Translational Science

Company Snapshot

- The world's leading drug development and regulatory consultancy assisting companies to maximise their chance of success in product approvals and market access
- Translational Sciences experts with experience in the development of biological, biotechnological and advanced therapy medicinal product, focused on both strategic and operational aspects of enhanced product development
- Supported by 150 dedicated employees with extensive regulatory, clinical and industry experience
- Supported by Standing Advisory Boards comprised of former HTA and Regulatory Agency leaders
- Supported by a network of over 1,000 disease thought leaders, former regulators, and subject matter experts

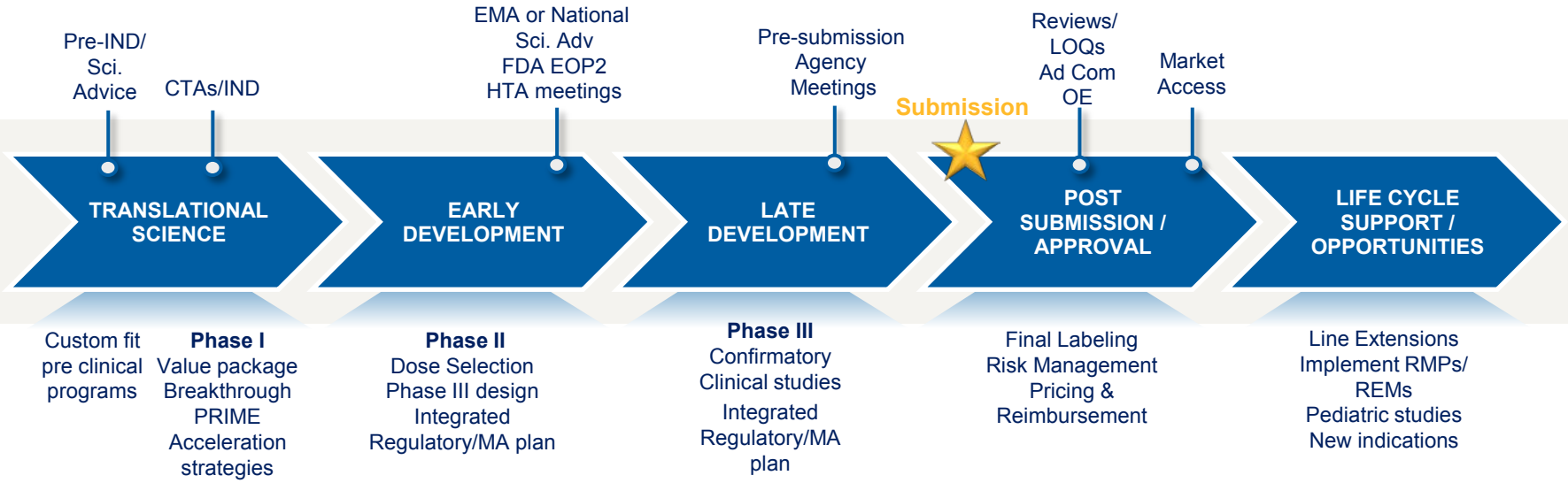
Our Mission

To streamline the global development process to accelerate patient access to important medical therapies

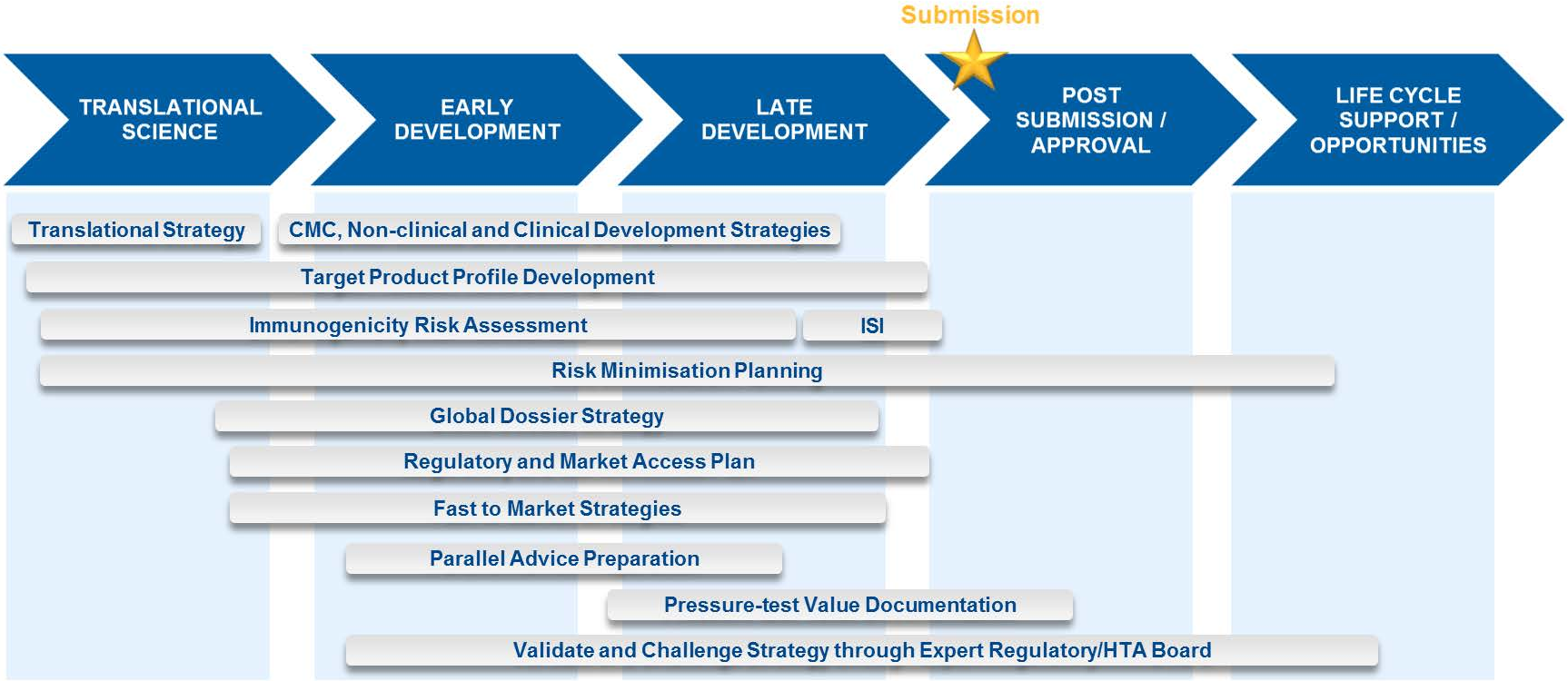
We achieve this by:

- Driving integrated drug development
- Training clients to excel in mission critical regulatory communications
- Preparing for high stakes meetings
- Managing milestone agency interactions, procedures and submissions

Where We Help



How NDA Helps You Drive Evidence Generating Strategies



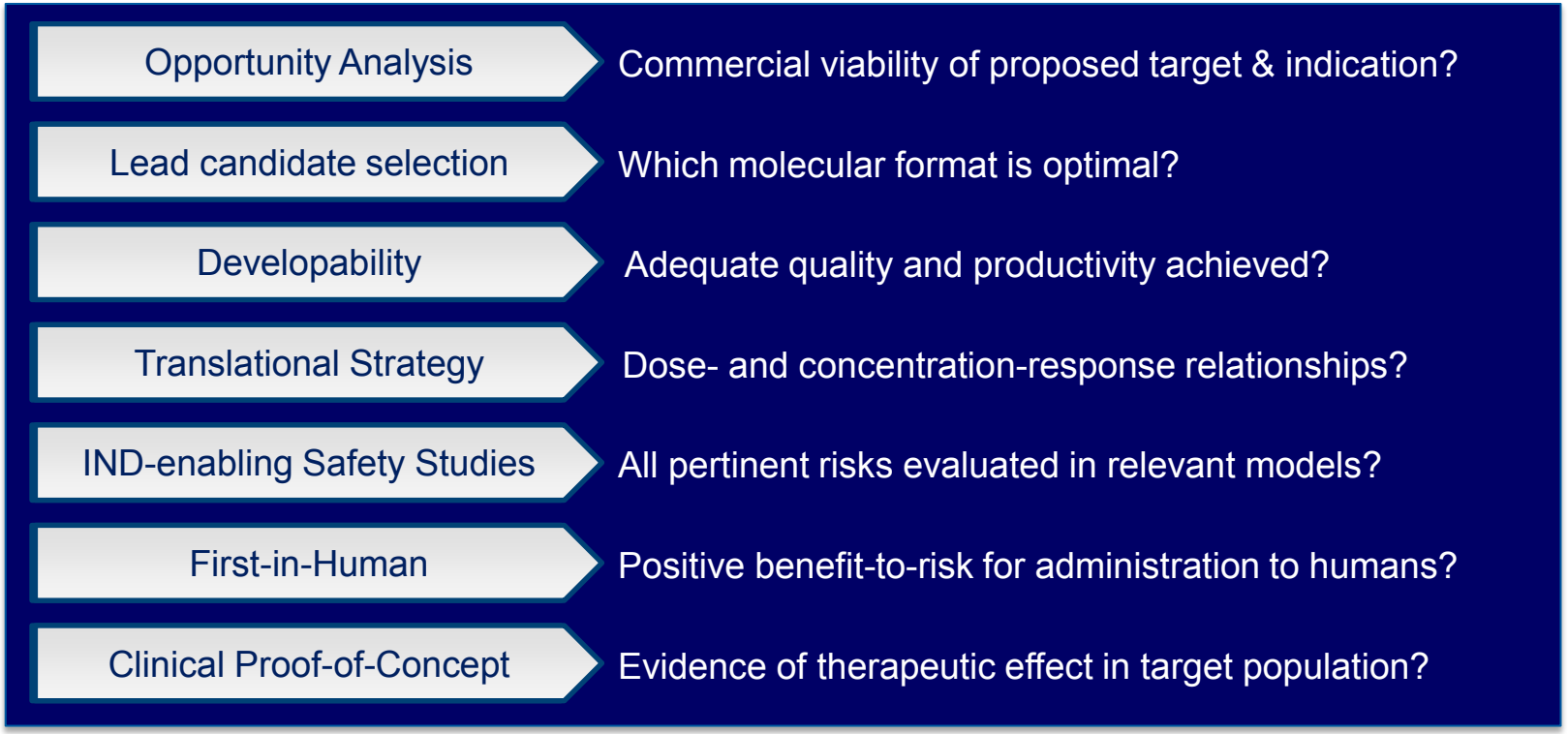
NDA Approach

- Translational Sciences Support
  - Provides integrated advice during development up to First-in-Human trials, optimised for value inflection points
  - Stage gate and integrated risk management approach to enable you to make go-no go decisions and to advance projects with a high probability of success, thereby increasing R&D returns and allowing for favorable “exit” strategies

The “Stage-gate” approach

- Focuses on defining input data to inform decision-making at critical stages:
  - Prioritises resource allocation on activities most likely to add commercial value while minimising regulatory risk;
  - Stratifies incremental investment in adaptable pathway for achieving overall objective;
  - Defines multi-disciplinary inter-dependencies for coordinated project management and informed decision making

Stage-Gates for Early Development



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Opportunity Analysis

Opportunity Analysis — Commercial viability of proposed target and indication?

Making the right choices:
- Understand target biology and relevance in disease or condition and the competition
- Select technology platform
- Identify translational strategy to demonstrate meaningful treatment benefit

Planning for success:
- Develop initial Target Product Profile
- Risk management tool and exit scenarios
- Ensure clinical endpoints and benefit/risk analysis of TPP support commercialisation and reimbursement

Understanding stakeholder expectations:
- Regional differences (commercial and regulatory)
- Current clinical treatment guidelines and future developments
- Development scenarios (resource, budget)
- Go/No Go criteria, value inflection points and gated milestones

Trouble-shooting:
- Technology risk management
- Regulatory strategy

Lead Candidate Selection

Lead candidate selection — Which molecular format is optimal?

Making the right choices:
- Molecular format
- Selection and screening toolbox
- Target structure / activity profile
- Models for proof-of-mechanism
- Expression system

Planning for success:
- Minimise immunogenic potential
- Characterise MoA
- Biomarker identification
- Ensure appropriate pharmacology and toxicology profile

Understanding regulatory expectations:
- Robustness of analytical procedures
- Justify lead candidate characteristics (efficacy and safety)
- Identify indicators/markers to assess safety and efficacy and justify translation in clinical benefit/risk

Trouble-shooting:
- Support development of analytical methods
- Select expression platform
- Pharmacology and safety (immunogenicity) risk assessment and management

Developability

Developability — Adequate quality and productivity achieved?

Making the right choices:
- Contract Manufacturing Organisation
- Raw materials
- Cell line
- Analytical methods
- Drug product formulation

Planning for success:
- Manufacturing plan
- Quality Agreements with 3rd parties
- Estimating material supply needs
- Minimisation of quality related risk factors
- QTTP development

Understanding regulatory expectations:
- Cell bank
- Control of adventitious contaminants
- Drug substance/product specifications
- Test method qualification / validation
- Stability data
- Reference standards
- GMP compliance

Trouble-shooting:
- Identifying & controlling impurities
- Understanding sources of instability

Translational Strategy in Nonclinical Development

Translational strategy

Dose- and concentration-response relationships for pharmacology and adverse effects?

Making the right choices:
- Appropriate *in vitro* assays and tools
- Selection of relevant animal models
- Use of *in vitro* studies to address limitations of animal models
- PK-PD-ADA-Safety endpoints measured
- Study designs and selection of CROs
- Translational strategy informs PK-PD and delivers IND-enabling data

Planning for success:
- Bioanalytical and biomarker plan
- Immunogenicity risk minimisation
- Estimating material supply needs

Understanding regulatory expectations:
- Justification for species selection
- Justification of dose, route, schedule and duration of treatment/exposure
- Quality of bioanalytical assays
- Comparability of GLP-GMP material
- GLP compliance

Trouble-shooting:
- Understanding of target biology and safety liabilities
- Exploratory endpoints included in studies based on MoA
- Immunogenicity risk assessment

IND-Enabling Safety: Associated Activities

IND-enabling Safety Studies — All pertinent risks evaluated in relevant models?

Making the right choices:
- Selection of animal models
- Selection of bioanalytical methods
- CRO evaluation and selection
- Selection of supportive studies/experiments

Understanding regulatory expectations:
- Justify species
- Justify size of study population, assessments and parameters
- Justify relevance of findings in safety studies and translation in clinical investigations

Planning for success:
- Robust bioanalytical methods
- Robust pharmacology
- Identify potential safety/toxicology signals, detection and management in clinical practice

Trouble-shooting:
- Interpret safety findings and provide risk assessment/ management plan
- Rescue plan

First-in-Human Studies: Associated Activities

First-in-Human → Positive benefit-to-risk for administration to humans?

Making the right choices:
- Study population and cohort size
- Dose level and frequency
- Primary vs. exploratory endpoints
- Optimal sample scheduling
- Quality of drug product

Planning for success:
- Feasibility exercise
- Translational models – acceleration cPOC
- Well characterised pharmacology and safety profile – risk/benefit analysis

Understanding regulatory expectations:
- Justify study population
- Justify clinical starting dose and dose escalation
- Justify treatment algorithm, integration of translational elements, study analysis
- Safety assessment and risk management (incl. immunogenicity)

Trouble-shooting:
- Pharmacology/safety risk analysis
- Adapt clinical investigation (plan)

Early Clinical Development: Associated Activities

Clinical POC — Evidence of therapeutic effect demonstrated?

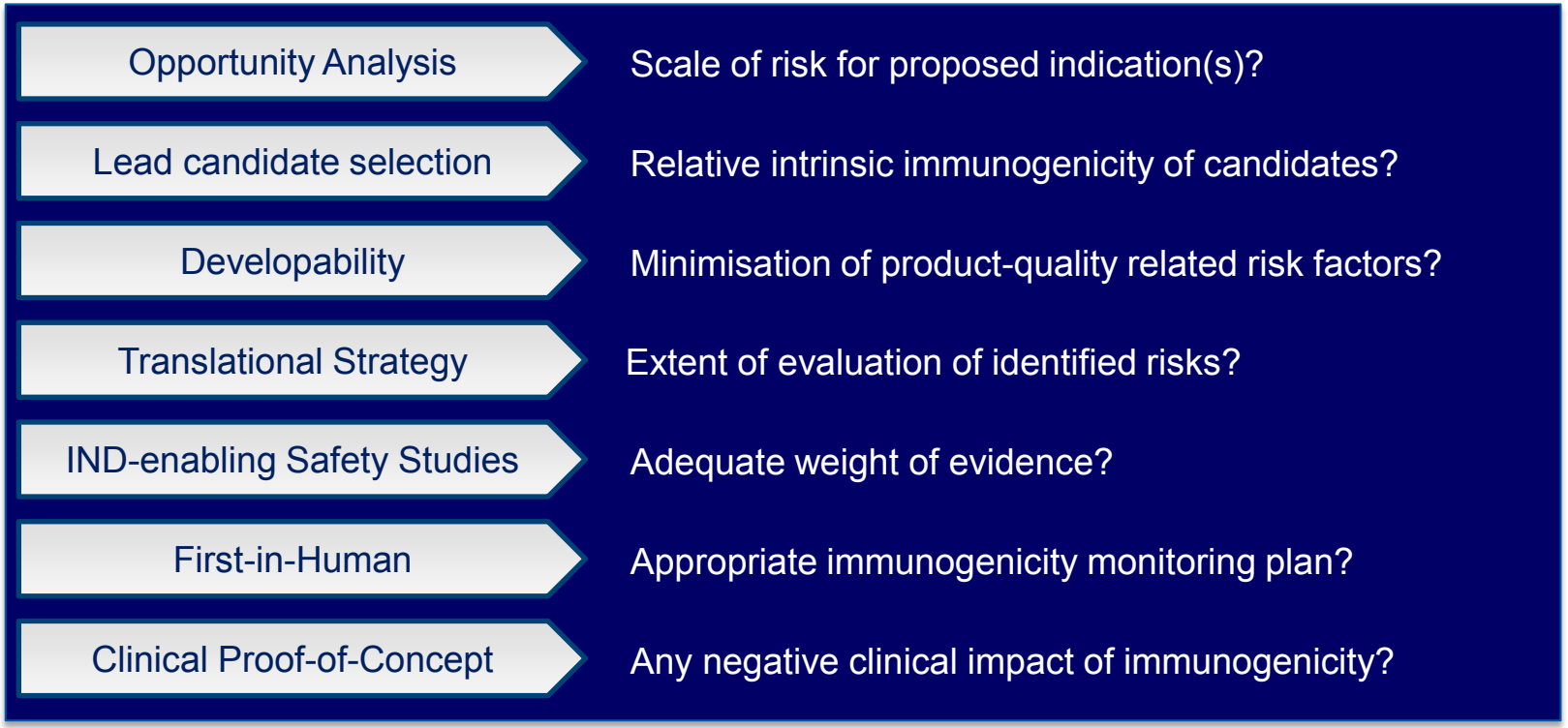
Making the right choices:
- Target patient population
- Translational models (PK/PD)
- Study endpoints
- Investigators, study centers, vendors

Planning for success:
- Clinical Advisory board
- Clinical Development plan
- Translational strategy
- Risk/Benefit assessment and risk management plans

Understanding regulatory expectations:
- Address safety risks and management
- Justification of dose and schedule
- Heterogeneity of patient population
- Measuring treatment outcome
- Analytical tools
- GCP compliance

Trouble-shooting:
- Immunogenicity risk assessment and management
- Assess treatment outcome and tools

Integrated Immunogenicity Risk Assessment – The Critical Questions



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Why use NDA Translational service?

- The NDA team provides unique strategic partnership
- 100s of man-years expertise in exactly the area the you have limited expertise in
- NDA can help you map out the development opportunities, assess the risks, provide risk mitigation and management tools
- NDA can help you determine a clear path forward to the next value inflection point

What can NDA provide?

- A “sounding board” for business ideas
  - support development of business plan
  - input in financing requirements (development scenarios and costs)
  - “sparring partner” for investment pitches
  - ”networking partner” for scientific, development, clinical, regulatory and commercial evaluation/validation of business idea/business plan

What can NDA provide?

- A “strategic partner” – how do you get from idea to value
  - define the road-map (big picture and intermediate steps)
  - gap analysis (available assets and resources and what is missing)
  - mapping of competences (in-house and external)
  - development planning (start with the value proposition and end-customer in mind)
  - mapping of work-packages (discovery → development → commercial) with focus on value inflection points for company
  - mapping of resource requirements (FTE and costs)

What can NDA provide?

- An “execution partner” – how do you execute projects efficiently within the resource constrains
  - conduct gap analysis of research and development plans
  - critical path analysis and risk analysis/mitigation plan
  - provide strategic support to manage challenges/gaps identified
  - project management – stage gate process
  - support of research and development functions
  - oversight/execution of defined work-packages
  - regulatory agency representation
  - counseling/consultation in partnering situation

Benefits of this approach

- Tailored drug development advice to meet the regulatory requirements and expectations for both the EU and the US
- Expert critical input and assessment of alternative routes for product development
- Increased efficiency due to the identification of common (core) requirements, resulting in a core FIH clinical dossier for the EU and US
- Clear establishment of acceptable product profile and identification of strategies to mitigate any challenges/gaps
- Consistent, clear product messages and identification of supporting data
- Early assessment of benefit/risk which is developed through life cycle
- Focus resources, accelerate development, provide choices for exit scenarios