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Development roadmap towards first-in-human clinical studies

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Content*

From bench to First-in human clinical study (FIH)

- Translation from research to development
- Designing the FIH
- The nonclinical package for FIH
- CMC data at FIH stage

Regulatory strategy

- Regulatory strategy towards the FIH study
- Agency interactions at FIH stage

*focus on biopharmaceuticals

From bench to First-in human clinical study (FIH)

At that stage, your company moves….

….from research (lead candidate identification) to development (make a drug out of it)

- Research: academic interest, find something new and characterise it for its potential use in clinic
  - Main drivers: science, innovation and curiosity
  - Target identification (which is an area on its own)
  - Excursions into manifold directions as new scientifically interesting questions always arise
- Development: the drug candidate is developed to a drug
  - Main drivers: regulatory rules and guidelines
  - Regulatory science is now part of the process

Agencies ….

…… focus on compliance with drug development principles

- Scientifically justified and reasonable review
- Review of data in line with the requirements relevant for the development stage
  - Quality compliance with state of the art requirements
  - Safety supports the use
  - Rationale of use and dosing as proposed by applicant are justified
  - Clinical studies are suitable to support the claims made by applicant for clinical use of the product
- Benefit/Risk balance is positive
  - Continuously justified at each development stage (and post-approval)

Basis for development: target product profile (TPP)

Example: Clinical TPP of COVID19 treatment candidate (mAb)

Criteria	Minimum
Value proposition	Prevention of critical COVID-19 disease in virus-positive subjects
Indication	Prevention of progress into severe / critical disease
Target patient population	Virus positive subjects at risk of developing severe disease
Dosing and administration	i.v. infusion, high dose immediately after positive virus test/early onset of symptoms, possibly second dose within few days
Efficacy • Primary endpoints • Secondary endpoints	1st: Prevention of critical illness 2nd: Other benefits: e.g. less long-term sequelae, mean improvement relative to baseline, ICU-free days, hospitalization-free days
Safety & tolerability	Acceptable in target population, impact on physiology
Special population(s)	e.g., elderly
Combinations and drug-drug interactions	e.g., compatible with Standard of Care

mAb monoclonal antibody

Considerations on typical FIH study design

- First investigation of a novel drug candidate in human beings
- Primary objective: safety
  - Based on nonclinical tox and safety data, plus risk assessment
- Other objectives: PK and investigation of the dose (and possibly a dosing regimen)
  - Entry into clinic with a starting dose
  - Based on nonclinical PK and PD data, plus modelling of animal data and literature to humans
  - Requires set-up of bioanalytical methods
- Population: HV or patients
- Typical design: SAD
  - Combination possible: SAD as Part A in HV and MAD as a Part B in patients
  - SAD typically without placebo arm, MAD usually with control arm
- Inclusion/exclusion criteria suitable to support the objective of the study
- Efficacy related objectives?
  - Limited
  - To prepare for potential proof-of-concept: include PD related markers as broadly as possible

SAD: Single Ascending Dose
MAD: Multiple Ascending Dose
HV healthy volunteers
CTA Clinical Trial Authorisation

Nonclinical program enabling FIH study

Objectives

- Rationale of use of product
- Characterisation of the safety and risk profile of the product
  - Known risk factors
  - Potential risk factors
  - Risk mitigating measures
- Determination of the (safe) starting dose and expected dose range for escalation

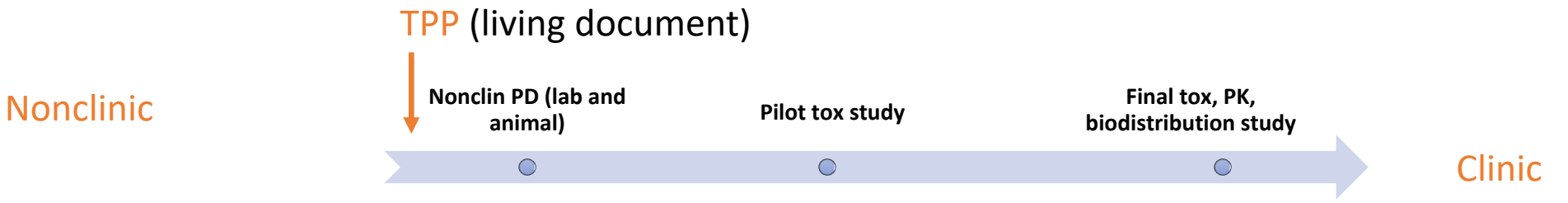
In practise done

- Pharmacodynamics (primary and secondary pharmacology)
- Pharmakokinetik
- Single dose tox study
  - Repeat dose tox only if FIH is designed with repeat dose regimen
- Local tolerance

Typical caveats for the nonclinical part

- GLP
- Relevant animal
- Material used in nonclinic to be representative of the material used in the FIH
- CROs with limited slots (or planned/asked too late)
- Bioanalytical strategy (PK, PD)
  - Set of assays to support nonclinical and clinical studies
  - Appropriate assay reagent availability
  - ADA testing is typically not considered necessary in FIH

Integration of CMC and nonclinical development towards FIH



CMC

Cell line selection
Research cell bank
GMP Master cell bank

Process development lab scale

- Cell bank characterisation
- Initial process parameters/hold time
- Formulation development
- Method development/optimisation
- Stability studies

Pilot scale

- Non-clinical pre-phase I studies (tox)
- Reduced scope forced degradation studies
- Early phase method validation
- Stability
- Initial reference standard
- Characterisation of impurities

GMP batch

- (Process consistency)
- Pilot (engineered) vs GMP
- Stability
- Compatibility/In-use study

TPP Target Product Profile
IND (US)/IMPD (EU): Dossiers needed for clinical trial

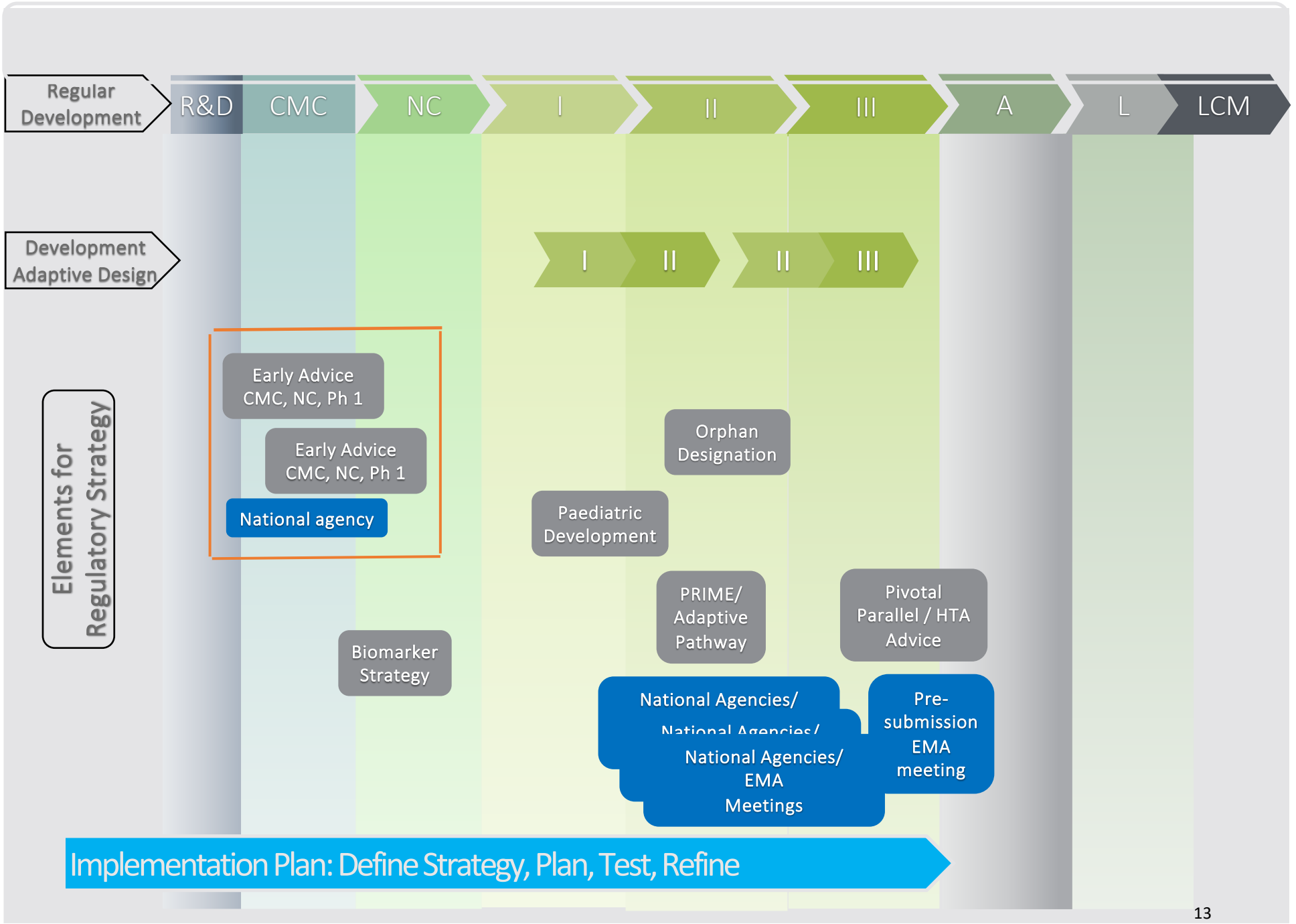
CMC for early clinical development

- EU: product to be manufactured by GMP process
- Typically (only) one DP GMP batch is available
- Drug product formulation is available and stable
- Analytical methods for release of the DS and DP batch(es) are established by qualification
- Potency assay is required
- Full information on genetics and on starting material
- Product is characterised for its structure, molecular features, biofunction, and principle impurities
- Virus/adventitious agents safety is shown by virus validation study
- Data on compatibility of product with infusion sets etc. used in the clinical study

DS drug substance, DP drug product

Regulatory strategy

EU Integrated Drug Development and Regulatory Strategy



Modified following

D. Seimetz: The Key to Successful Drug Approval - An Effective Regulatory Strategy,

Life Science Venturing, Springer Verlag 2017

Scientific advice for a FIH study

What works *typically* best

- For FIH: EU national agencies
  - Scientific advice at national level
  - Before start of clinical program, also before major nonclinical investments
  - As pre-CTA meetings, with the agency of the country where the FIH is planned
- Topics typically covered
  - CMC
    - Manufacturing process, process controls, specifications, stability data, potency assay
  - Nonclinical aspects
    - Tox study outline, animal species, starting dose justification, minimal nonclinical study package
  - Clinical aspects
    - FIH study design, population, endpoints

Practice: same principle for all agencies, but individual logistics

- EMA: always written advice, *rarely* with (online) discussion meeting
- FDA: always written advice, *regularly* with (online) meetings
- National agencies: *typically* (online) meetings, meeting minutes
- For all:
  - Reserve a slot for the meeting
  - Prepare a briefing book / package with information on the product and its development program
  - Questions to agency and company positions on them
- No open questions, be always specific: *"does agency agree to our program, approach proposed"*
- Agencies do not comment on
  - Open questions, such as *"which development candidate is the best"*
  - Regulatory questions (EMA), as they are handled by separate procedures (Exception: FDA)

Thank you.

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