

Key Considerations for a new chemical entity (NCE)

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Overview



- **SME initiative**
- **Quality requirements in the dossier for a NCE**
(Key considerations and common issues)
 - **Drug substance**
 - **Drug product**
- **Sterile Products**
- **Conclusion**
- **References**

SME Initiative

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- Primary aim: to promote innovation and the development of new medicinal products by smaller companies.

Incentives

- The EU incentives offered by Regulation (EC) No 2049/2005 apply equally to the human and veterinary sectors, and include:
 - Administrative and procedural assistance from the EMEA's SME Office;
 - Fee reductions for scientific advice, inspections and (for veterinary medicines) establishment of maximum residue limits;
 - Fee exemptions for certain administrative services of the EMEA;
 - Deferral of the fee payable for an application for marketing authorisation or related inspection;
 - Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful;
 - Assistance with translations of the product information documents submitted in the application for marketing authorisation.

Quality incentives/derogations?

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- 90% fee reduction for scientific advice (all issues relating to the development of new medicinal products)
- 90% fee reduction for any Good Manufacturing Practice (GMP) inspection requested by the EMEA

No difference in the information expected in the M3 dossier

User Guide for Micro, Small and Medium-sized Enterprises (SMEs)

The administrative and procedural aspects of the provisions, laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs

- how to access financial and administrative assistance
- concise overview of the scientific data requirements for obtaining a marketing authorisation in the European Union (EU)

<http://www.emea.europa.eu/pdfs/SME/20679806en.pdf>

Quality requirements in the dossier for a NCE

Focus specifically on NCE for human medicinal products

(guide also refers to veterinary products as well as orphan medicines and paediatrics)
(mainly focus on drug substance for a solid oral dosage form – sterile products/solutions in some cases more data required (aseptic manufacture/sterilisation validation, packaging requirements, in-use stability) and some cases less (physical characteristics))

Requirements in relation to 2001/83/EC Directive (as amended) & ICH/CHMP guidelines - Key considerations and common issues

Drug Substance (3.2.S.1)

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The drug substance should be well characterised and manufactured by well-described and adequately controlled manufacturing methods

NtA Volume 2B CTD Module 3 – summary of specific requirements and reference to relevant CPMP-ICH guidelines.

International Non-Proprietary Name (INN)

- Apply for early in the clinical development (WHO)

3.2.S.1. General Information

- Structural formula, including stereochemistry, molecular formula and molecular mass
- ★ Physico-chemical properties which might impact on safety and efficacy; solubilities, pKa, log P, permeability, polymorphism* and isomerism*

Drug Substance (3.2.S.2)

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Manufacture

- GMP
- The process should be described in detail (flow charts, process parameters, IPCs, reagent quantity and yields)
- ★ Starting materials should be assigned appropriately!
 - Simple or complex molecules (commercially available or synthesised in-house)
 - fully characterised (appropriate specifications) – analytical method validation
 - potential impurities (carry-over)
- Control of Intermediates
- The Quality (Pharmacopoeia requirements) and use of reagents, catalysts, solvents should be justified.

Drug Substance (3.2.S.2)

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- ★ Intermediate specifications and IPCs and batch data (process validation) reassure that the process is well controlled, understood and reproducible.
 - NCE – years of clinical development can often call on numerous batches to demonstrate suitability of the process.
 - Minimum of 3 primary (pilot scale) batches manufactured by the same synthetic route and method of manufacture as the proposed commercial process with reassurance of scale up capability.
- ★ Significant changes to the manufacturing process. Evidence to demonstrate that there is no change to the overall quality of the drug substance is required.

Drug Substance (3.2.S.3)

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Characterisation

- ★ Elucidation of structure using available analytical methods (NMR, UV, IR, mass spec, elemental analysis)
- ★ Identification of chiral centres and stereochemistry, potential for isomerism (cis/trans) and polymorphism - may impact on safety and efficacy.

Stereochemistry (for molecules with one or more chiral centre)

- With reference to the synthetic route the absolute stereochemistry should be defined
- Single enantiomer – evidence of formation of this stereoisomer
- Racemate – specific optical rotation, m.p. Justification for use?
- Need to be aware that if development commenced with a racemate prior to use of a single enantiomer additional pre-clinical and clinical studies may be required.
- Where a racemate is used, PD and PK studies and data for both enantiomers would normally be expected

Drug Substance (3.2.S.3)

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Polymorphism

- Drug substance may exist in different solid state forms (polymorphs, solvates, hydrates)
- Different physico-chemical properties
- Possible effects on dissolution, bioavailability, stability and processability

Particle size: Drug substances often milled or micronised to generate drug substance with desirable particle size. Need to demonstrate that these processes do not result in the generation of amorphous material or different crystalline polymorphs

Drug Substance (3.2.S.3)

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Impurities

- ★ Summary of actual and possible impurities originating from starting materials and synthetic route (process impurities) and storage (degradation products)
- Reference to ICH guidelines
- Qualification of impurities based on adequate toxicological and clinical studies
- Analytical results for impurities from all batches used for safety and clinical studies as well as stability and submission batches should be provided. (Also allows review of the development of the manufacturing process)
- Potential genotoxic impurities – recent guideline (CHMP/SWP/5199/02)
- Residual solvents (ICH) and inorganic impurities limits defined.

Drug Substance (3.2.S.4)

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Control of the drug substance

- Universal criteria: Description, ID, assay, related substances
- Include anything which may be critical in terms of this particular drug substance (specific optical rotation, XRD, residual solvents, particle size etc)
- ★ Specifications should be justified based on data obtained during development and in line with ICH and Pharmacopoeia requirements

Analytical methods and validation

- ★ Common source of the most questions asked (mainly validation)
 - Define appropriate system suitability parameters and use to demonstrate method robustness
 - Reference to ICH guidelines
 - Determination of impurities – reference standards or determined as a percentage of the principal peak. RRf values? Justification
 - Validated over appropriate ranges
 - Method transfer – re-validation

Drug Substance (3.2.S.7)

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Stability

★ **At least 3 primary batches:**

- Minimum of pilot scale – same synthetic route, same method of manufacture that simulates production process
 - Quality representative of production scale material
 - Container/closure system simulate commercial pack
 - Test appropriate physical, chemical, biological, microbiological attributes
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- Continue studies on 3 production scale batches through re-test period
 - Further studies to a total of at least 3 production scale batches
 - If no data on production scale batches, place first 3 production scale batches on store

Drug Substance (3.2.S.7)

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Data at submission:

- 6 months $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \pm 5\%$
- 6 months $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $65\% \pm 5\%$
- 12 months $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \pm 5\%$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $65\% \pm 5\%$

- If designed for refrigerated storage:
 - Long term: 12 months $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$
 - Accelerated: 6 months $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \pm 5\%$

- If designed for storage frozen:
 - 12 months $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$
 - Short term excursions supported by $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ or $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$

- Forced degradation and Photostability testing

Drug Product (3.2.P.2)

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Pharmaceutical development ★

Aim is to demonstrate a logical progression of development work resulting in a robust, optimised formulation proposed for marketing

- Reiterate the general information on the drug substance (3.2.S.1.)
- Investigate particle size (solubility), flow properties/bulk density (process-ability)
- ★ Identify critical attributes – allow justification of the choice of excipients and manufacturing process
- Excipient compatibility studies
- Novel excipients (new or new route of admin.): Similar data required as that for the drug substance!

Drug Product (3.2.P.2)

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Formulation/manufacturing changes during clinical development ★

- A summary of formulations used during clinical development should be provided
- Any changes between the proposed commercial formulation and the formulations used in early and pivotal clinical studies should be described and justified
- ★ Comparative in vivo bioequivalence (bridging) studies and/or in vitro dissolution studies will be required

WHAT'S REQUIRED – Bioequivalence or Dissolution?

- Significant changes (change of dosage form, qualitative formulation changes) likely to require bioequivalence studies to demonstrate similarity
- Manufacturing process/excipient change (minor) – (variation guideline; 18 & 33)
- IVIVC (level A)
- in vitro dissolution over a pH range (1 – 8). Discriminatory method

Drug Product (3.2.P.3)

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Manufacture

Manufacturing process development should have already been discussed and justified in 3.2.P.2.

Reassurance that the manufacturing process is designed to consistently produce a product of the intended quality ★

- Process should be adequately described, critical process steps identified and IPC's defined
- Process validation – data requirements
 - Standard process: typically 3 pilot scale batches with commercial scale validation protocol
 - Non-standard process: commercial scale validation data required

Quality by Design (Design Space & PAT)?

Drug Product (3.2.P.5)

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Control of the drug product

- Specifications set in accordance with the type of dosage form and the guidelines for new drug products
- Limits proposed for batch release and shelf-life on the basis of batch analytical and stability data with consideration of general quality requirements and ICH guidance.
- Description and validation of analytical methods (requirements as for the drug substance)

Drug Product (3.2.P.8)

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Stability

★ **At least 3 primary batches:**

- Same formulation and market packaging
 - Manufacturing process simulates production process
 - At least two pilot scale batches
 - Where possible different batches of active substance
 - Test each strength & container size unless bracketing / matrixing used
 - Test appropriate physical, chemical, microbiological, biological attributes, preservative content, functionality
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- Stability commitments
 - Continue studies on 3 production scale batches
 - Further studies to at least 3 production scale batches
 - Place first 3 production scale batches on store

Drug Product (3.2.P.8)

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- **Data at submission:**
 - 6 months $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \pm 5\%$
 - 6 months $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $65\% \pm 5\%$
 - 12 months $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \pm 5\%$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $65\% \pm 5\%$
- **Significant change**
 - 5% change in assay – or failure to meet potency criteria
 - Any degradation product exceeding acceptance criteria
 - Failure to meet acceptance criteria unless justified

Sterile products

Whilst most of the key issues for the development of a NCE are similar (3.2.S). Below is a brief summary of some key considerations when the NCE is to be developed as a sterile product.

- Manufacturing authorisation should state type of product (e.g. lyophilised aseptically prepared) and EU GMP (not WHO).
- No microbial limits for excipients or active substance
- Vial headspace gas should be sterile filtered
- No justification for method of sterilisation
- Effect of sterilisation method (terminal) on packaging. Ensuring all parts of the packaging are sterilised using the proposed method
- Pre-filtration bioburden not stated or too high
- No data to support bulk holding times
- Lack of media fill data or information
- Lack of process validation data at production scale when non-standard processes are used.

Conclusions



- Make use of the fee incentives for scientific advice.
- Drug substance synthesis is robust and well controlled. Starting materials are adequately defined. Potential impurities have been identified and have been accurately determined.
- The quality of the drug substance is maintained throughout clinical development.
- The commercial formulation of the drug product is optimised, can be reproducibly manufactured to the intended quality and is stable.
- The results of pivotal clinical studies can be linked to the commercial formulation through appropriate bridging studies.
- Refer to specific EU guidelines for products intended for marketing in EU

References



Scientific advice

<http://www.emea.europa.eu/pdfs/human/sciadvise/426001en.pdf>

SME User Guide

<http://www.emea.europa.eu/pdfs/SME/20679806en.pdf>

European Commission > Enterprise and Industry > Pharmaceuticals

- Pharmaceutical Legislation
- Notice to Applicants
- Guidelines

<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>

ICH website

<http://www.ich.org>

EMA website

<http://www.emea.europa.eu/htms/human/humanguidelines/background.htm>



Thanks for listening