The Pharmaceutical & Fine Chemical Company

Aspetti regolatori delle proprietà fisiche di un API

April 23rd 2015

Annalisa Scali – Regulatory Affairs
Euticals SpA

Presentation approach

- General overview of the most important definitions ;
- General overview of the regulatory guidelines requirements ;
- Discussion of the regulatory aspects of the information that is required for the API Prequalification ;

Some definitions

Active Pharmaceutical Ingredient (API) (or Drug Substance)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Drug (Medicinal) Product

The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Physical properties

-moisture content

-solid state/crystallography (eg. polymorphism, level of solvation, crystalline/amorphous character)

-particle properties (eg. particle size)

EUTICALS

Some definitions

Enantiomers

Compounds with same molecular formula as substance but differ in spatial arrangement of atoms and are non-super imposable mirror images

Polymorphism

Different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudo polymorphs) and amorphous forms. Per the current regulatory scheme, different polymorphic forms are considered the same active ingredients.

Co-crystals

solids that are crystalline materials composed of two or more molecules in the same crystal lattice. Given the association of two or more molecules in the co-crystal lattice, it is useful to consider the association of components more generally.

EUTICALS

Available information on API

Applicants should collect and analyze available information of the API in a systematic approach that

- Leads to a sound scientific understanding of the API, with respect to properties, stability, specifications, etc.
- Assists in API manufacture and DMF compilation
- Leads to the appropriate choice of API manufacturer (source)
- Assists in dossier compilation
- Is important for FPP pharmaceutical development
- Leads to reduction of time / cost

EUTICALS

Literature information on API

- Standard works / series / books
- Scientific Journals
- Pharmacopoeial monographs (current)
- Analysis of structure & stereochemistry

EUTICALS

Information from literature and structures

APIs which are organic compounds, have unique chemical structures & stereochemistry

These structures, together with the solid/liquid state conditions, are basically responsible for chemical and physical properties of the APIs

Literature support

The literature information used in the dossier should always be accompanied by :

- Full traceable reference citations
- Photocopies of publication or relevant pages

Guidelines

- Guideline on Active Substance Master File Procedure EMEA/CVMP/134/02 Rev 3/Corr - EMEA/CVMP/134/02 Rev 3/Corr

- GUIDELINE ON ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILE (APIMF) PROCEDURE

- Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier [CPMP/QWP/297/97 Rev 1 corr]

- ICH IMPURITIES IN NEW DRUG SUBSTANCES Q3A(R2)

- ICH SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES Q6A

- SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS Q6B

- ICH PHARMACEUTICAL DEVELOPMENT Q8(R2)

- ICH DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES) Q11

EUTICALS

Guidelines

- Health Canada Draft Guidance Document - Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

- FDA Guidance for Industry Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well- Characterized, Therapeutic, Biotechnology-derived Products

- FDA GUIDELINE FOR SUBMITTING SUPPORTING DOCUMENTATION IN DRUG APPLICATIONS FOR THE MANUFACTURE OF DRUG SUBSTANCES

- Biopharmaceutics Classification System Based Biowaiver

- Stereochemical Issues in Chiral Drug Development

- Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing, and Controls Information,

EUTICALS

Properties of APIs

Scenarios

API not described in Official Monographs (Non - compendial)

Considered new
(?) information on (adverse) drug reaction
Risk estimation high
Profound information necessary

API described in Official Monographs (compendial)

Considered in use
Information on (adverse) drug reaction (monitored)
Risk estimation based on available data
Information necessary limited to data beyond the monograph
Essential control by the monograph

EUTICALS

Properties of API(s)

NON COMPENDIAL APIs

a) Evidence of chemical structure

- spectral data
  - Single crystal X-ray structure (sufficient) or
  - Spectrometric data (IR, ^{1}H & ^{13}C NMR, MS, etc.): certified copies of the spectra and tabulated data with assignments against structure/interpretation of data (narrative)

b) Evidence of chemical structure

- Isomerism
- Stereochemistry
- Discussion of potential isomeric forms

EUTICALS

Properties of API(s)

Properties relevant/critical for the performance of the API

c) Potential polymorphic forms

Influence on physicochemical and physical characteristics (solubility, hardness, compressibility, density, melting point, etc.) Must be controlled

d) Particle size distribution

requirement for low solubility drugs (dissolution, bioequivalence)

e) Additional characteristics

critical characteristics to be controlled to ensure consistent performance of the API (e.g. hygroscopicity)

EUTICALS

Properties of API(s)

Proof of structure/stereochemistry correctness

Correlation against API spectral data from peer reviewed literature, preferable innovator publication (in tabulated form). Strongly recommended

EUTICALS

Properties of API(s)

COMPENDIAL APIs

–Evidence of chemical structure by suitable compendial identification tests

–Properties relevant/critical for the performance of the API (not necessarily covered by the monograph)

a) potential polymorphic forms
Influence on physicochemical and physical characteristics (solubility, hardness, compressibility, density, melting point, etc.) Must be controlled

b) particle size distribution
requirement for low solubility drugs (dissolution, bioequivalence)

c) additional characteristics
critical characteristics to be controlled to ensure consistent performance of the API (e.g. hygroscopicity)

EUTICALS

Properties of API(s)

Physical-chemical and other relevant properties, e.g.

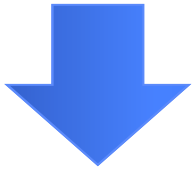
- Solubility in water (effect of pH), other solvents such as ether, ethanol, acetone and dichloromethane
- pKa, partition coefficient
- Existence/absence of polymorphs and pseudo-polymorphs e.g. solvates (with XRPD, DSC, IR)
- Hygroscopicity
- Particle size

EUTICALS

Physical Properties of API(s)

Physicochemical and other relevant properties of the drug substance can be used in developing the specifications, in formulating dosage forms, and in the testing for release and stability purposes.

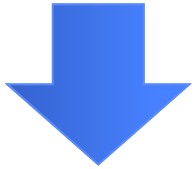
QbD Paradigm



From ICH Q8: "*The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g. solid state properties), should be identified and discussed*. "

Physical Properties of API(s)

Information on the physical and chemical properties of the drug substance covers



- physical description
- solubility in common solvents (e.g. including those used in the manufacturing process, analytical methods or for cleaning)
- quantitative aqueous pH solubility profile
- polymorphism,
- pH and pKa values,
- UV absorption maxima and molar absorption
- melting point
- refractive index (for a liquid)
- hygroscopicity
- partition coefficient

EUTICALS

Physical Properties of API(s)

Physical Properties of API(s)

Physical description (e.g. polymorphic form, solvate, hydrate)

The description should include appearance, colour, and physical state. Solid forms should be identified as being crystalline or amorphous. If the drug substance can exist in more than one physical form, the information included in S.1.3 should be for the form (or forms) of the drug substance that will be used in the manufacture of the drug product or formed through in-situ conversion. Detailed information on the characterization of these and other physical forms should be provided in S.3.1.

Solubility/quantitative aqueous pH solubility profile

Information on the solubility of the drug substance in a number of common solvents (e.g. water, alcohols, buffers, solvents used for manufacturing) should be provided. Information on the solubility over the physiological range, pH 1.2-6.8, should also be provided to determine the Dose/Solubility volume ratio where applicable (e.g. solid orals). If this information is not readily available (e.g. literature references, 'Open' DMF), it should be generated in-house

EUTICALS

Physical Properties of API(s)

Confirmation of structure based on e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

For drugs with a compendial reference standard, it is generally sufficient to provide copies of the IR and UV spectra of the drug substance from the proposed suppliers run concomitantly with suitable primary reference standard. A suitable primary reference standard could be obtained from the Schedule B compendia (e.g. USP, Ph.Eur, BP) or a batch of the drug substance that has been fully characterized (e.g. IR, UV, NMR, MS).

To establish pharmaceutical equivalence (e.g. in an ANDS), include a summary of any comparative studies performed.

The studies carried out to elucidate and/or confirm the chemical structure of new chemical entities normally include elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), and Mass Spectra (MS) studies. Other tests could include X-ray diffraction (XRD), solid state studies or Molecular weight distribution where relevant.
It is recognized that some drugs (e.g. certain antibiotics, enzymes, and peptides) present challenges with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the drug substance to ensure a reproducible drug substance.
If a drug substance consists of more than one active component (e.g. conjugated estrogens), the physicochemical characterization of the components and their ratio should be submitted.

Physical Properties of API(s)

Potential for Isomerism and Identification of Stereochemistry

When a drug substance contains one or more asymmetric centres, structural elucidation should confirm whether the drug substance is a specific stereoisomer or a mixture of stereoisomers or a mesoisomer.
If, based on the structure of the drug substance, there is no potential for isomerism, it is sufficient to include a statement to this effect.

EUTICALS

Physical Properties of API(s)

Polymorphs

If the potential for polymorphism is a concern, results from an investigation of several batches of the drug substance, recrystallized from several solvents, should be provided to determine if the drug substance exists in more than one crystalline form. The study should include the characterization of the batch(es) used in the clinical and/or comparative bioavailability studies, using a suitable method (e.g. X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR)). The absence of the potential for polymorphism can further be confirmed by providing the results of a literature search.
Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs) which should be appropriately characterized using solid state studies.

In-Situ Conversion:
Where investigation of the drug product reveals that the physical (e.g. polymorphic or pseudopolymorphic) or chemical (e.g. free acid/base to salt) form of the API is altered during the manufacturing process or during storage of the drug product, section S.3.1 should include relevant information (e.g. solubility, crystalline structure) for both forms - the API and medicinal ingredient contained in the drug product.

EUTICALS

Physical Properties of API(s)

Co-Crystals

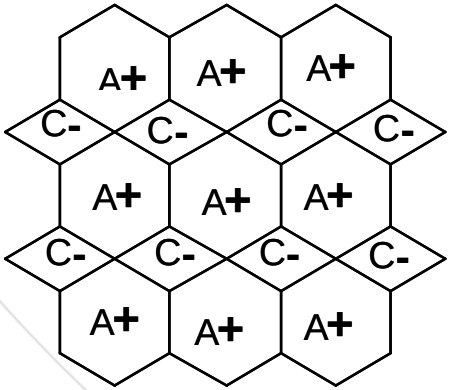
Traditionally, solid-state polymorphic forms of an API are classified as either crystalline, amorphous, or solvate and hydrate forms, and applicable regulatory schemes for these solid-state polymorphic forms are well-defined .

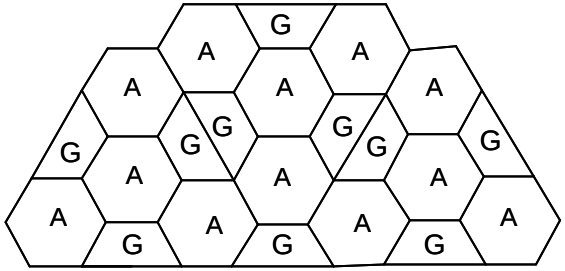
Co-crystals are distinguishable from these traditional pharmaceutical solid-state forms.

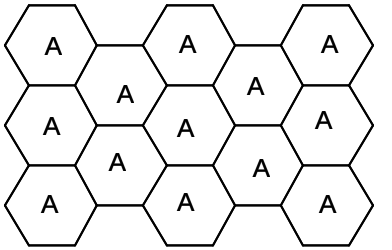
Co-crystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice. Given the association of two or more molecules in the co-crystal lattice, it is useful to consider the association of components more generally. A drug product is a finished dosage form (e.g., tablet; capsule; or solution that contains an active pharmaceutical ingredient (API) generally, but not necessarily, in association with inactive ingredients (excipients)).

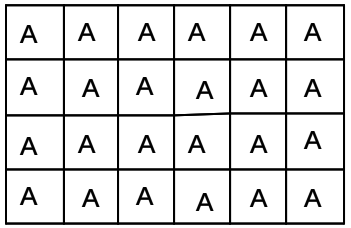
EUTICALS

Physical Properties of API(s)









Crystalline Molecular Complexes: Co- Crystal / Salt Continuum

Crystalline Molecular Complexes: Analogous to Polymorph Solvate (Except other Component in Crystal Lattice is a Solid (not Liquid))

EUTICALS

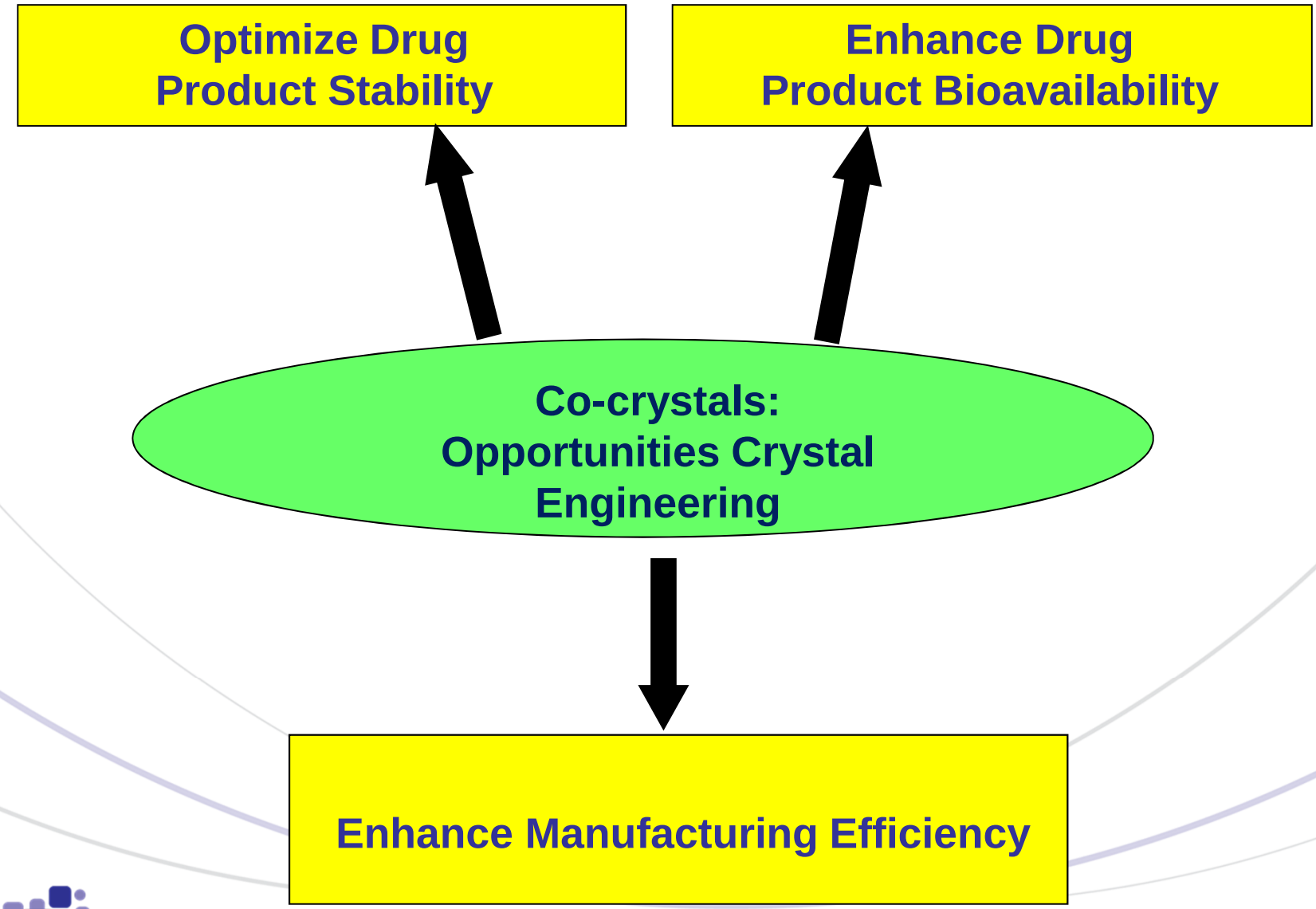
Physical Properties of API(s)

Pharmaceutical co-crystals have opened the opportunity for engineering solid-state forms designed to have tailored properties to enhance drug product bioavailability and stability, as well as enhance processability of the solid material inputs in drug product manufacture.

Pharmaceutical co-crystals are of interest because they offer the advantage of generating a diverse array of solid-state forms from APIs that lack ionizable functional groups needed for salt formation.

EUTICALS

Physical Properties of API(s)



EUTICALS

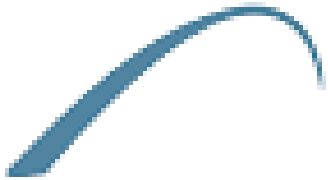
Physical Properties of API(s)

Particle size distribution

For poorly soluble drug substances, the particle size distribution of the material can have an effect on the *in vitro* and/or *in vivo* behaviour (e.g. absorption of the drug from the gastrointestinal tract) of the drug product. Particle size can also be important in dosage form performance (e.g. optimum delivery of inhalation products to the lungs), achieving uniformity of content in low-dose tablets (e.g. 5 mg or less), achieving a smooth suspension to prevent irritation in ophthalmic preparations, and stability and redispersibility of suspensions.

If particle size distribution is important (e.g. as in the above cases), results from an investigation of several (at least three) batches of the drug substance should be provided, including characterization of the pivotal batch(es) (e.g. batches used in the pivotal clinical and/or comparative bioavailability studies). If applicable, the acceptance criteria should include controls on the particle size distribution to ensure consistency with drug substance in the batch(es) used in pivotal studies (e.g. limits for d10, d50, and d90).

The choice of particle size acceptance criteria (single point, multiple point controls) should be discussed based on the desired goal for particle size control and the particle size distribution observed (e.g. bimodal, polydisperse, monodisperse).
If the drug substance is dissolved during the drug product manufacturing process then control of particle size distribution may not be necessary.



THANK YOU
FOR
YOUR ATTENTION

EUTICALS