Thursday, October 31 | 8:00 – 9:45 am ET

Efficient Nonclinical Development Processes Leading to Successful Treatment of Nano-rare Patients

PRESENTER

Julie Douville, PhD

Executive Director, ASO Discovery and Development

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

Integrated Processes & Building a Cohesive Team

Providing an optimal ASOs to nano-rare patients is the product of high-quality processes and years of expertise and experience

Sarah Glass

Molecular Geneticist
Clinical trial expertise
Operational Management

Konstantina (Nadina) Skourti-Stathaki

RNA Expert
ASO discovery and design

Julie Douville

Toxicologist
ASO expertise
Nonclinical development

Laurence (Laury) Mignon

Neuroscientist
ASO expertise
Clinical development

Amy Williford

Communications
Educator
Fundraising expertise

Establishing Systems Processes Creating Unified Cohesive Team | Creating Optimal ASOs ATTC - RMC | Preclinical to Regulatory RMC - IND | Clinical & Safety Patient Mgmt & Treatment STAR - DSMB | Supporting Patient Journey Communication /Education

Topics Covered Today

- Transition of ASOs from discovery into development
- Nonclinical processes supporting the development of individualized ASOs
- Regulatory processes and current status
- Accumulation of knowledge leading to more efficient processes

Nonclinical Processes Supporting n-of-1 Treatments

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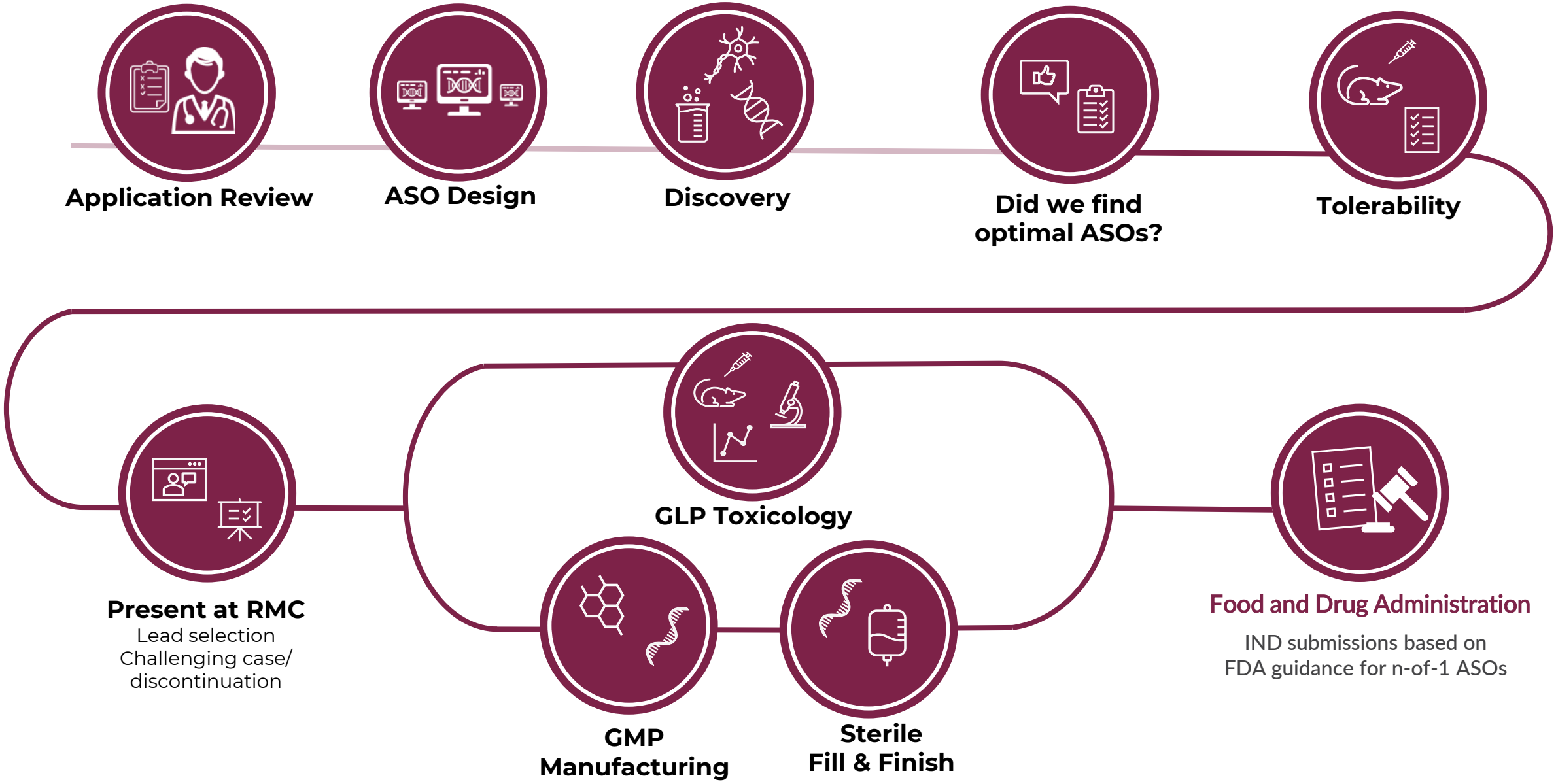
Continuity in the Nonclinical Process



Nonclinical Team: Bringing Complementary Skills Together

Julie Douville
Exec. Dir. Discovery & Development

RMC Lead
ATTC Member
ASO Development Lead
Regulatory Interactions

Toxicologist, ASO expertise, Individualized ASO program expertise, CNS drug delivery, nonclinical development

Nadina Skourti-Stathaki
Director ASO Design and Discovery

RMC Contributor
ATTC Member
ASO Discovery Lead

RNA biology expertise, cellular and molecular biology expertise, ASO design and discovery, basic research

Thuy Nguyen
Associate Director CMC

RMC Contributor
ASO Manufacturing Lead
Regulatory Interactions

Chemist, project management, ASO manufacturing expertise, sterile fill and finish expertise, analytical expertise

Catherine Parisien
Sr. Scientist Preclinical Development

RMC Contributor
Toxicology Lead
Regulatory Interactions

Toxicologist, project management, CNS drug delivery, neurobehavioral assessment, nonclinical development

Stan Crooke, MD, PhD
CEO

R&D Oversight
Clinical Development

ASO technology founder, drug development expertise from biotech to large pharma

Nonclinical Team Plays Many Critical Roles

ATTC

- Appropriateness of patients based on **genotype**
- Appropriateness of patient based on **phenotype**
- In partnership with **external experts**

CRO Management

- Establish **contracts** and **schedules**
- **Coordinate** ASO and sample movement
- **Monitor** activities. r**eview data** generated and ensure compliance
- **Analyze** tolerability and toxicology **markers**
- Write or review **reports** to ensure accuracy and quality

CMO Management

- Establish **contracts** and **schedules**
- **Monitor** synthesis activities
- **Coordinate** ASO movement for **sterile fill**
- **Review batch records** and ensure compliance
- Coordinate **ASO shipment** to treatment site and **monitor inventory**

RMC

- **Review** technically **challenging cases**
- Prepare and review **lead ASO data package**
- Discuss any challenges as needed to find **efficient and robust** solutions
- **External experts** provide oversight

IND / Regulatory interactions

- Authoring of various **IND** sections
- **IND** submission
- **FDA** interactions
- Meticulous **tracking** of milestones
- In partnership with **Laury and team**

Research Management Committee (RMC): Assuring an Appropriate ASO for the Patient

Lead ASO Selection

Review *in vitro* and *in vivo* screening data across all n-Lorem programs to select the ASO moving into development

Challenging Cases

Review cases that are technically challenging to help assess whether all avenues have been explored prior to discontinuation

Additional Challenges

Optimizing CROs/ CMOs
Standardization of phenotypic data collection
Any other relevant topic

Seamless Transition from Discovery to Development

- Once in vitro screening is completed, the Lab team 'hands over' the ASOs to the Nonclinical Development team
- Next steps involve working with partners
  - Assessing the safety of our ASOs (tolerability and toxicology)
  - Synthesizing the ASOs
  - Formulating the ASOs

Moving things faster and more efficiently,
to bring an ASO to the patient sooner

Collaboration with Contract Organizations Increases Efficiencies

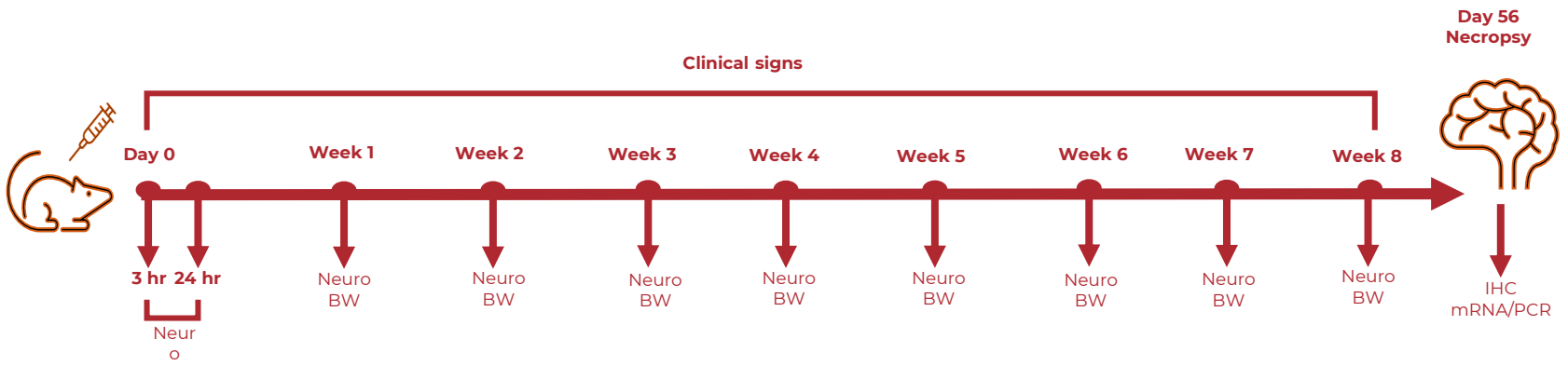
- n-Lorem leverages the expertise of CROs/ CMOs which have many years of experience of working with Ionis
- This maximizes efficiency while reducing costs
- The n-Lorem team oversees the activities conducted at the CROs/ CMOs
  - Mitigates risks and errors
  - Ensures study stays on track from a timeline perspective
  - Ensures adherance to protocol
  - Proactively identifying and addressing issues
- Collectively, the n-Lorem nonclinical team has 63 years of experience in drug development

Redundancy is Important

- n-Lorem has built a network of CRO and CMO partners
  - 6 partners for animal studies
  - 4 partners for ASO synthesis
  - 3 partners for formulation of the ASOs
- CROs and CMOs work with other clients across the industry, including large pharmas; they are busy!
- Having redundancy at this step is essential to ensure optimal pricing and flexibility in scheduling

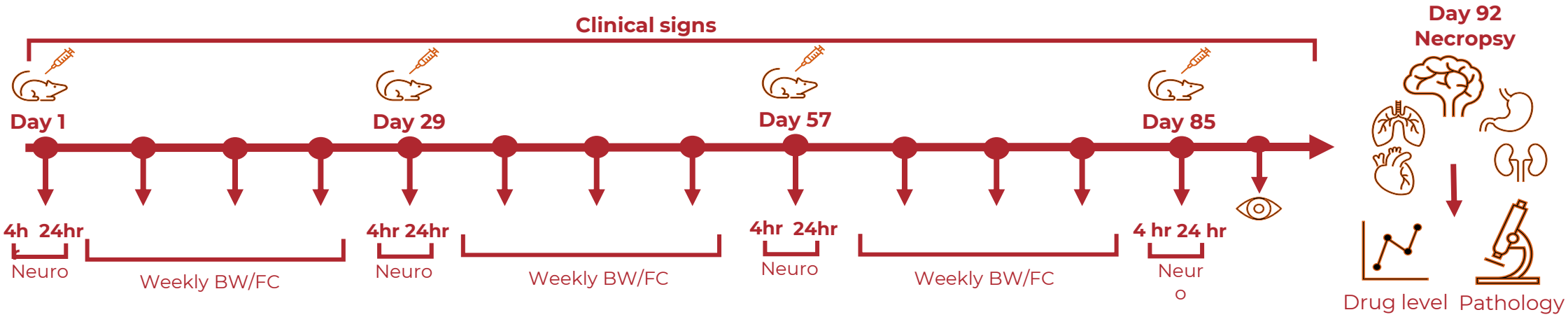
In Vivo Tolerability Study

- Rapid screen in rodents designed to identify ASOs that might be problematic
- Study duration is around 8 weeks and animals are evaluated for a short battery of endpoints that are critical
- ASOs that are not meeting criteria are not moving forward



GLP Toxicology Study

- The purpose of this study is to identify the potential toxicity of the ASO selected to move to the clinic
- This is a repeat dose study of a 3-month duration where animals are thoroughly evaluated for an extended battery of parameters (general and organ-specific)



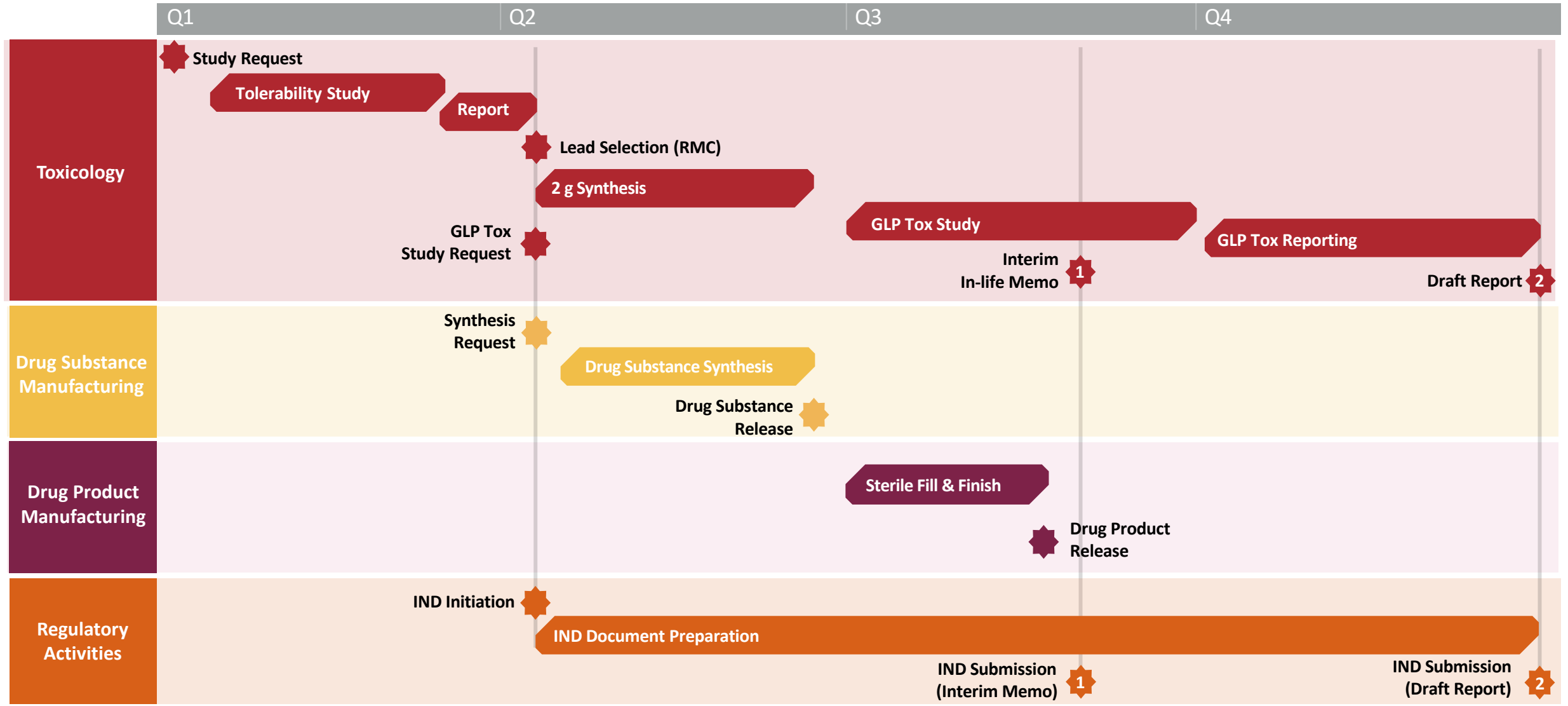
GMP Manufacturing: Drug Substance

- GMP manufacturing is regulated and operates by a set of rules ensuring quality and reproducibility at every step
- The lead ASO is first manufactured as a ‘drug substance’ which is a powder form
- Strict criteria for purity, salt content, bioburden, etc, are applied to ensure adequacy for human administration
- A single batch typically yields sufficient material to treat a patient for 10 years or more

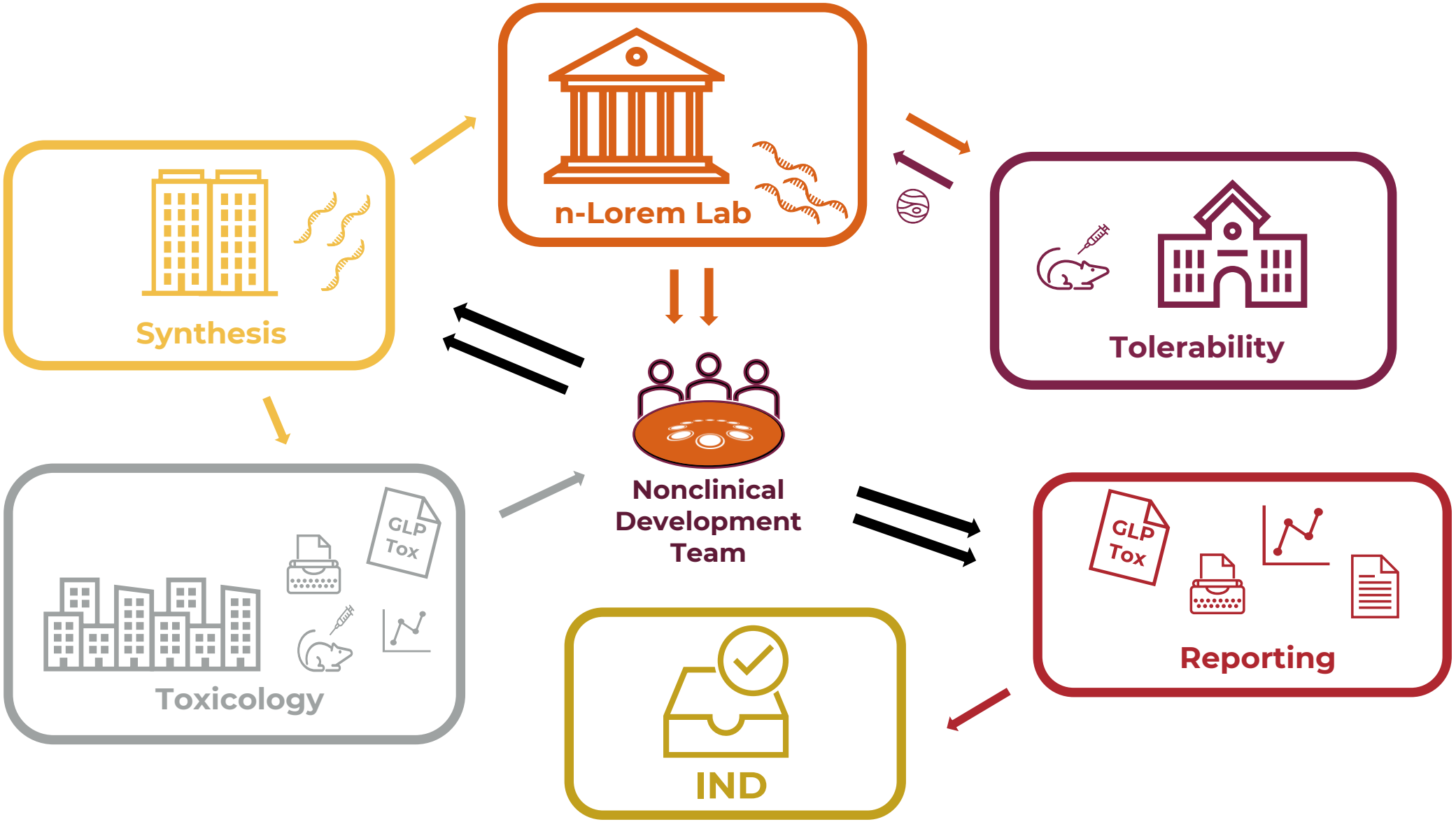
GMP Manufacturing: Drug Product

- The drug substance needs to be further manufactured as ‘drug product’, which is a liquid solution
- This process is often called ‘Sterile Fill and Finish’
- Strict criteria purity, sterility, endotoxin, etc, to ensure that the material is safe to administer to humans
- This will generally yield 200-300 vials, which will be tested on a yearly basis to confirm the stability of the drug

Optimized Timeline for Nonclinical Program



Efficient Orchestration is Essential



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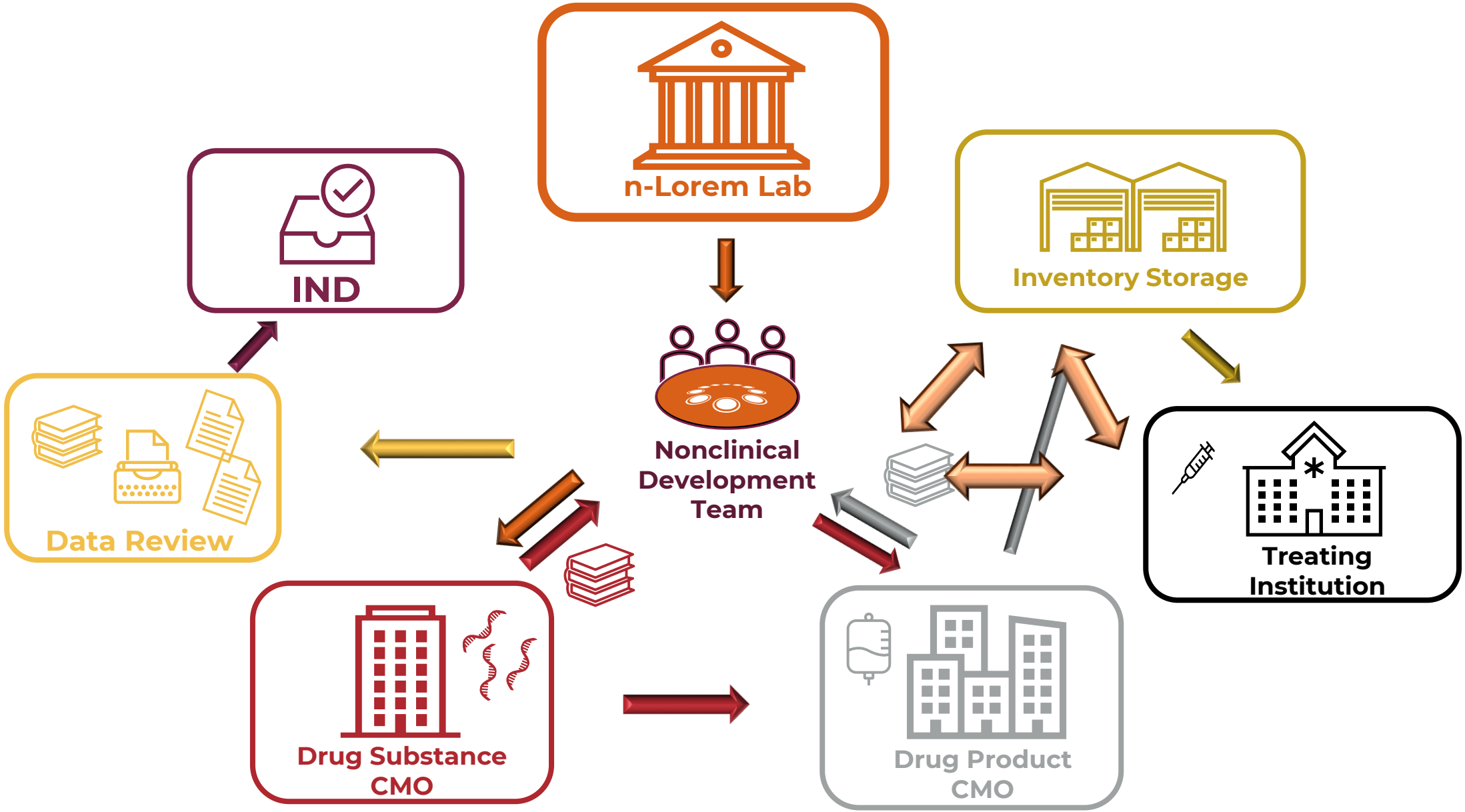
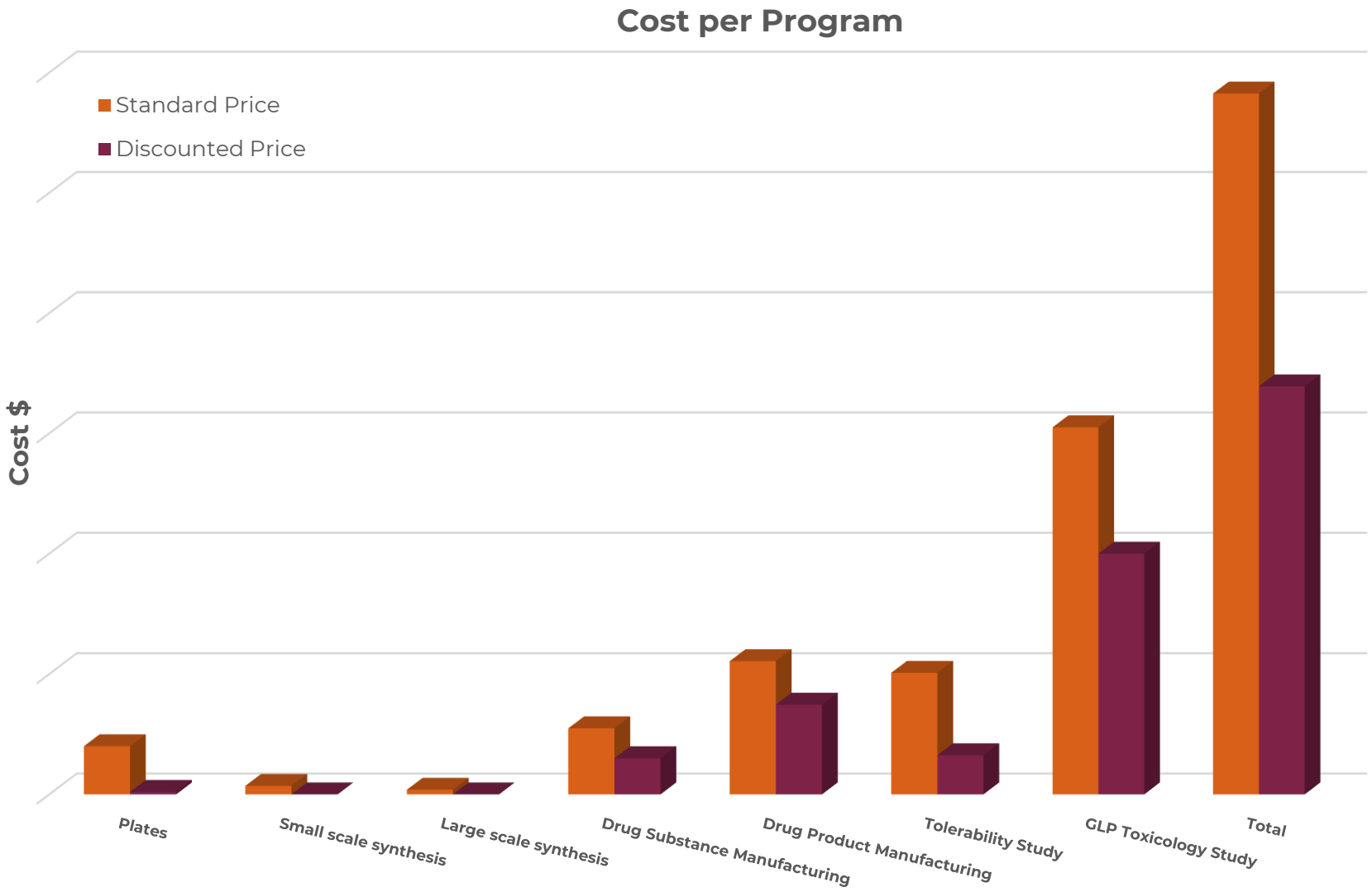
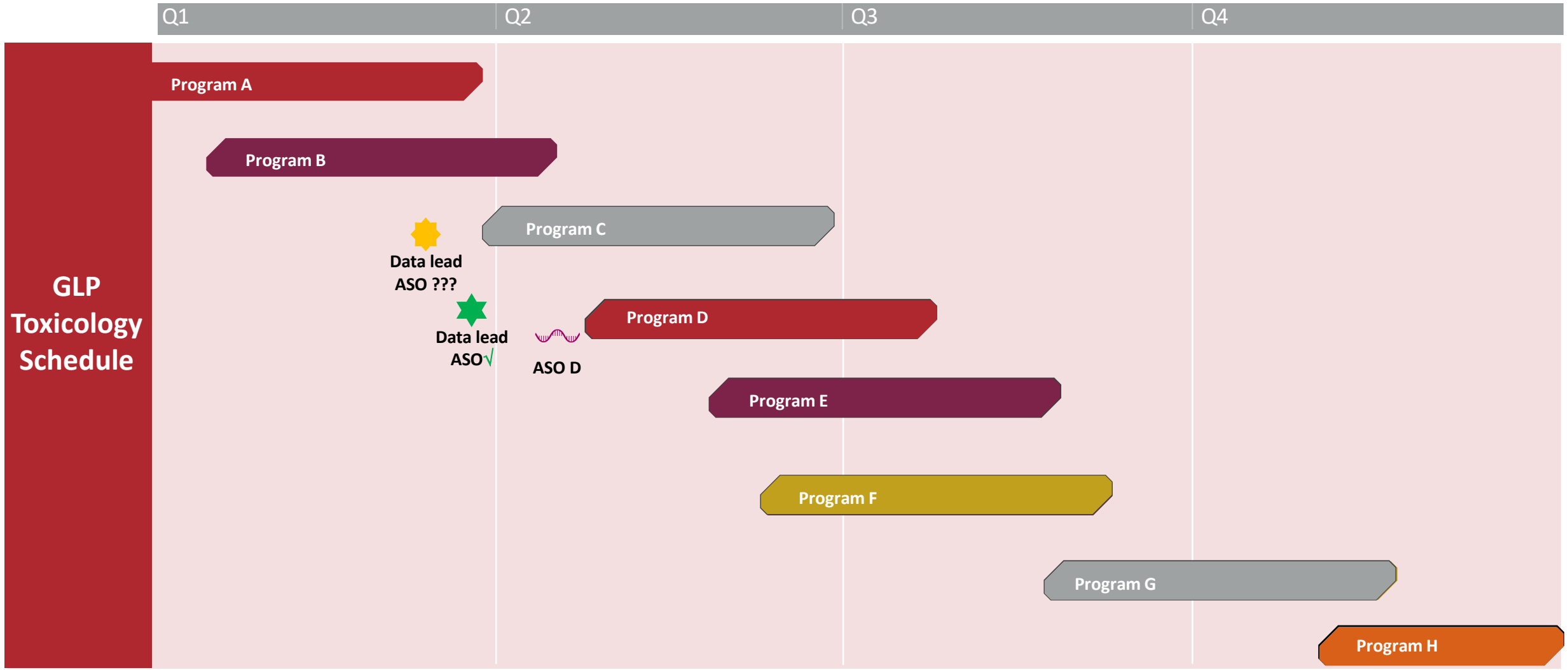


Partnering to Maximize Cost Efficiencies



Collaboration with our partners reduces the cost by 40%

Nimble Scheduling Means More Opportunities for Nano-rare Patients



Regulatory Activities

What is an IND?

- IND stands for:
  - Investigational New Drug Application
- In a commercial model, it would be followed by a NDA
  - New Drug Application
- Research INDs include:
  - Administrative documents
  - Chemistry, manufacturing and controls documents
  - Nonclinical documents
  - Clinical documents
- Typically 1200-1500 pages

IND: Administrative Module

- Cover Letter
- General Investigational Plan
- Environmental Assessment
- Principal Investigator CV
- Form 3674
- Form 1572
- Form 1571

IND: Chemistry, Manufacturing and Controls Module

- 3.2.S Drug Substance
- 3.2.P Drug Product
- 3.2.D Diluent
- Certificate of Analysis for Drug Substance
- Certificate of Analysis for Drug Product
- Certificate of Analysis for Diluent
- Investigational Labels
- Pharmacy Manual

IND: Nonclinical Module

- Nonclinical Study Reports
  - 8-week rodent tolerability
  - 13-week GLP toxicology
- 2.4 Nonclinical Overview
  - Details on the ASO design, potency, selectivity, on target and off target liability, in vivo tolerability and GLP toxicology

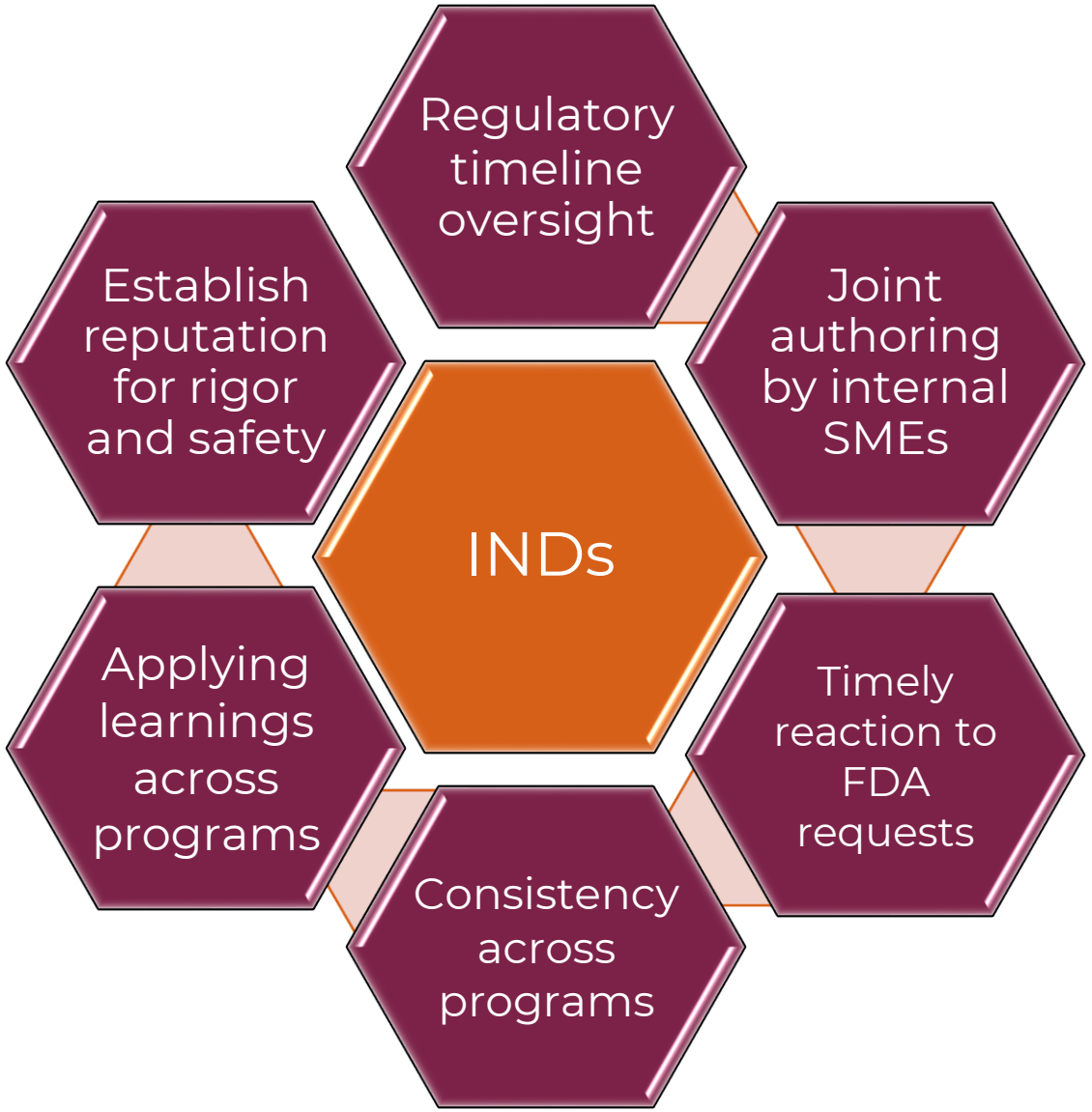
IND: Cinical Module

- Clinical Protocol
  - Outlines dose level, dose escalation, dosing intervals, and endpoints to be measured before and after dosing
- Informed Consent
- 2.5 Clinical Overview
  - Details on the patient's specific mutation and phenotype, target gene, biological effects of the mutation, how the ASO will act on the target, overall treatment goals, outcome measures, and risk/ benefit assessment

What Happens after Submission

- FDA can ask for clarification or additional information on any portion of the submitted IND
- They often request a response very quickly, from 1 week to a few hours
- FDA has 30 days from the date of submission to provide a response
- 3 possible responses:
  - Approval to proceed
  - Partial Clinical Hold
  - Clinical Hold

Streamlining the Regulatory Approach



Regulatory Metrics

- n-Lorem has had over 130 regulatory interactions with the FDA so far
- 5 formal pre-IND meetings with the FDA
- 4 informal meetings to discuss other challenges, including n=few
- n-Lorem has submitted 21 INDs in ~2 years
  - ALL INDs have been approved
- 29 patients are covered by these INDs

Moving Beyond n = 1

- No clear guidelines to treat more than 1-2 patients
- Different reasons can push the transition from n=1 to n=few or many
  - Known prevalence increases as WGS becomes more available
  - Demand emerges once treatment becomes available
  - Strategy changes from allele-selective to non allele selective
  - SNPs used to design ASOs are commonly present

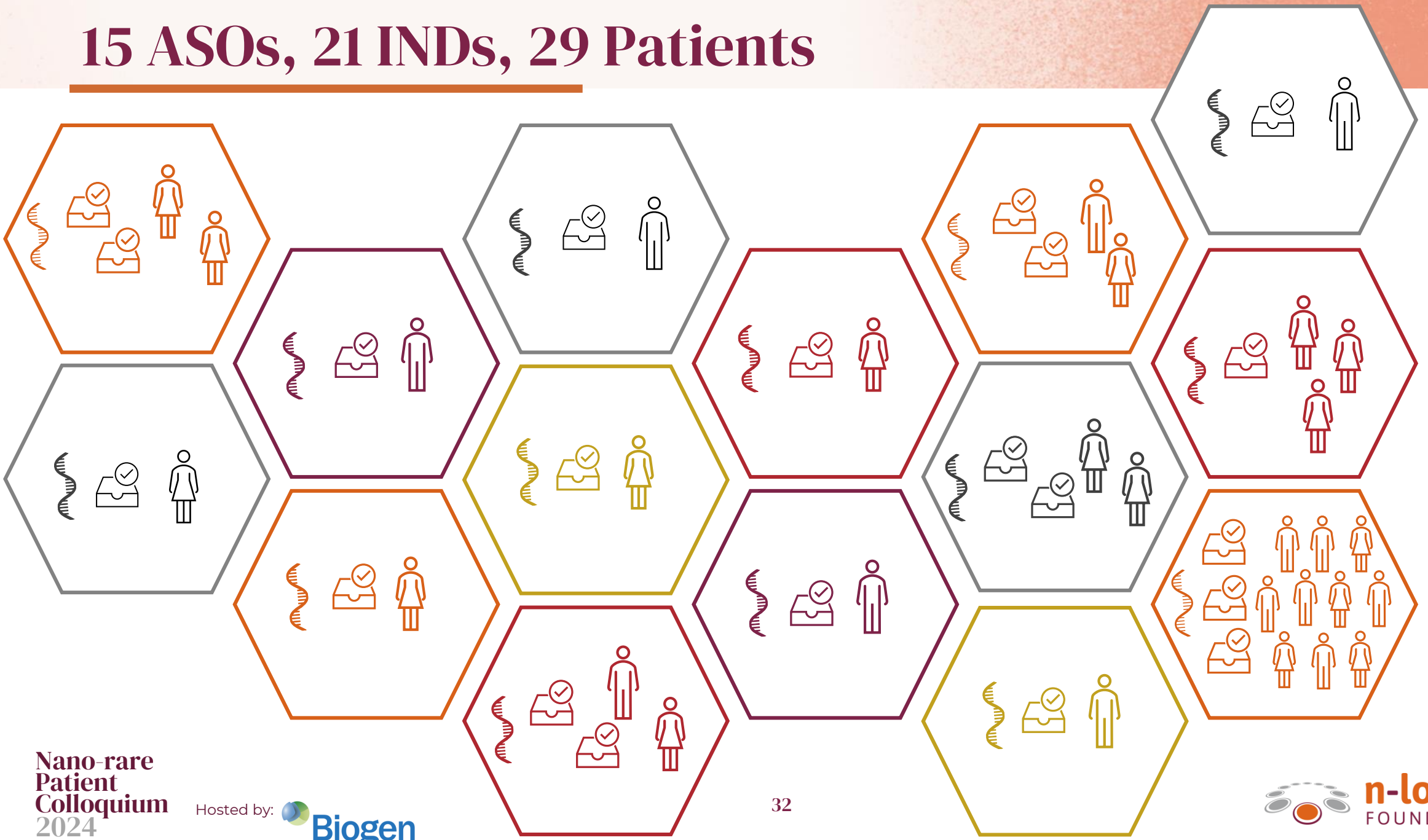
Applying Learnings Across Programs

- As we prepared and filed more INDs, we gained knowledge and experience
- If an IND already exists for this ASO, we can leverage documents that were already submitted
- If a small number of patients have the same mutations and phenotype, it can be possible to group them into a single IND

Industrialization of the Regulatory Process Increases Efficiencies

We Now Have 5 Different ASOs Approved to Each Treat 2 to 9 Patients

15 ASOs, 21 INDs, 29 Patients



Conclusions

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- n-Lorem has successfully industrialized every step from ASO discovery to regulatory approval
- Quality and efficient processes established
- Integrated team of experts ensuring seamless and speedy movement of ASO from the lab to the clinic
- Industry partners are making a difference in timing and cost

This means more ASO treatments, for more patients, more rapidly, leading to more knowledge, that can be directly applied

Support From Leaders Across All Areas of Drug Discovery, Development and Manufacturing *More than 30 Partners Support Nano-rare Patients*

Biotech/Pharma Companies

IONIS

Biogen

ALEXION AstraZeneca Rare Disease

Alnylam Pharmaceuticals

ultragenyx

La Jolla Labs

Takeda

Genomic Sequencing

Children's Mercy Kansas City

COVANCE by labcorp

GeneDx

illumina

PacBio

Access to Appropriately Characterized Patients and Investigators

UDN Undiagnosed Diseases Network

Other personalized medical centers

Pre-clinical Toxicology CROs

charles river

KIT Korea Institute of Toxicology

Greenfield Pathology Services, Inc.

KreaMedica Your Partner in Drug Development

IPST

Disease Focused

ASXL3

FSHD2

MAPK8IP3

Silence ALS

Manufacturing

ChemGenes Corporation

cytiva

Hongene Biotech

IDT Integrated DNA Technologies

Nitto Avecia

CardinalHealth™

Clinical Management

parexel

Foundations Grant Organizations

The Conrad Prebys Foundation

TARGET ALS

SOLVE FSHD

Wolverine Foundation

Anonymous Donor

URGenT NIH Grant

danaher

Sterile Fill Product

ARGONAUT Manufacturing Services

Nitto Avecia Pharma Services

Other

COMBINED

Cooley

COWEN

STIFEL

J. Wood Capital Advisors

sysnav Health Care

Data Partners

Across Healthcare

Unipr

Thank you

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