Designing a Modular CMC Platform for Lentiviral Gene Therapies

Session: Leveraging Prior Knowledge in Early Development of ATMPs

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Targeting lysosomal storage disorders as a disease group

Fondazione Telethon: Mission and Vision

We are a ***non-profit*** Italy-based organisation founded in 1990 in response to calls by people suffering from ***rare genetic diseases***

OUR MISSION

ADVANCE BIOMEDICAL RESEARCH TOWARDS THE CURE OF RARE GENETIC DISEASES

OUR VISION

CONVERT THE RESULTS OF EXCELLENT RESEARCH INTO THERAPIES AVAILABLE FOR ALL PATIENTS

- Two intramural institutes, ***San Raffaele Telethon Institute for Gene Therapy*** (SR-TIGET) and ***Telethon Institute of Genetics and Medicine*** (TIGEM).
- Pipeline from pre-clinical through marketing stages covering ten different indications.
- In 2023, FTELE became the first non-profit marketing authorization holder of a cell and gene therapy medicinal product (Gene therapy for ADA-SCID)

OUR TRACK RECORD

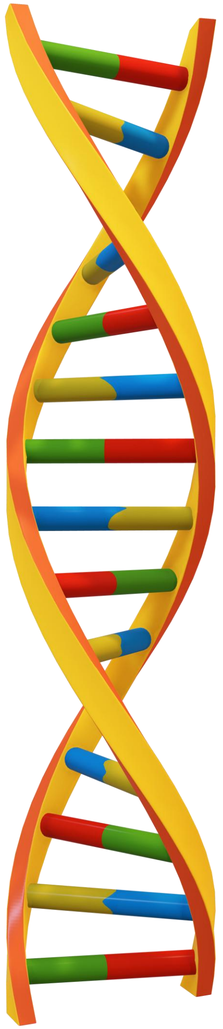
- **698** million euro invested
- **1,771** researchers
- **3,024** funded projects
- **637** studied diseases
- **86** patented inventions
- **19** orphan drug designations (17 EU, 2 US)
- **153** treated patients
- **2** marketed therapies

Why a platform model is important for rare genetic diseases

- Development of ATMPs for ultra-rare diseases is ***disregarded by major industry investments***
    - high development and maintenance costs
    - compensated only by a few treatments per year

- When addressing a group of diseases, similar in terms of pathophysiological mechanisms, target tissues and genetic mechanism, a **platform development approach** can be drawn up

- ***One-disease-at-a-time development*** to a ***many-diseases-at-a-time*** parallel approach that focuses on ***biological and modality-relevant commonalities*** across different diseases



Platform benefits

Developers

- ✓cost savings
- ✓shorter development timeline
- ✓portfolio strategy

Patients

- ✓earlier access to new life-saving therapies
- ✓shared impact on similar diseases patient communities

Regulators

- ✓streamlined regulatory processes

Appropriately using funds for small patient populations

- **7000 types of rare disease in existence**
- **approximately 300 million people live with rare diseases**
- **about 30% of children with a rare disease die before age 5 years**
- **about 95% lack approved treatments**

(Data source: *The landscape for rare diseases in 2024*, The Lancet Global Health)

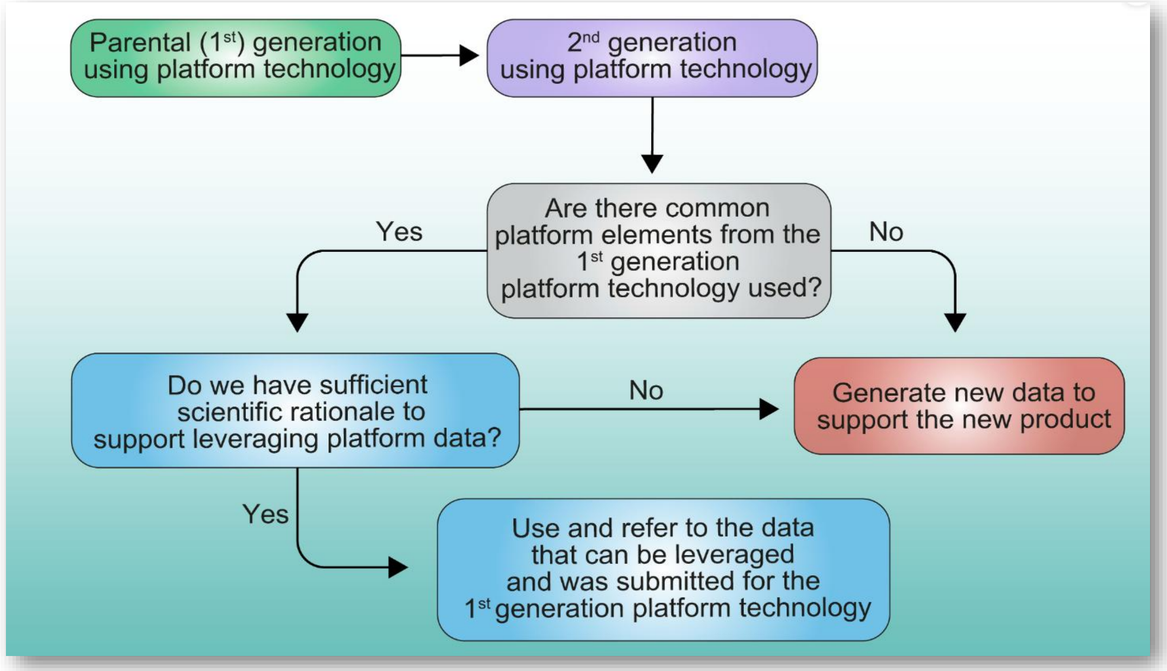
This “simultaneous/platform” approach should:

- increase the development success rate
- reduce development time and costs
- leveraging on scientific robust platform data
- avoid repetitions and the use of unnecessary animals
- while safeguarding products’ quality and patient safety

Thus **maximizing the potential return on the overall investment through spreading of costs across multiple diseases** thus potentially making the ***development of ATMPs for ultra-rare diseases more sustainable***.

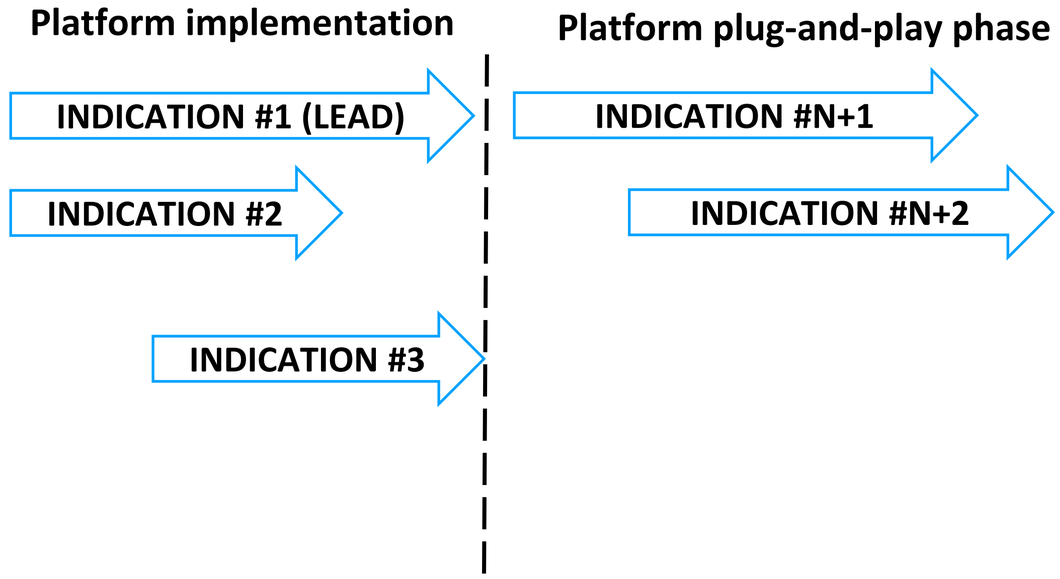
Two different implementation models of Platform ATMP development approaches: leveraging data across products

PARENT-CHILD APPROACH



Ammar *et al*. 2023, Frontiers in Immunology

FONDAZIONE TELETHON PARALLEL-SEQUENTIAL APPROACH

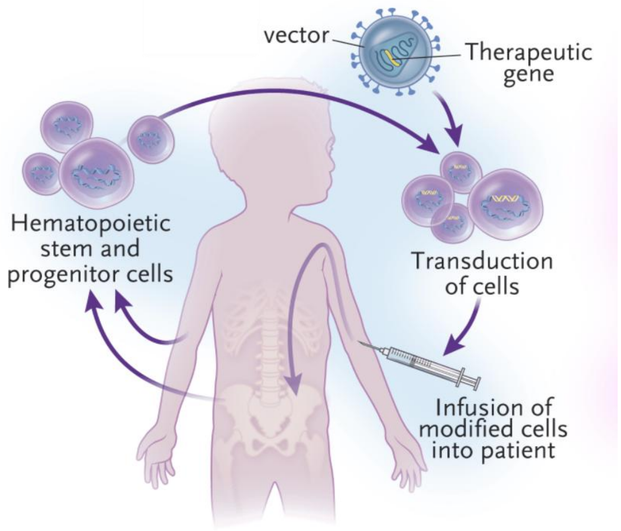


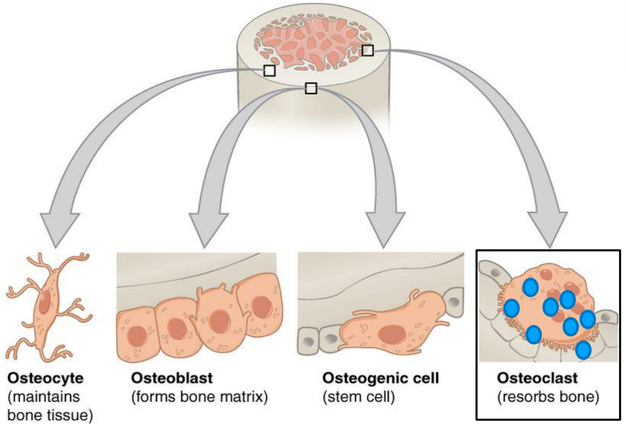
Fondazione Telethon's Case Study: ex vivo gene therapies for lysosomal storage diseases with skeletal involvement

To leverage the power of the **platform vector construct** and **disease relatedness** to help deliver on the promise of gene therapy to patients with rare diseases of limited commercial interest

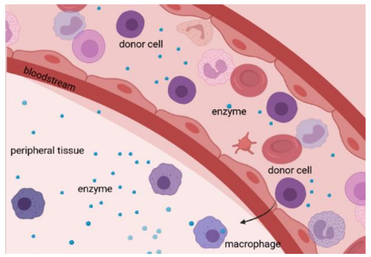
In parallel, to fully exploit and value development data already obtained in previous HSPC-GT programs at SR-Tiget

Working hypothesis for LSD with skeletal involvement

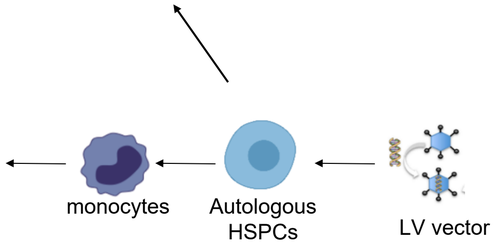




Resident microglia and osteoclasts cell source of enzyme



Circulating myeloid and lymphoid cell source of enzyme



Cross-correction of non-hematopoietic cells is mediated by the release of therapeutic enzyme at supraphysiologic levels from gene-corrected derived circulating and resident cells

Fondazione Telethon's Case Study: A platform approach for the treatment of multiple lysosomal storage disorders

Leveraging on the **similarities among lysosomal enzymatic disorders**:

- Type and localization of the defective enzyme
- Possibility of the enzyme of being secreted and internalized by neighboring cells
- Clinical phenotype of affected patients

Lysosomal Storage Disorder (LSD) Platform

Horizon scanning to select LSDs

	LSD #1	LSD #2	LSD #n
Inheritance/prevalence	AR, 1:71,000	AR, 1:179,000	AR, 1:500,000/1,000,000
Gene	Gene #1	Gene #2	Gene #n
Enzyme	Enzyme #1	Enzyme #2	Enzyme #n
Accumulation	Oligosaccharide(s) #1	Oligosaccharide(s) #2	Oligosaccharide(s) #n
Skeletal involvement	skeletal and joint abnormalities, short stature, coarsening of facial features		
CNS involvement	NO	YES (mild)	YES
Immunological involvement	NO	NO	YES
Enzyme replacement therapy	YES	NO	YES
HSCT	YES	NO	YES

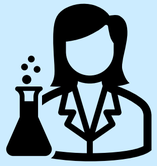
Platform approach v 1.0

Fondazione Telethon Platform Strategic Impact

Institute Development

Fondazione Telethon Institute

- Disease concepts & pathophysiology
- Technology
- Processes
- GLP Tox approach

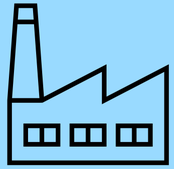


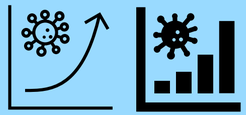
Expert Team

CMC development

Expert Know-how for manufacturing & Quality management

CDMO GMP





Similar Quality testing using matrixing and leveraging

Quality outputs similar

Cell therapies / lines

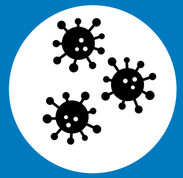
plasmids

Gene therapies

SAME CMC

Clinical

High Quality GMP Medicinal Products

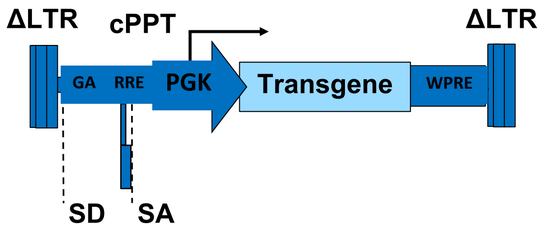


Reduced timelines and costs for trials and Patient treatment

Areas that can be cross-utilised in the Platform model – view across CMC, non-clinical and clinical

Key Starting Materials

- **3 packaging plasmids**
- **1 disease-specific transfer plasmid**



Identification of QTPPs, CQAs, Manufacturing steps, stages, IPCs, CCP, CMAs

293T cell line

Platform LVV manufacturing

Patient cell transduction (HSPC)

Patient CD34+ cells

Medicinal product packaging

Medicinal product administration

Key Enabler

Same LV construct

Difference is Transgene for treating disease

(LVV is Platform)

Fixed components

Pre-defined variable components

Areas that can be cross-utilised in the Platform model – view across CMC, non-clinical and clinical

- Same LV manufacturing & purification process
- Same baseline Quality Assays (+ product-specific testing)
- Same cell-transduction process
- Same packaging & administration route
- Same Quality metrics & risks/controls

Robust, Reliable and Reproducible Development steps

LEAD PROJECT (#1 LSD)

FULL Data Package:

- Main CMC data package
- Full Non-Clinical data
- Full Clinical data

LEVERAGING

PLATFORM PROJECTS (#2 LSD, #3 LSD)

REDUCED Data Package:

- Completion of CMC data package
- Supportive Platform data
- + Product-specific data

Cross-utilisation in CMC, non-clinical and clinical areas – fixed components

CMC	Non-clinical	Clinical
• Therapeutic plasmid #1, #2, #n • Autologous HSPC #1, #2, #n • Identity & Potency test #1, #2, #n • ATMP #1, #2, #n	• Toxicology test #1, #2, #n • Biodistribution #1, #2, #n	• Disease #1, #2, #n • IMP #1, #2, #n

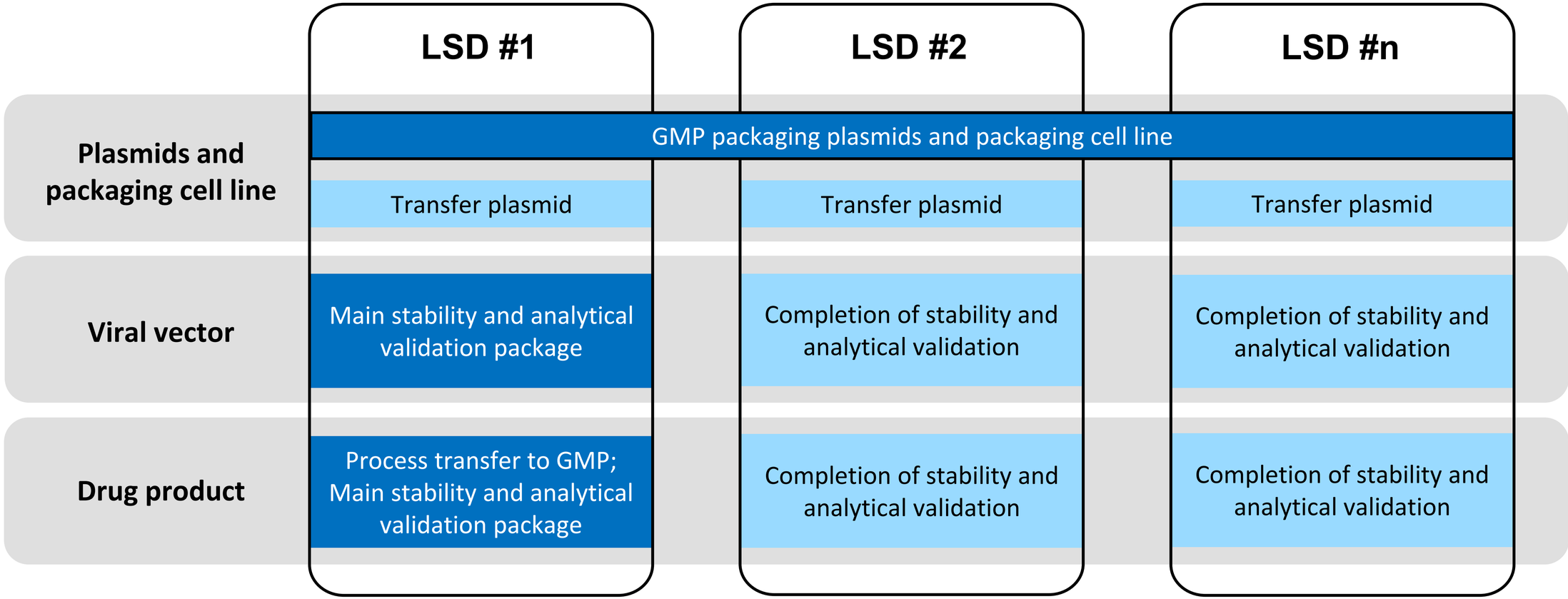
Assessment of variability of the source material from different patients and subsequent impact on drug product and CQAs

Control Variability: ICH Q9 FMEA risk assessment as a QbD approach
Patient → QTPP → CQAs → CMC Control strategy.

Cross-utilisation in CMC, non-clinical and clinical areas – variable components

CMC	Non-clinical	Clinical
• Packaging cell line • Packaging plasmids • Transfer plasmid design • LV vector design • CDMO & manufacturing processes • Drug product release panel • Drug product shelf-life	• Toxicology control group • Integrated biodistribution analysis	• Umbrella Ph I/II clinical trial
→ matrix of analytical and manufacturing validation and long term and in-use stability studies generating **manufacturing platform data** instead of a full data package for each product	→ matrix of GLP studies generating **GLP platform data** instead of a full data package for each product	→ single **platform clinical protocol** to test the safety and efficacy of three different IMPs

Developing a design space for plasmids, vectors, drug product, analytics and supply chain without duplication



Specific opportunities and challenges/areas of limitation when using this model

Considerations

- *Each drug product will stand alone at MAA*
- *Cross-referencing of data to achieve more rapid translation of concept to clinic*
- *Platform CMC verification and validation could be enabled for early translation considering the similarities between the products*

Specific opportunities

- *Lack of consensus on Platform definition do not readily facilitate translation from concept to clinic*
- *Clinical trial cross-referencing may not be fully appropriate*
- *Moving away from a one-disease-at-a-time strategy for the manufacture*

The main area of discussion and further optimization

- *Ensure the minimum dataset to support each product as a standalone*
- *Developing robust, phase appropriate, but ultimately acceptable at MAA methodologies and ways to present the attribution of residual risk and mitigations to fixed and variable components*

Standard vs Platform approach

Product	Standard Approach	Platform Approach
LSD GT #1	Single stability package; Single analytical validation package; Specific release panel	Full stability study on the first indication, reduced panel for 2nd product onwards
LSD GT #2		Analytical validation package performed as combined approach (e.g. one representative batch from each indication)
LSD GT #3		Same release panel (except for potency and identity product-specific)

Concepts for risk mitigation and acceptance of risk in relation to CMC design space

RISKS

Different stability profile of the three products

Different product characteristics affecting the interference of the substrate with the analytical method

Differences in impurities/residuals

MITIGATION

Transgenes with similar length and proteins with similar localization and function

Products resuspended in the same formulation medium

Transgenes encode for enzymes with similar function and end localization

Platform approach v 2.0 – Integration of prior knowledge

Prior Knowledge

Internal knowledge from a company's proprietary development and manufacturing experience

External knowledge such as reference to scientific and technical publications

FT is holder of two marketed products and sponsor of approved phase I/II clinical study

Modules definition

Plasmid

- Specification: easy set-up or same of alredy used
- Stability already available or supportive for transfer gene
- Analytical procedures already in place or easy to adapt

LVV

- Specification
  - Easy set-up
- Stability
  - Leverage on collected data from available studies
- Analytical procedures
  - leverage on platform approach and available data

Drug product

- Specification
  - Easy to set-up (only potency and identity specific)
- Stability
  - Leverage on similar products using HD material
- Process development
  - Leverage on availabe data for identification of risks/CQA/controls

Example 1: LVVs stability study

Prior knowledge

LVV with identical or very similar manufacturing process and same formulation

+

Platform approach

Complete validation stability for lead indication + completion with other two

→

Integrated approach

Complete validation stability for lead indication +reduced stability for other LVVs

Supporting data

Different transgenes do not affect stability of LVVs

Similar trends of stability data from prior knowledge (e.g statistical analysis)

Preliminary stabilty data on LSD LVV

Example 2: Validation of Analytical procedure for safety (DP)

Prior knowledge

Same analytical procedures for different DP with same formulation

+

Platform approach

Combined approach (i.e. one representative batch from each indication)

→

Integrated approach

Validation performed using DPs from only one or two indications

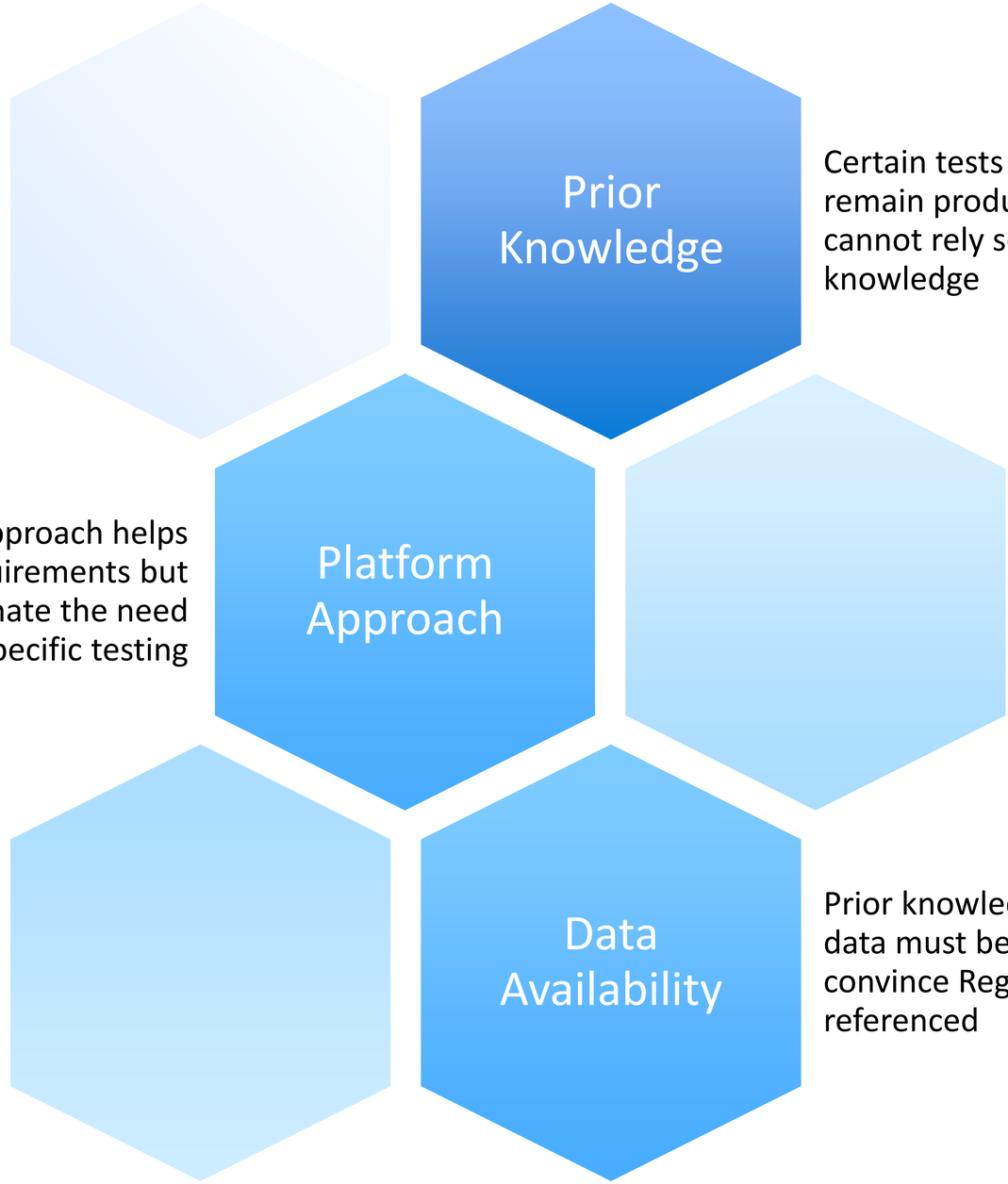
Supporting data

Demonstration that different products have been validated

Demonstration that platform processe are identical

Provide validation data on LSD DPs

Limits of Prior Knowledge and platform approach



Certain tests like potency assays remain product-specific and cannot rely solely on prior knowledge

Platform approach helps reduce CMC requirements but does not eliminate the need for product-specific testing

Prior knowledge and platform data must be available to convince Regulators, not only referenced

Conclusions: Platform development and prior knowledge offers significant potential benefit to the rare genetic disease space

- Fixed and variable attributes can be determined in diseases that share similarities
- Risk assessment drives appropriate contribution of a core package vs development of disease/product specific data
- Leveraging a platform approach can facilitate a many-at-a-time development approach
- Leveraging on prior knowledge speed-up the development and decrease the burden of data without affecting quality and safety

- ***Reducing time and cost burden on translation of concept to clinical trial***
- ***Access to potential life-changing therapeutic options for patients that would be overlooked in a one-at-a-time development model***
- ***Benefits of cross-leveraging knowledge as a basis for development and non-repetition far outweigh potential residual risks***