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ICH guidelines of manufacturing and quality assurance of drugs and cosmetics

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ABSTRACT

The key events in the development of the generic drug industry after the Hatch-Waxman Act of 1984 are systematically reviewed, including the process of approval for generic drugs, bioequivalence issues including "switchability", bioequivalence for complicated dosage forms, patent extension, generic drug safety, generic substitution and low-cost generics. The backlog in generic review, generic drug user fees, and "quality by design" for generic drugs is also discussed. The evolution of the US generic drug industry after the Hatch-Waxman Act in 1984 has afforded several lessons of great benefit to other countries wishing to establish or re-establish a domestic generic drug industry.

Keywords: Generic Drugs, Quality by Design, Patent Extension

ICH GUIDELINES IN MANUFACTURING

Introduction ICH Guidelines

This guideline describes approaches to developing process and drug substance understanding and also provides guidance on what information should be provided in CTD sections 3.2.S.2.2 – 3.2.S.2.6. It provides further clarification on the principles and concepts described in ICH guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality Systems (Q10) as they pertain to the development and manufacture of drug substance.

A company can choose to follow different approaches in developing a drug substance. For the purpose of this guideline, the terms "traditional" and "enhanced" are used to differentiate two possible approaches. In a traditional approach, set

points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and more extensive scientific knowledge are used to select process parameters and unit operations that impact critical quality attributes (CQAs) for evaluation in further studies to establish any design space(s) and control strategies applicable over the lifecycle of the drug substance. As discussed in ICH Q8 for drug product, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provided in the application for marketing authorisation.

Traditional and enhanced approaches are not mutually exclusive. A company can use either a traditional approach or an enhanced approach to drug substance development, or a combination of both.

SCOPE

This guideline is applicable to drug substances as defined in the Scope sections of ICH Guidelines Q6A and Q6B, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. It is particularly relevant to the preparation and organisation of the contents of sections 3.2.S.2.2 – 3.2.S.2.6 of Module 3 of the Common Technical Document (ICH M4Q). The guideline does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages. Regional requirements for post-approval changes are not covered by this guideline.

MANUFACTURING PROCESS DEVELOPMENT

General principles

The goal of manufacturing process development for the drug substance is to establish a commercial manufacturing process capable of consistently producing drug substance of the intended quality.

Drug Substance Quality Link to Drug Product

The intended quality of the drug substance should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development of the drug product (e.g., the solubility of the drug substance can affect the choice of dosage form). The Quality Target Product Profile (QTPP) and potential CQAs of the drug product (as defined in ICH Q8) can help identify potential CQAs of the drug substance. Knowledge and understanding of the CQAs can evolve during the course of development.

Process development tools

Quality Risk Management (QRM, as described in ICH Q9) can be used in a variety of activities including assessing options for the design of the manufacturing process, assessing quality attributes and manufacturing process parameters, and increasing the assurance of routinely achieving acceptable quality results. Risk assessments can be carried out early in the development process and repeated as greater knowledge and understanding become available. It is neither always appropriate nor always necessary to use a formal risk management process (using recognised tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.

Knowledge management (as described in ICH Q10) can also facilitate manufacturing process development. In this context, potential sources of information can include prior knowledge and development studies. Prior knowledge can include established biological, chemical and engineering principles and applied manufacturing experience. Data derived from relevant prior knowledge, including platform manufacturing (see glossary) can be leveraged to support development of the commercial process and expedite scientific understanding.

Approaches to Development

ICH Q8 recognizes that "Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission." These concepts apply equally to the development of the drug substance manufacturing process. An applicant can choose either a traditional approach or an enhanced approach to drug substance development, or a combination of both. Manufacturing process development should include, at a minimum, the following elements:

Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on product quality can be studied and controlled;

Defining an appropriate manufacturing process;

Defining a control strategy to ensure process performance and drug substance quality (see Section 6 on Control Strategy).

An enhanced approach to manufacturing process development would additionally include the following elements:

A systematic evaluation, understanding and refining of the manufacturing process, including; Identifying, through e.g. prior knowledge, experimentation and risk assessment, the material attributes and process parameters that can have an effect on drug substance CQAs; Determining the functional relationships that link material attributes and process parameters to drug substance CQAs;

Using the enhanced approach in combination with QRM to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing (RTRT).

The increased knowledge and understanding obtained from taking an enhanced approach could facilitate continual improvement and innovation throughout the product lifecycle (see ICH Q10).

Drug substance critical quality attributes

Linking Material Attributes and Process Parameters to Drug Substance cqas

The manufacturing process development program should identify which material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be controlled. Risk assessment can help identify the material attributes and process parameters with the potential for having an effect on drug substance CQAs. Those material attributes and process parameters that are found to be important to drug substance quality should be addressed by the control strategy.

Using an enhanced approach, the determination of appropriate material specifications and process parameter ranges could follow a sequence such as the one shown below:

- **Identify potential sources of process variability;**
- **Design Space**

Submission of Manufacturing Process Development Information

The information provided on the development of the drug substance manufacturing process (primarily in section 3.2.S.2.6 of the application) should identify significant changes during process development, link relevant drug substance batches with the developmental stage of the manufacturing process used to prepare them, and explain how prior knowledge, risk assessments, and experimental studies (e.g., modelling, simulations, engineering and scientific principles) were used to establish important aspects of the manufacturing process and control strategy. The significance of a drug substance manufacturing change during development should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). Process development information should be logically organised and easy to understand. Manufacturers can present process development information in a number of different ways, but some specific recommendations are provided below for consideration.

Overall process development summary

It is recommended that the manufacturing process development section begin with a narrative summary that describes important milestones in the development of the process and explains how they are linked to assuring that the intended quality of the drug substance is achieved. The following should be included in the summary:

Drug Substance CQAS

The CQAs of the drug substance should be listed, and the rationale for designating these properties or characteristics as CQAs should be

provided. In some cases, it might be appropriate to explain why other properties or characteristics that might be considered potential CQAs are not included in the list of CQAs. Links or references should be provided to information submitted elsewhere in the submission (e.g., 3.2.S.3.1, Elucidation of Structure and other Characteristics) that supports the designation of these properties or characteristics as CQAs. Some discussion of drug substance CQAs as they relate to drug product CQAs can be appropriate in the pharmaceutical development section of the application (e.g., 3.2.P.2.1, Components of the Drug Product).

Manufacturing process history

A description and discussion should be provided of significant changes made to the manufacturing process or site of manufacture of drug substance batches used in support of the marketing application (e.g., those used in nonclinical or clinical studies or stability studies in support of a marketing authorisation) and, if available, production-scale batches. The description should follow a chronological sequence ending with the proposed commercial process.

The reason for each significant change should be explained, together with an assessment of its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). Batch information (batch size or scale, site and date of manufacture, route and process used, and intended purpose (e.g., in a specified toxicology or clinical study)) and supporting data from comparative analytical testing on relevant drug substance batches should be provided or referenced (e.g., batch analysis section 3.2.S.4.4).

For biotechnological/biological products, the manufacturing process history section should include a discussion of comparability during development as described in ICH Q5E. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance and the corresponding drug product can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

Manufacturing developmental studies

The studies and risk assessments used to establish important aspects of the commercial manufacturing process and control strategy cited in the application should be listed (e.g., in tabular form). The purpose or end use of each cited study or risk assessment should be provided.

Each cited study or risk assessment should be summarized with a level of detail sufficient to convey an understanding of the purpose of the study, the data collected, how it was analyzed, the conclusions reached, and the impact of the study on the manufacturing process or further development of the manufacturing process. The particular parameters and ranges studied should be described and discussed in relation to the proposed operating conditions for the commercial manufacturing process (as described in 3.2.S.2.2). The risk assessment tools and study results on which a design space is based should be adequately described. Example 2 shows a possible communication tool for risk ranking of parameters. Where development refers to specific prior knowledge, the relevant information and data should be provided and, where appropriate, the relevance to the particular drug substance should be justified.

Small-scale models used to support process development studies should be described.

Description of Manufacturing Process and Process Controls

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls (see ICH M4Q (3.2.S.2.2).

The description of the manufacturing process should be provided in the form of a flow diagram and sequential procedural narrative. The in-process controls for each step or stage of the process should be indicated in the description. Scaling factors should be included for manufacturing steps intended to span multiple operational scales when the process step is scale dependent. Any design spaces in the manufacturing process should be included as part of the manufacturing process description. Example 3 gives an example of the

presentation of a design space for a biotechnological product.

To facilitate the approval of a design space for a complex product, such as a biotechnological/biological product, an applicant can choose to provide information on how movements within the design space will be managed post approval. This could help the reviewer understand how residual risk will be managed.

Many biotechnological/biological products have complex upstream processes and use splitting and pooling to create a drug substance. An explanation of how batches of drug substance are defined by the manufacturer (e.g., splitting and pooling of harvests or intermediates), should be provided. Details of batch size or scale and batch numbering should be included.

SELECTION OF STARTING MATERIALS AND SOURCE MATERIALS

General principles

- Selection of Starting Materials for Synthetic Drug Substances
- Selection of Starting Materials for Semi-synthetic Drug Substances
- Selection of Source Materials for Biotechnological/Biological Products

Cell banks are the starting point for manufacture of biotechnological/biologics products. Guidance appropriate for cell banks is contained in ICH Q5A, Q5B, and Q5D.

Submission of Information for Starting Material or Source Material

Applicants should identify all proposed starting materials or source materials and provide appropriate specifications. Proposed starting materials should be justified.

Justification of Starting Material Selection for Synthetic Drug Substances

The applicant should provide a justification for how each proposed starting material is appropriate in light of the general principles for the selection of starting materials outlined above in Section 5.1.1. This can include information on:

The ability of analytical procedures to detect impurities in the starting material; The fate and purge of those impurities and their derivatives in subsequent processing steps; How the proposed specification for each starting material will contribute to the control strategy;

The applicant should provide, as part of the justification, a flow diagram outlining the current synthetic route(s) for the manufacture of the drug substance, with the proposed starting materials clearly indicated. Changes to the starting material specification and to the synthetic route from the starting material to final drug substance are subject to regional, post-approval change requirements. In addition, regional requirements concerning starting material suppliers may also be applicable.

An applicant generally need not justify the use of a commercially available chemical as a starting material. A commercially available chemical is usually one that is sold as a commodity in a pre-existing, non-pharmaceutical market in addition to its proposed use as starting material. Chemicals produced by custom syntheses are not considered to be commercially available. If a chemical from a custom synthesis is proposed as a starting material, it should be justified in accordance with the general principles for the selection of starting materials outlined.

In some instances, additional purification steps might be called for to ensure the consistent quality of a commercially available starting material. In these instances, the additional purification steps should be included as part of the description of the drug substance manufacturing process. Specifications should normally be provided for both incoming and purified starting material.

Justification of Starting Material Selection for Semi-Synthetic Drug Substances

Qualification of Source Materials for Biotechnological/Biological Products

Guidance is contained in ICH Q5A, Q5B and Q5D.

CONTROL STRATEGY

General principles

A control strategy is a planned set of controls, derived from current product and process understanding that assures process performance and product quality (ICH Q10). Every drug substance

manufacturing process, whether developed through a traditional or an enhanced approach (or some combination thereof), has an associated control strategy.

A control strategy can include, but is not limited to, the following:

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc.);
- Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (Biotechnological/Biological Products), or order of addition of reagents (Chemical Products));
- In-process controls (including in-process tests and process parameters);
- Controls on drug substance (e.g., release testing).

Approaches to Developing a Control Strategy
Considerations in Developing a Control Strategy

Submission of Control Strategy Information

Description of Manufacturing Process and Process Controls (3.2.S.2.2);

Control of Materials (3.2.S.2.3);
Controls of Critical Steps and Intermediates (3.2.S.2.4);
Container Closure System (3.2.S.6);
Control of Drug Substance (3.2.S.4).

Process Validation/Evaluation
Principles Specific to Biotechnological/Biological Products

Submission of Manufacturing Process Development and Related Information In Common Technical Documents (CTD) Format

The use of an enhanced approach to process development results in the generation of information for which a location in the CTD is not defined. Process development information should usually be submitted in Section 3.2.S.2.6 of the CTD. Other information resulting from development studies could be accommodated by the CTD format in a number of different ways and some specific suggestions are provided below. The applicant should clearly indicate where the different information is located. In addition to what is submitted in the application, certain aspects (e.g., lifecycle management, continual improvement) of this guideline are handled under the applicant's pharmaceutical quality system (see ICH Q10).

Quality Risk Management and Process Development
Critical Quality Attributes (CQAs)
Design Space
Control Strategy
Lifecycle Management

Illustrative examples

These examples are provided for illustrative purposes and only suggest potential uses. This Appendix is not intended to create any new expectations beyond the current regulatory requirements.

Example 1: Linking Material Attributes and Process Parameters to Drug Substance CQAS - Chemical Entity

This example illustrates development of a design space using prior knowledge and chemistry first principles. It depicts both a traditional and enhanced approach to determination of the ranges for parameters controlling the formation of a hydrolysis impurity during Step 5 of the following reaction scheme (Also used in Example 4).

For the purpose of this simplified example, this is the only reaction of intermediate F that occurs during this reflux. The following assumptions where used in the design of the process:
The concentration of intermediate F remains approximately constant.
Temperature remains constant.

The acceptance criterion for the hydrolysis impurity in Intermediate F is 0.30%. (This is based on the CQA in the drug substance and the demonstrated capacity of the subsequent steps to purge the impurity.)

The initial amount of water in the reflux mixture depends on the amount of water in Intermediate E, which can be controlled by drying.

Time of reflux and water concentration were identified as the most important parameters affecting the hydrolysis of intermediate F. Other potential factors were determined to be

insignificant based on prior knowledge and risk assessment.

The reaction was expected to follow second-order kinetics according to the equation below:

$$d\,hydrolysis\_impurity_{k\,H2O\,F}\,dt$$

Where F refers to the concentration of intermediate F.

Through simple experimentation the following graph linking the extent of hydrolysis to time and the water content of intermediate E can be generated

Traditional Approach

In a traditional approach this information would be used to set a proven acceptable range for % water and time that achieves the acceptance criteria for the hydrolysis impurity of 0.30% in intermediate F. This is typically done by setting a target value and maximum such as:

Dry Intermediate E to a maximum water content of 1.0%

Target reflux time of 1.5 hours and a maximum reflux time of 4 hours

Enhanced Approach:

The 2nd order rate equation can be integrated and solved explicitly (Chemical Reaction Engineering, Levenspiel 2nd Edition, 1972).

Solving this equation for time (t) permits the calculation of the maximum allowable reflux time for any combination of initial water content and target level for the hydrolysis impurity. (The initial concentration of intermediate F in the reflux mixture will essentially be constant from batch to batch.) The following graph shows the combination of conditions required to ensure that the hydrolysis impurity remains below 0.30% in intermediate F.Interdependence of Reflux Time and Water Content in the Formation of Hydrolysis Impurity The area below the line in the plot above could be proposed as the design space.

Lifecycle management options

Risk should be reassessed throughout the lifecycle as process understanding increases. Recommendations regarding lifecycle management changes can be found in the Pharmaceutical Quality System (PQS) as described in ICH Q10.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and consequently any extension of ranges for higher risk parameters (i.e. parameters A-F) would normally initiate a regulatory post approval change process.

An applicant can include in the original submission a proposal for how specific future changes to parameters G, H, and I will be managed during the product lifecycle. Extension of ranges for lower risk parameters (J-T) does not require prior regulatory approval, although notification may be called for depending on regional regulatory requirements and guidance. If it is determined subsequently to the filing that there is a change in the risk ranking, such that an extension of ranges for a parameter represents a higher risk, this change should be appropriately filed through the regional regulatory process.

Guide Lines For BE Studies for Approval of ANDA

This guidance is intended to provide recommendations to sponsors and/or applicants planning to include bioavailability (BA) and bioequivalence (BE) information for orally administered drug products in investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and their supplements. This guidance is a revision of the October 2000 guidance. This revised guidance changes recommendations regarding

1. Study design and dissolution methods development,
2. Comparisons of BA measures,
3. The definition of proportionality, and
4. Waivers for bioequivalence studies.

The guidance also makes other revisions for clarification. The revisions should provide better guidance to sponsors conducting BA and BE studies for orally administered drug products. This guidance contains advice on how to meet the BA and BE requirements set forth in part 320 (21 CFR part 320) as they apply to dosage forms intended for oral administration. The guidance is also generally applicable to non-orally administered drug products where reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). The guidance should be useful for applicants planning to conduct BA and BE studies during the IND period for an NDA, BE

studies intended for submission in an ANDA, and BE studies conducted in the post approval period for certain changes in both NDAs and ANDAs.

Ensuring uniformity in standards of quality, efficacy and safety of pharmaceutical products is the fundamental responsibility of CDSCO. Reasonable assurance has to be provided that various products, containing same active ingredients, marketed by different licensees, are clinically equivalent and interchangeable.

Accordingly, the bioavailability of an active substance from a pharmaceutical product should be known and reproducible. In most cases, it is cumbersome and unnecessary to assess this by clinical studies. Bioavailability and bioequivalence data is therefore required to be furnished with applications for new drugs, as required under Schedule Y, depending on the type of application being submitted.

Both bioavailability and bioequivalence focus on the release of a drug substance from its dosage form and subsequent absorption into the systemic circulation. For this reason, similar approaches to measuring bioavailability should generally be followed in demonstrating bioequivalence.

Bioavailability can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the early drug development can serve as a benchmark for subsequent BE studies.

GENERAL

Bioavailability

Bioavailability is defined in § 320.1 as:

The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

This definition focuses on the processes by which the active ingredients or moieties are released from an oral dosage form and move to the site of action.

From a pharmacokinetic perspective, BA data for a given formulation provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the BA data for a solution, suspension, or intravenous dosage form (21 CFR 320.25(d)(2) and (3)). In addition, BA studies provide other useful pharmacokinetic information related to distribution, elimination, the effects of nutrients on absorption of the drug, dose proportionality, linearity in pharmacokinetics of the active moieties and, where appropriate, inactive moieties. BA data may also provide information indirectly about the properties of a drug substance before entry into the systemic circulation, such as permeability and the influence of presystemic enzymes and/or transporters (e.g., p-glycoprotein).

Good clinical practice (gcp) guidelines

Good Clinical Practice Guidelines issued by Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India.

Modified release dosage forms

Modified-release dosage forms are those for which the drug-release characteristics of time course and/or drug-release location are chosen to accomplish such therapeutic or convenience objectives that are not offered by immediate-(conventional) release dosage forms.

Pharmaceutical equivalents

Pharmaceutical equivalents are drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients.

Pharmaceutical alternatives

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester.

Pharmacodynamic evaluation

Pharmacodynamic evaluation is measurement of the effect on a patho- physiological process as a function of time, after administration of two different products to serve as a basis for bioequivalence assessment.

Pharmacokinetics deals with the changes of drug concentration in the drug product and changes of concentration of a drug and/or its metabolite(s) in the human or animal body following administration of the drug product, i.e., the changes of drug concentration in the different body fluids and tissues in the dynamic system of liberation, absorption, distribution, body storage, binding, metabolism, and excretion.

Non-linear pharmacokinetics

Nonlinear kinetics or saturation kinetics refers to a change of one or more of the pharmacokinetic parameters during absorption, distribution, metabolism, and excretion by saturation or overloading of processes due to increased dose sizes.

Reference product

For purpose of these guidelines, the reference product is a pharmaceutical product which is identified by the Licensing Authority as "Designated Reference Product" and contains the same active ingredient(s) as the new drug. The Designated Reference Product will normally be the global innovator's product. An applicant seeking approval to market a generic equivalent must refer to the Designated Reference Product to which all generic versions must be shown to be bioequivalent. For subsequent new drug applications in India the Licensing Authority may, however, approve another Indian product as Designated Reference Product.

Supra-bioavailability

This is a term used when a test product displays an appreciably larger bioavailability than the reference product.

Sustained release dosage form

These are modified release dosage forms where the liberation (drug release) rate constant is smaller than the unrestricted absorption rate constant.

Steady state

Steady state is the state when the plasma concentration of drug at any time point during any dosing interval should be identical to the concentration at the same time during any other dosing interval. The steady state drug concentrations fluctuate (oscillate) between a maximum and a minimum steady state concentration within each of the dosing intervals.

Therapeutic equivalents

Therapeutic equivalents are drug products that contain the same active substance or therapeutic moiety and, clinically show the same efficacy and safety.

Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve.

SCOPE OF THE GUIDELINES

Bioavailability and Bioequivalence studies are required by regulations to ensure therapeutic equivalence between a pharmaceutically equivalent test product and a reference product. Several in vivo and in vitro methods are used to measure product quality**.**

DESIGN AND CONDUCT OF STUDIES

Pharmacokinetic studies

Study Design

The basic design of an in-vivo bioavailability study is determined by the following:

1. What is the scientific question(s) to be answered.
2. The nature of the reference material and the dosage form to be tested.
3. The availability of analytical methods.
4. Benefit-risk ratio considerations in regard to testing in humans.

The study should be designed in such a manner that the formulation effect can be distinguished from other effects. Typically, if two formulations are to be compared, a two-period, two-sequence crossover design is the design of choice with the two phases of treatment separated by an adequate washout period which should ideally be equal to or more than five half life's of the moieties to be measured. Alternative study designs include the parallel design for very long half-life substances or the replicate design for substances with highly variable disposition. Single-dose studies generally suffice. However situations as described below may demand a steady-state study design:

- Dose or time-dependant pharmacokinetics.
- Some modified release products (in addition to single dose investigations)

- Where problems of sensitivity preclude sufficiently precise plasma concentration measurements after single-dose administration.
- If intra-individual variability in the plasma concentration or disposition precludes the possibility of demonstrating bioequivalence in a reasonably sized single-dose study and this variability is reduced at steady state.

Study Population

1. Selection of the Number of Subjects
2. Selection Criteria for Subjects

Genetic phenotyping

Phenotyping and/or genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design. It may also be considered in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons. If a drug is known to be subject to major genetic polymorphism, studies could be performed in panels of subjects of known phenotype or genotype for the polymorphism in question. While designing a study protocol, adequate care should be taken to consider Pharmacogenomic issues in the context of Indian population.

Study conditions

Standardisation of the study environment, diet, fluid intake, post-dosing postures, exercise, sampling schedules etc. is important in all studies. Compliance to these standardisations should be stated in the protocol and reported at the end of the study, in order to reassure that all variability factors involved, except that of the products being tested, have been minimised. Unless the study design requires, subjects should abstain from smoking, drinking alcohol, coffee, tea, xanthine containing foods and beverages and fruit juices during the study and at least 48 hours before its commencement.

1. Selection of Blood Sampling Points/Schedules
2. Fasting and Fed State Considerations
3. Steady State Studies

In following cases - an additional "steady state study" is considered appropriate:

Characteristics to be investigated during bioavailability /bioequivalence studies

In most cases evaluations of bioavailability and bioequivalence will be based Upon the measured concentrations of the active drug substance(s) in the biological matrix. In some situations, however, the measurements of an active or inactive metabolite may be necessary. These situations include (a) where the concentrations of the drug(s) may be too low to accurately measure in the biological matrix, (b) limitations of the analytical method, (c) unstable drug(s), (d) drug(s) with a very short half-life or (e) in the case of prodrugs. Racemates should be measured using an achiral assay method. Measurement of individual enantiomers in bioequivalence studies is recommended where all of the following criteria are met:

a. the enantiomers exhibit different pharmacodynamic characteristics
b. the enantiomers exhibit different pharmacokinetic characteristics
c. primary efficacy / safety activity resides with the minor enantiomer
d. non-linear absorption is present for at least one of the enantiomers

The plasma-time concentration curve is mostly used to assess the rate and extent of absorption of the study drug. These include pharmacokinetic parameters such as the C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

For studies in the steady state $AUC_{0-\tau}$, C_{max}, C_{min} and degree of fluctuation should be calculated.

Bioanalytical methodology

The bio analytical methods used to determine the drug and/or its metabolites in plasma, serum, blood or urine or any other suitable matrix must be well characterized, standardized, fully validated and documented to yield reliable results that can be satisfactorily interpreted.

Although there are various stages in the development and validation of an analytical procedure, the validation of the analytical method can be envisaged to consist of two distinct phases:

1. The pre-study phase which comes before the actual start of the study and involves the validation of the method on biological matrix human plasma samples and spiked plasma samples.

2. The study phase in which the validated bioanalytical method is applied to the actual analysis

of samples from bioavailability and bioequivalence studies mainly to confirm the stability, accuracy and precision.

Pre-study Phase

The following characteristics of the bioanalytical method must be evaluated and documented to ensure the acceptability of the performance and reliability of analytical results:

Stability of the drug/metabolites in the biological matrix

Stability of the drug and/or active metabolites in the biological matrix under the conditions of the experiment (including any period for which samples are stored before analyses) should be established. The stability data should also include the influence of at least three freezing and thawing cycle's representative of actual sample handling. The absence of any sorption by the sampling containers and stoppers should also be established.

Specificity/selectivity

Data should be generated to demonstrate that the assay does not suffer from interference by endogenous compounds, degradation products, other drugs likely to be present in study samples, and metabolites of the drug(s) under study.

Sensitivity

Sensitivity is the capacity of the test procedure to record small variations in concentration. The analytical method chosen should be capable of assaying the drug/metabolites over the expected concentration range. A reliable lowest limit of quantification should be established based on an intra- and inter-day coefficient of variation usually not greater than 20 percent. The limit of detection (the lowest concentration that can be differentiated from background levels) is usually lower than the limit of quantification. Values between limit of quantification and limit of detection should be identified as "Below Quantification Limits."

Precision and accuracy

Precision (the degree of reproducibility of individual assays) should be established by replicate assays on standards, preferably at several concentrations. Accuracy is the degree to which the 'true' value of the concentration of drug is estimated by the assay. Precision and accuracy should normally be documented at three concentrations (low, medium, high) where 'low'

Comparative clinical studies

In several instances (For example, section 3.1.1(e) above), the plasma concentration time-profile data may not be suitable to assess equivalence between two formulations. Whereas in some of the cases pharmacodynamic studies can be an appropriate tool for establishing equivalence, in other instances this type of study cannot be performed because of lack of meaningful pharmacodynamic parameters which can be measured and a comparative clinical study has to be performed in order to demonstrate equivalence between two formulations. Comparative clinical studies may also be required to be carried out for certain orally administered drug products when pharmacokinetic and pharmacodynamic studies are not feasible. However, in such cases, the applicant should outline what other methods were tried and why they were found unsuitable. If a clinical study is considered as being undertaken to prove equivalence, the appropriate statistical principles should be applied to demonstrate bioequivalence. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects in bioequivalence studies.

The following items are important and need to be defined in the protocol in advance:

a. The target parameters which usually represent relevant clinical end-points from which the intensity and the onset, if applicable and relevant, of the response are to be derived.
b. The size of the acceptance range has to be defined case-to- case taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance range in clinical trials cannot be based on a general consensus on all the therapeutic classes and indications.
c. The presently used statistical method is the confidence interval approach. The main concern is to rule out that the test product is inferior to the reference product by more than the specified amount. Hence, a one-sided confidence interval

(for efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.

d. Where appropriate, a placebo leg should be included in the design.
e. In some cases, it is relevant to include safety end-points in the final comparative assessments.

In Vitro studies

In certain situations a comparative *in vitro* dissolution study may be sufficient to demonstrate equivalence between two drug products. The test methodology adopted should be in line with the pharmacopoeial requirements unless those requirements are shown to be unsatisfactory. Alternative methods may be acceptable provided they have sufficient discriminatory power. Dissolution studies should generally be carried out under mild agitation conditions at 37±0.5°C and at physiologically relevant pH. More than one batch of each formulation should be tested. Comparative dissolution profiles, rather than single point dissolution test data, should be generated.

CONCLUSION

Today various pharmaceutical companies developing generic drug products. Bioequivalence study is important for generic drug approval process. It is our hope that, this will provide an easy quick overview for Regulatory consideration required for bioequivalence study in different countries. This review covers major aspect of requirement of bioequivalence study along with the regulatory specification of various countries.

The modern US generic pharmaceutical industry was created by the Hatch-Waxman Act and began accepting the first ANDAs in November 1984. The industry got off to a bad start with widespread bribery and fraud characterizing the first 5 years. The generic drug scandal damaged the reputation of the FDA and shook public confidence in the Agency and in generic drugs. However, the changes made as a result of the scandal changed the relationship of FDA with the generic drug industry and ultimately restored public confidence in generic drug products.

Generic drugs were about 13% of all prescriptions in 1984 and grew rapidly after the Hatch-Waxman Act was passed. By the late 1990s generic drugs were about 50% of prescriptions. They remained at this level until the mid-2000s when prescription growth resumed following patent expiration for a number of key “first in class” drugs. Generic prescription growth has accelerated in the last few years and in calendar 2012, reached 84% of prescriptions.

The growth of generic drug use in the US has been impressive, and likely beyond the most optimistic estimates at the time the law was passed. This has been driven by a number of factors, the success of the generic product substitution system with its provider profit motivation, the high cost of brand products which creates a lot of “pricing space” for cheaper generic alternatives, the gradual addition of most major therapeutic classes to the generic drug product range, the lack of productivity of the brand industry in finding new small molecule drugs, and government efforts to increase generic drug use through government entitlement programs have all helped to drive generic drug utilization. Generic drug use now stands at an all-time high. The brand industry now has a prescription share of less than 20% and is attempting to maintain profitability by increasing prices on existing products rather than on new products which have historically driven the brand industry. This situation cannot persist for more than a few more years and the future of the brand industry looks uncertain.

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