Tom Quinci and Keith Henry, Leaders of Partnering and Business Development at Celanese

"Localized and systematic drug delivery for sustained release: small molecules, peptides, mAbs and RNA"

VitalDose is a flexible and biodurable polymeric (ethylene vinyl acetate [EVA]) drug delivery platform for patient-centric, portfolio-enabling solutions.

Systemic or localized drug delivery.

- Diverse dosage forms contain a range of API amounts. Typically:
  Intravitreal <1mg; Ocular Insert 5-10mg; SC Implant 50-200mg; and Intravaginal Ring 1000-2000mg.
- New form factors can be developed, particularly for localized delivery (e.g., anchor the implant for intra-tumor delivery).

Long implant duration with sustained drug release across dosage forms (6 months and beyond).

- EVA is biostable (Contraceptive implant remained implanted with sustained release for 3 to 5y) and retrievable, if needed.
- Tunable drug release via core matrix (drug loading, E:VA ratio, process, excipients) and platform construction (monolithic vs multilayer-membrane type).

Broad API compatibility.

- EVA matrix can be formulated with diverse APIs from small molecules to high molecular weight proteins such as monoclonal antibodies and solubility).
  Peptides, small molecules, biologics, and RNA therapeutics have been successfully released from the EVA system.

Broad therapeutic applicability.

- Currently translating the platform for oncology, rare diseases, ophthalmology, women's health, CNS, infectious diseases, and endocrinology applications.

VitalDose pipeline.

Internal Programs are in early-stage development (Feasibility to Preclinical).

- Formulation work to assess stability and release of different molecules (small molecules to biologics).
- Development of model compounds for different treatment indications. Examples include:
  Small molecules (solid tumor oncology; ocular inflammation; glaucoma; psychiatric disorders; and osteoporosis).
  mAbs (immunotherapy for solid tumor oncology, including localized therapy).
  RNA therapeutics (retinal disorders).

Partnered Programs span development (Feasibility, Pre-clinical, Clinical, and Marketed products).

- Development of fit-for-purpose devices with partners seeking long-acting solutions. Examples of existing partnerships:
  Population Council (sustained-release dual-API); Bachem (LA sustained delivery of peptides); Nanoform (enhanced drug delivery through small implants); Glaukos (sustained release of glaucoma treatment); Alessa Therapeutics (advancement of oncology treatments); JHU (sustained ocular drug delivery to suprachoroid space); Bill and Melinda Gates Foundation (LA refillable contraceptive device).

Common device configurations.

- Core matrix.
  Dissolution and diffusion-based strategies; Tunable parameters include drug loading, particle size/distribution, process, and excipients.
- Range of APIs.
  Single and co-administration of APIs is possible (segment different implant types or incorporate multiple APIs into the polymer matrix).
- Platform construction.
  Monolithic-type implants are a primary focus; Multilayer membrane design for rate-control functionality, if needed.
- Technical design freedom.
  Size, geometry, and other options for delivery routes; may need to develop a form factor.

Internal formulation work – *In vitro* studies demonstrate differential drug release using different core matrix and platform constructions.

Small molecules.

- API diffuses through the EVA matrix and EVA membrane for sustained release.

- Higher E:VA ratios (40% vs 28% vs 9% VA) and higher drug loadings (40% vs 50% vs 60% ISL in EVA) yield higher release rates.
  - ***High-loaded systems are typical (60% to 80% API in EVA), and release rates can become quite high.***
- Multilayered membranes yield lower release rates than monolithic membrane construction.
  - ***We are developing the engineering know how to modulate the release of high-loaded small molecule systems using multi-layer membranes.***

Large molecules.

- API elutes by migrating through a network of microporous channels.
  - Multi-layer membrane construction modulates the release rate observed with monolithic construction.
  - ***We are developing engineering know-how, expertise, and IP around how to control and modulate the release of biologics to achieve a variety of dosing-type profiles*** (i.e., how to form the core matrices and how to develop and form the membranes).

Simultaneous development of product technology and scalable process technology.

Hot Melt Extrusion (HME) is simple and scalable.

- Drug and polymer are dry blended (ground EVA + powdered API) and is fed into HME to yield the final product form.

EVA matrix is inherently flexible and biostable.

- Favorable physicochemical characteristics.
  Low melting, thermoplastic, biologically and chemically inert, non-resorbable; water insoluble; and alcohol insoluble.

In vitro studies demonstrate the stability and sustained release of Trastuzumab (mAb).

- Formulation conditions: Monolithic implant processed via HME (45% API loading; pH 7.4 PBS buffer at 37° C).
  *Stability confirmed via SEC analysis.
- HME processing does not impact mAb stability (mAb stability maintained for 6 months post extrusion); Minimal protein aggregation noted; Achieved sustained release > 6months.

Summary.

- Many internal programs are in early-stage development – we are developing model compounds for diverse indications (Prototype and formulation development; prototyping; and drug-release testing).
- We leverage internal engineering know how (product and process technology) and inherent features of the VitalDose EVA drug delivery platform to achieve long-release profiles.
- A current engineering focus is how to form core matrices and how to develop and form multi-layer membranes (micro-porous systems) to control and modulate the release kinetics of small and large molecules.

"What could you do with some of these neutralizing antibodies or other modalities that might be in your thought process? I think we can do quite a bit. Celanese had demonstrated compatibility with these agents and we are actively seeking new partnerships and collaborations to develop drug-products for clinical evaluation."