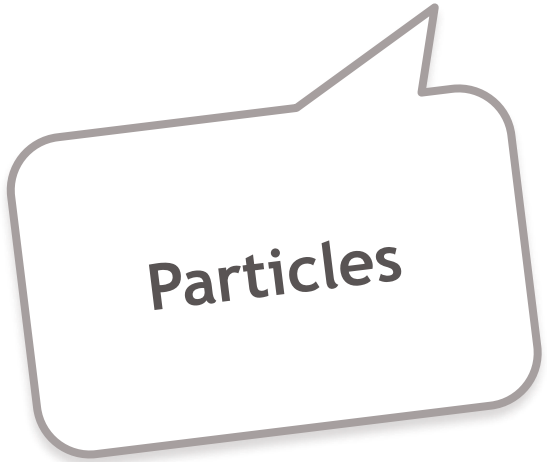

Beads


Granules


Pellets


Sprinkles


Minitablets


Particles

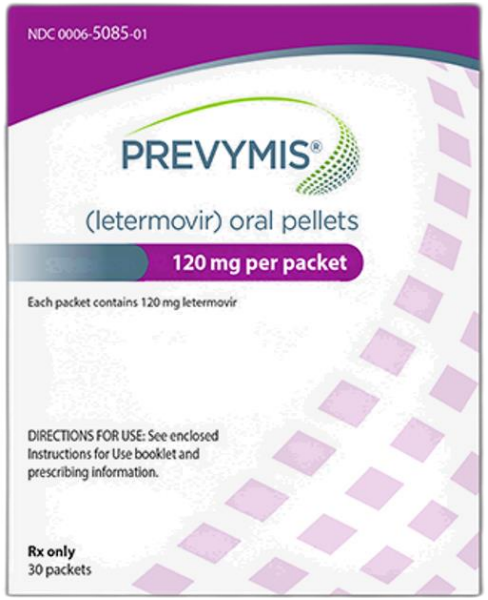
Drug product development

- Manufactured as discrete units
- Unit defined before dose → faster, more efficient development
- Dose achieved by adjusting unit number
- "Minitablets" used consistently across development

  → Carried into regulatory filings

FDA feedback received by IQ members

*In the IND, the drug product is referred to as **tablets, mini-tablets and oral granules**. We refer you to USP <1151> for the dosage form nomenclature for this drug product. Per USP <1151>, **pellets** are small solid dosage forms that can be designed as single or multiple entities.*



https://www.merckconnect.com/prevymis/hsct-dosing-administration/

The European perspective

- EDQM Standard Terms define dosage form terminology in EU submissions
- Multiparticulate oral dosage forms are classified as 'Granules' (and variants)
- 'Medicated pellets' exclusively for veterinary use.
- No 'oral pellets' term for human medicines.

https://standardterms.edqm.eu/

Pharmacopeial definitions - circa 2009

- **USP ⟨1151⟩ Pellets**: "See Implants" — defined as small sterile solid masses intended for implantation in the body, usually subcutaneously. No oral pellet dosage form existed.
- **USP ⟨1151⟩ Granules**: No discrete entry. Granules were referenced only within the **Powders** section as an alternative form for drugs unstable in liquid dosage forms — "Drugs that are unstable in aqueous suspensions or solutions may be prepared in the form of granules or powders.“

- **Ph. Eur. (0499) Granules**: Solid, dry aggregates of powder particles sufficiently resistant to withstand handling, intended for oral administration — swallowed, chewed, or dispersed in liquid. Granules are presented as single-dose or multidose preparations. For single-dose granules, each dose is enclosed in an individual container, for example a sachet, a paper packet or a vial.
- No definition for pellets

- “Granules” was the most suitable available term for minitablets.

Pharmacopeial definitions – currently official

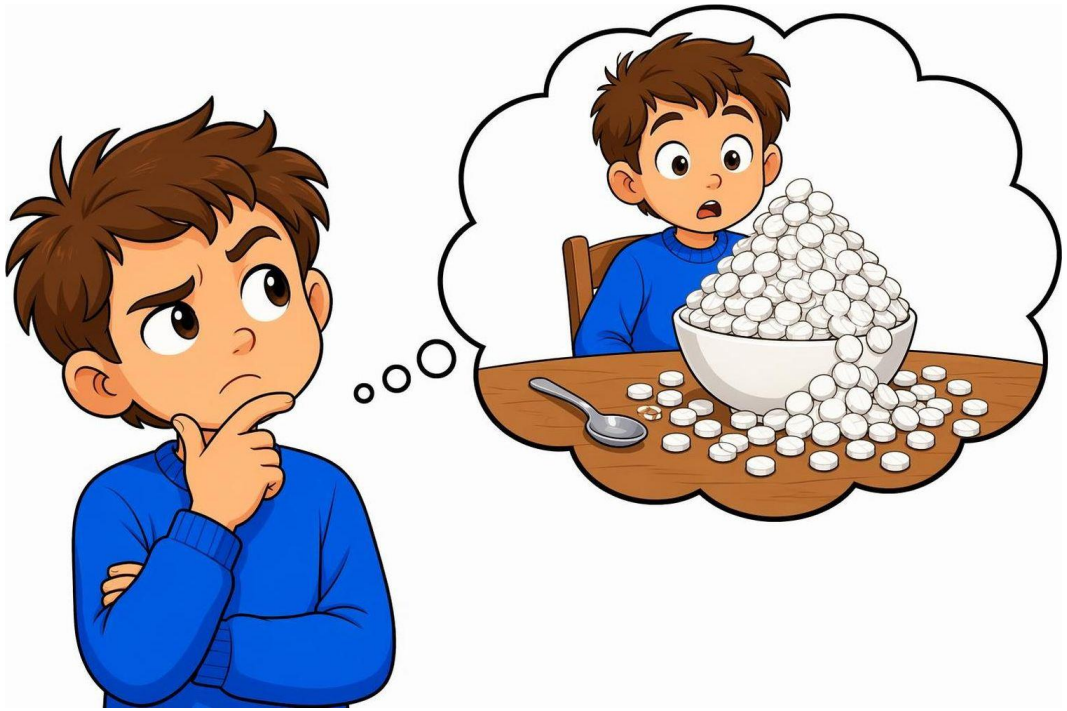
- **USP ⟨1151⟩ Pellets**: Small solid dosage forms, single or multiple entities, spherical shape not required. Oral administration including sprinkle on food. Manufactured by compression, extrusion/spheronisation, or coating.
  ⚠ Note: Despite stating that 'pellet' for implantable dosage forms is "no longer preferred," there are references to injectable/surgical administration; and states that manufacture by compression is largely restricted to the production of material for subcutaneous implantation.
- **USP ⟨1151⟩ Granules**: Granules are defined as solid dosage forms composed of agglomerations of smaller particles, prepared for oral administration to facilitate flexible dosing, taste masking, and administration to special populations. Often used as pharmaceutical intermediates for tablet compression or capsule filling, though numerous commercial products are granule-based.

- **Ph. Eur. (0499) Granules**: The core definition is essentially unchanged; however, it was revised to include "very small tablets (rather than granules) presented in a sachet intended for oral administration as a single dose." This is clearly appropriate for minitablets.
- Ph. Eur./EDQM: no "pellets" term for human medicines

Shift from “oral granules” → “oral pellets” in US-approved products over time

#	Product Name	Active	Company	US Approval year
1	Lamisil Oral Granules	Terbinafine hydrochloride	Novartis	9/28/2007
2	Zenpep Delayed-release Capsules	Pancrealipase	Eurand Pharma LTD	8/27/2009
3	Pancreaze Delayed-release Capsules	Pancrealipase	McNeil Pediatrics	4/12/2010
4	Kalydeco Oral Granules	Ivacaftor	Vertex Pharmaceuticals	3/17/2015
5	Tekturna Oral Pellets	Aliskiren hemifumarate	Noden Pharma	11/14/2017
6	Orkambi Oral Granules	Ivacaftor; lumacaftor	Vertex Pharmaceuticals	8/7/2018
7	Harvoni Oral Pellets	Ledipasvir; sofosbuvir	Gilead Sciences	8/28/2019
8	Sovaldi Oral Pellets	Sofosbuvir	Gilead Sciences	8/28/2019
9	Epclusa Oral Pellets	Sofosbuvir	Gilead Sciences	6/10/2021
10	Mavyret Oral Pellets	Glecaprevir; pibrentasvir	Abbvie	6/10/2021
11	Trikafta Oral Granules	Elexacaftor; tezacaftor; ivacaftor	Vertex Pharmaceuticals	4/26/2023
12	Entresto Sprinkle Oral Pellets (in capsule)	Sacubitril; valsartan	Novartis	4/12/2024
13	Prevymis Oral Pellets	Letermovir	MSD	8/30/2024
14	Orladeyo Oral Pellets	Berotralstat	Biocryst	12/11/2025

What to call minitablets?



- The term “minitablets” is not formally recognised by Health Authorities
- It remains a practical and intuitive name within Pharm Dev (unit-based dosing)
- However, terminology may be misinterpreted outside Pharm Dev → “tablets” can imply administration of multiple conventional tablets
- Using “pellets” or “oral granules” aligns with regulatory expectations and broader understanding; but cannot be aligned across both FDA and EMA at present

Call to action: harmonise dosage form nomenclature

- Increasing use of multiparticulate dosage forms, particularly for paediatric patients
- Current terminology is not harmonised across pharmacopeial definitions and regulatory application
- This creates:
  - Regulatory risk (inconsistent labelling across regions)
  - Filing complexity and potential delays
  - Cross-functional confusion (CMC, regulatory, clinical)
- Global terminology variation extends beyond FDA and EMA to other Health Authorities (e.g., China, Japan)
- Harmonised nomenclature is needed to support consistent global development of paediatric medicines and simplify regulatory submissions

Thank-you