MINISTRY OF HEALTH

For a healthier life

Drug Development - Points to Consider

The Regulator View

ד"ר עפרה אקסלרוד
מנהלת המכון לביקורת ותקנים של חומרי רפואה וס. מנהל מערך הרקוחות והאכיפה
אוקטובר 2018

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

Keep in mind

- Know your product
- Know the regulatory requirements
- Determine data requirements according risk-based approach
- Build analytic panel early, inclusion potency assay
- Design trial to increase product knowledge
- Consider the market

Ilona Reischl, PhD
BAGS/AGES

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

Strategic thinking

Your clinical data can only be considered as reproducible, if

the investigational product is sufficiently characterized

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

Questions to be asked

- **Mechanism of Action (MOA)-** how is the product supposed to work in patients?
- What would you have to study clinically to asses safety and efficacy based on MOA?
- **Critical Quality Attribute (CQA)** - what critical properties do you need to control, in order to achieve the desired safety and efficacy?
- **Critical Process Parameter(CPC)** - what processes need to be controlled to assure process produce the desired product quality?
- What are the most crucial lot release specifications?

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

- **CQA and CPP are not meant to be static** –they should be continually evaluated and revised as needed
  - Additional product characterization
  - Clinical outcome
  - additional manufacturing experience
- It is generally easier and less risky to make changes early in product development than later

Should be revised cautiously

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

Early phases-main concerns

- Preclinical animal studies should be conducted using product manufactured like it will be used in clinic

- Safety
  - Safety of source material, reagents and processing
    - Research grade reagents-can be used if properly qualified
    - Human derived materials-Licensed products
    - Human serum-at least donor eligibility questions, viral tests
  - Human Safety Testing(sterility, endotoxin, mycoplasma, identity, purity …)

- Ability to manufacture the product

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

Strategic thinking

Your clinical data can only be considered as reproducible , if the investigational product is sufficiently characterized

IMPD-Investigational Medicinal Product Dossier

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

IMPD

- EU Directive 2001/20 (“clinical trials directive”) requires sponsors to submit information on:
  - **the quality and manufacture of the investigational medicinal product**
  - **any toxicological and pharmacological tests**
  - **the protocol**
  - **clinical information on the investigational medicinal product including investigator's brochure**

to the concerned competent authority

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

Investigational medicinal product dossier(IMPD)

Quality - Chemistry, Manufacturing, Control (CMC) Module

WHY???

What???

MINISTRY OF HEALTH

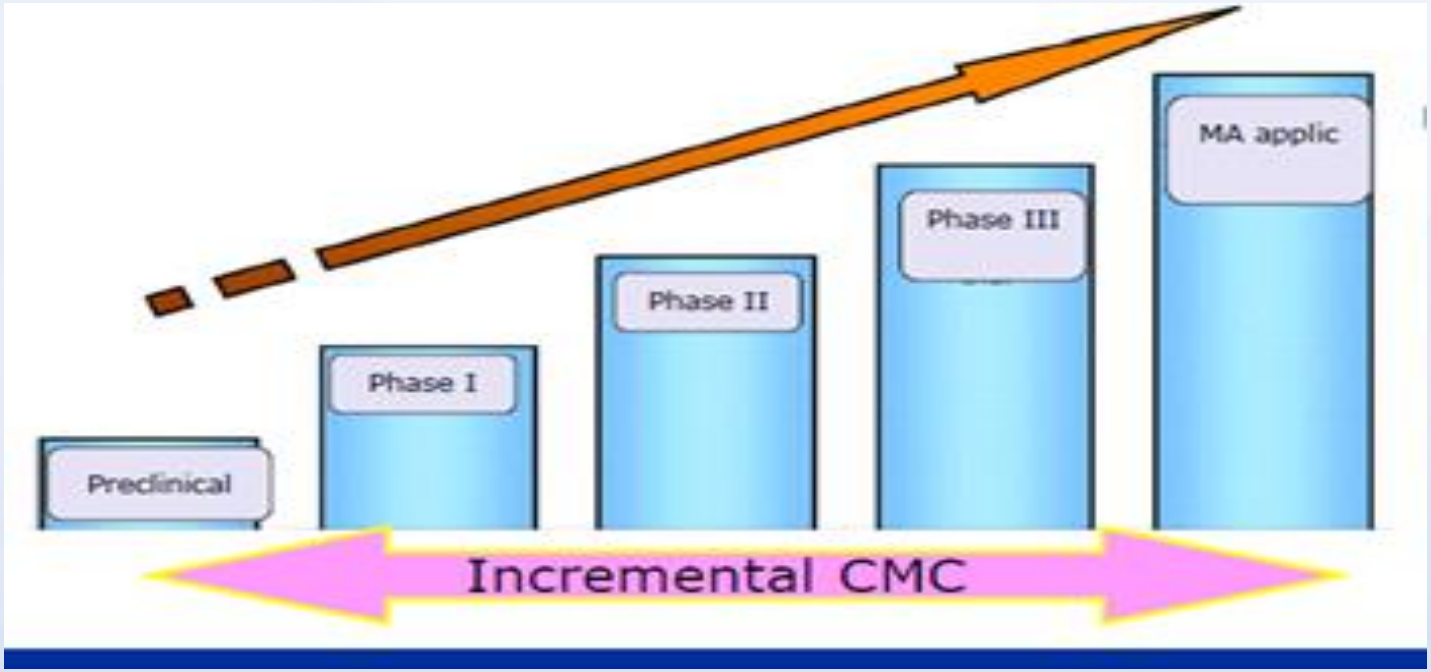
משרד הבריאות
לחיים בריאים יותר

IMPD-Quality

- Quality attributes to control the IMP are important to:
  - demonstrate pharmaceutical **quality**
  - demonstrate product **consistency** and **comparability** after process changes
  - improve the ability of **linking the quality of product from each study** and maximizing the relevance of the information gained

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר



MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

General Structure of Quality Module of Investigational Medicinal Product

- **IMPD or IND equivalent**
  - **logical structure**, such as the headings of the current version of the IMPD Guideline (CHMP/QWP/185401/2004 final).
  - CTD structure where appropriate- Module 3 - Quality
    - **IMPD: limited and "growing" during development**
    - **Safety of patients is not compromised**

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

IMPD Structure on Quality Data

- 2.1.S Drug Substance
  - 2.1.S.1 General Information
  - 2.1.S.2 Manufacture
  - 2.1.S.3 Characterisation
  - 2.1.S.4 Control of the Drug Substance
  - 2.1.S.5 Reference Standards or Materials
  - 2.1.S.6 Container Closure System
  - 2.1.S.7 Stability
- 2.1.P IMP under Test
  - 2.1.P.1 Description and Composition
  - 2.1.P.2 Pharmaceutical Development
  - 2.1.P.3 Manufacture
  - 2.1.P.4 Control of Excipients
  - 2.1.P.5 Control of the Investigational Medicinal Product
  - 2.1.P.6 Reference Standards or Materials
  - 2.1.P.7 Container Closure System
  - 2.1.P.8 Stability

APPENDICES

- 2.1.A.1 Facilities and Equipment:
- 2.1.A.2 Adventitious Agents Safety Evaluation:
- 2.1.A.3 Novel excipients:
- 2.1.A.4 Solvents for Reconstitution and Diluents

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

- The IMP dossier required will depend on many factors,

  One size does not fit all;

- Some risk aspects
  - nature of the product e.g.
    - Biological molecules with novel mechanism of action
    - New agents with a high degree of species-specificity
    - New agents with immune system targets
  - state of development
  - patient population
  - nature and severity of the illness
  - No. of doses

Requirements for Phase I-III-Examples

	Phase I	Phase II	Phase III
Pharmaceutical development	Short description (when applicable)	Brief summary , taking into account changes of clinical relevance	summary , taking into account changes of clinical relevance
Control of critical Steps and intermediates	No data are required except for non standard and manufacture processes of sterile products	No data are required except for non standard and manufacture processes of sterile products	Additional information
Specifications	Oriented	Preliminary	Should be reviewed
Validation of analytical procedures	Suitability of + Table of acceptance limits for validation (required for microbial safety)	Tabulated summary of results	Validation report to be held
stability	Initiation	Increase availability	of data

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

IMPD-Guidelines

- **Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004)**
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials Draft(EMA/CHMP/QWP/834816/2015
- **Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials**

(EMA/CHMP/BWP/534898/2008)

- Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (EMA/CHMP/BWP/534898/2008 rev. 1)
- **Guideline on strategies to identify and mitigate risks for first in**

human CTs with IMPD (EMEA/CHMP/SWP/28367/07)

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

INDs - FDA guidelines

- Guidance for Industry: Content and Format of Investigational New Drug Applications(INDs)for Phase 1studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology – derived products

- Guidance for Industry: INDs for Phase 2 and Phase 3 Studies

  Chemistry, Manufacturing, and Controls Information

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

Thinking ahead!

A little planning up front,
can help avoid problems later

MINISTRY OF HEALTH

משרד הבריאות
לחיים בריאים יותר

תודה רבה על ההקשבה