Univerza v Ljubljani
Fakulteta za farmacijo

Biološka uporabnost in biološka ekvivalenca

Iztok Grabnar

Univerza v Ljubljani
Fakulteta *za farmacijo*

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Uvedba sistema medsebojno zamenljivih zdravil z najvišjo priznano ceno

Originalno vs. generično zdravilo

Generično zdravilo

ZZdr-1 (15. 3. 2006)

6. Člen (definicije)

Generično zdravilo je zdravilo, ki ima enako kakovostno in količinsko sestavo, učinkovine in farmacevtsko obliko kakor referenčno zdravilo in čigar bioekvivalenca z referenčnim izdelkom je dokazana z ustreznimi študijami biološke uporabnosti. Različne soli, estri, etri, izomeri, zmesi izomerov, kompleksi ali derivati učinkovine se obravnavajo kot enaka učinkovina, razen če se pomembno razlikujejo glede varnosti ali učinkovitosti ali obojega. V takem primeru mora predlagatelj predložiti dodatne informacije o varnosti ali učinkovitosti ali obojem različnih soli, estrov, derivatov učinkovine v zdravilu, ki je že pridobilo dovoljenje za promet z zdravilom. Različne peroralne oblike s takojšnjim sproščanjem se obravnavajo kot enake farmacevtske oblike. Študije biološke uporabnosti ni treba predložiti, kadar tako določajo ustrezna navodila, pripravljena v skladu z znanstveno tehničnimi dognanji.

Predlog za izdajo dovoljenja za promet z zdravilom vsebuje vlogo in naslednjo dokumentacijo

ZZdr-1, 23. člen

- **Splošni del**
- **Farmacevtsko-kemični in biološki del**
- **Neklinični farmakološko-toksikološki del**
- **Klinični del**

Splošni del

Vsebuje podatke o proizvajalcu, mestu izdelave, predlagatelju, bodočem imetniku dovoljenja za promet, podatke o zdravilu, podatke o že izdanih dovoljenjih za promet ali o zavrnitvi ali preklicu dovoljenja za promet, povzetek glavnih značilnosti zdravila, navodilo za uporabo, osnutek ovojnine, podatke o statusu zdravila sirote, če ga je zadevno zdravilo pridobilo, izvedenska poročila in povzetke, oceno razmerja med tveganjem in koristjo zdravila, oceno tveganja za okolje in ostale podatke, potrebne za varovanje javnega zdravja, posebej za rizična zdravila.

Farmacevtsko-kemični in biološki del

Vsebuje podatke o kakovostni in količinski sestavi, opis načina izdelave, kontrolo kakovosti vhodnih snovi, kontrole kakovosti v procesu izdelave, kontrolo kakovosti končnega izdelka, stabilnostne študije ter ostale potrebne podatke za varovanje javnega zdravja.

Neklinični farmakološko-toksikološki del

Vsebuje podatke o farmakodinamičnih in farmakokinetičnih lastnostih zdravila, toksičnosti zdravila, vplivu na reprodukcijske funkcije, podatke o embrio-fetalni toksičnosti, mutagenosti in rakotvornem potencialu, podatke o lokalnem prenašanju, o izločanju in ostale podatke, potrebne za varovanje javnega zdravja. Za zdravila, ki se uporabljajo v veterinarski medicini, farmakološko-toksikološki del vsebuje tudi podatke o ostankih in predlog karence.

Klinični del

Vsebuje splošne podatke o preskušanju, o izvajanju preskušanja, rezultate preskušanja, klinično-farmakološke podatke, podatke o biološki uporabnosti/bioekvivalenci (če je potrebna), podatke o klinični varnosti in učinkovitosti, dokumentacijo o izjemnih okoliščinah v preskušanju (če je potrebno) ter podatke o izkušnjah, pridobljenih po pridobitvi dovoljenja za promet v drugih državah, ter druge podatke, ki so potrebni za varovanje javnega zdravja.

Koncept bistvene podobnost

ZZdr-1, 25. člen

- Ne glede na določbe 23. člena tega zakona predlagatelju ni treba predložiti rezultatov nekliničnih farmakološko-toksikoloških ali kliničnih preskušanj, za zdravila za uporabo v veterinarski medicini tudi ne rezultatov testiranja ostankov, če dokaže, da je predmet postopka generično zdravilo, katerega referenčno zdravilo je pridobilo dovoljenje za promet v Republiki Sloveniji ali Evropski uniji pred najmanj osmimi leti.
- Generično zdravilo iz prejšnjega odstavka ne sme biti v prometu deset let od pridobitve dovoljenja za promet referenčnega zdravila.

- Če referenčno zdravilo iz prvega odstavka tega člena ni pridobilo dovoljenja za promet v Republiki Sloveniji, predlagatelj v vlogi za pridobitev dovoljenja za promet navede državo članico Evropske unije, v kateri je zdravilo pridobilo dovoljenje za promet.
- Organ, pristojen za zdravila, v 30 dneh po prejemu popolne vloge zahteva od pristojnega organa izbrane države članice Evropske unije potrdilo o izdanem dovoljenju za promet z referenčnim zdravilom in podatke o količinski in kakovostni sestavi učinkovine in pomožnih snoveh referenčnega zdravila ter po potrebi vso ostalo relevantno dokumentacijo.
- V skladu s predpisi Evropske unije država članica, ki je izdala dovoljenje za promet z referenčnim zdravilom, pošlje potrdilo in podatke iz prejšnjega odstavka v enem mesecu od prejema zahteve.

Podatkovna zaščita

Desetletno obdobje iz drugega odstavka prejšnjega člena se podaljša na največ 11 let, če v obdobju prvih osmih let trajanja desetletnega obdobja iz drugega odstavka prejšnjega člena imetnik dovoljenja za promet pridobi dovoljenje za eno ali več novih terapevtskih indikacij, za katere se predpostavlja, da bodo imele pomembno klinično korist v primerjavi z obstoječimi načini zdravljenja.

Dodatne zahteve in biološka zdravila

- Če zdravilo ne ustreza definiciji generičnega zdravila ali če bioekvivalence ni možno dokazati s študijami biološke uporabnosti ali ob spremembah učinkovin, indikacij, jakosti, farmacevtske oblike ali načina aplikacije glede na referenčno zdravilo, je treba predložiti rezultate ustreznih nekliničnih farmakološko-toksikoloških ali kliničnih študij.
- Če biološko zdravilo, ki je podobno referenčnemu zdravilu, ne ustreza definiciji generičnega zdravila zaradi razlik, ki zadevajo vhodne snovi ali postopek izdelave v primerjavi z referenčnim zdravilom, morajo biti k predlogu za pridobitev dovoljenja za promet dodani rezultati ustreznih nekliničnih farmakološko-toksikoloških ali kliničnih študij, ki se nanašajo na navedene razlike.

Dobro uveljavljena uporaba

Ne glede na določbe 23. člena tega zakona predlagatelju v vlogi ni treba predložiti lastnih podatkov o nekliničnih farmakološko-toksikoloških ali kliničnih preskušanjih, za zdravila za uporabo v veterinarski medicini pa tudi ne rezultatov testiranja ostankov, če dokaže, da imajo učinkovine zdravila že dobro uveljavljeno medicinsko ali veterinarsko uporabo z znano učinkovitostjo in sprejemljivo ravnjo varnosti in je v uporabi v primernem obsegu že najmanj deset let na območju Evropske unije in če obstaja dovolj objavljene literature o uporabi učinkovine. V takem primeru mora namesto lastnih podatkov predložiti ustrezne podatke iz literature.

Medsebojno priznavanje

- Nacionalni postopek za pridobitev dovoljenja za promet z zdravilom v Republiki Sloveniji.
- Decentralizirani postopek (medsebojno priznavanje) je postopek za pridobitev dovoljenja za promet z zdravilom, ki se začne hkrati v referenčni in v zadevnih državah članicah Evropske unije.
- Centralizirani postopek je postopek pridobitve dovoljenja za promet z zdravilom v Evropski uniji, kakor ga določa Uredba 726/2004/ES.

Bistvena podobnost (Essential similarity)

Bistvena podobnost zdravila je enaka kvalitativna in kvantitativna sestava učinkovine v enaki farmacevtski obliki (ali različne peroralne oblike s takojšnjim sproščanjem), z dokazano bioekvivalenco (če je potrebno), dokler se znanstveno ne dokaže pomembna razlika glede varnosti in učinkovitosti zdravil

Biološka uporabnost vs. bioekvivalenca

Biološka uporabnost
Bioavailability

EMEA, Note for guidance on the investigation of bioavailability and bioequivalence

2.3 Bioavailability

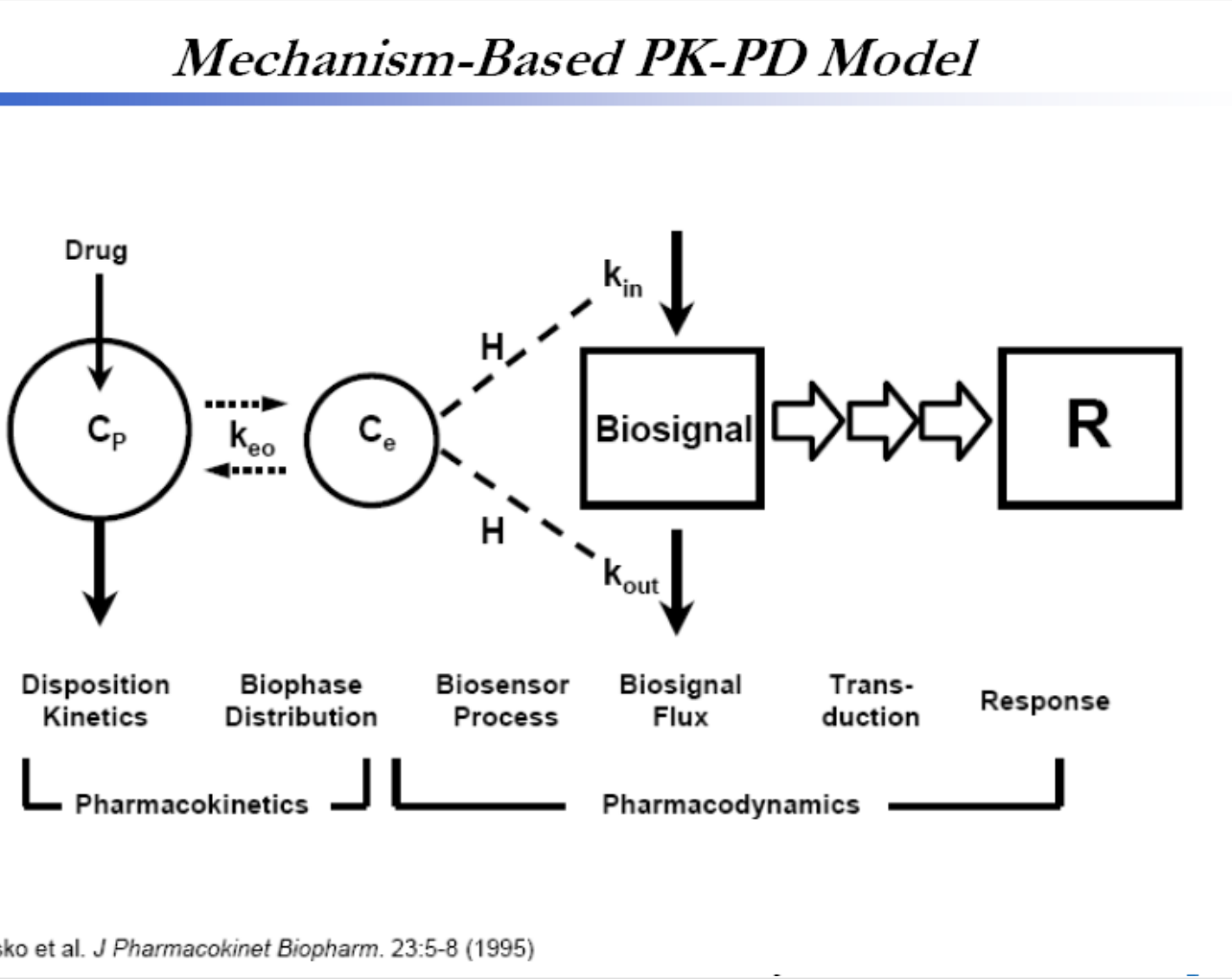
Bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

In the majority of cases substances are intended to exhibit a systemic therapeutic effect, and a more practical definition can then be given, taking into consideration that the substance in the general circulation is in exchange with the substance at the site of action:

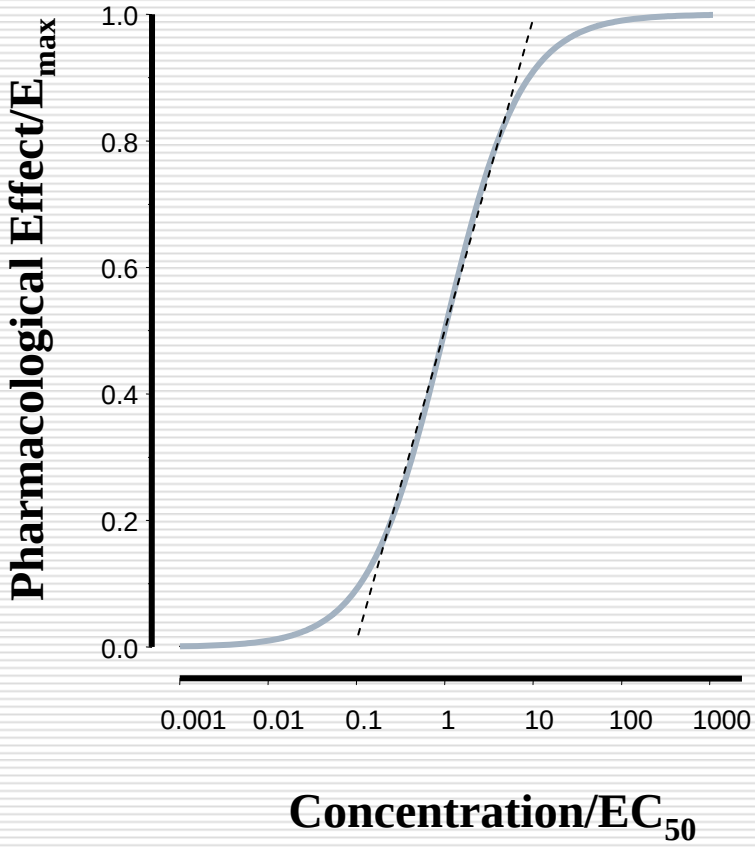
> -Bioavailability is understood to be the extent and the rate at which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non intravenous route (e.g. tablets vs. oral solution).

Farmakokinetika/farmakodinamika/ klinični učinki



Farmakodinamični model



Static Functions Related to Hill Equation

$$E = E_o \pm S.\ C_P \qquad \text{Eq 1}$$

$$E = E_o \pm S.\ ln\ C_P \qquad \text{Eq 2}$$

$$E = E_o \pm \frac{E_{max}.C_p^{\,n}}{EC_{50}^{\,n} + C_p^{\,n}} \qquad \text{Eq 3}$$

Absolutna vs. relativna biološka uporabnost

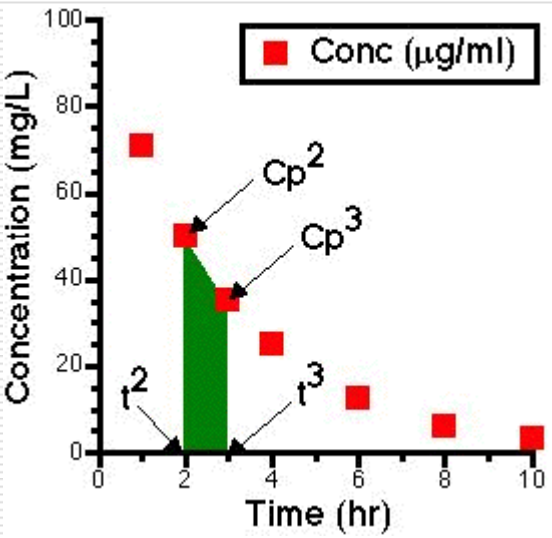
$$Cl = \frac{D_{iv}}{AUC_{iv}}$$

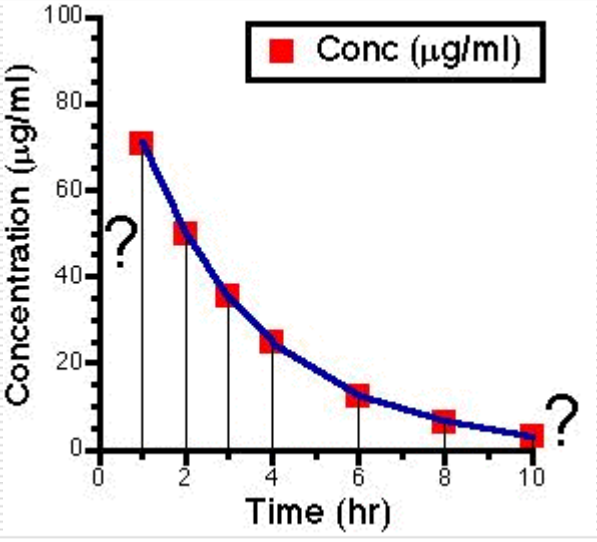
$$Cl = \frac{F\,D_{po}}{AUC_{po}}$$

$$F = \frac{D_{iv}\ AUC_{po}}{D_{po}\ AUC_{iv}}$$

$$F_R = \frac{F_A}{F_B} = \frac{D_B\ AUC_A}{D_A\ AUC_B}$$

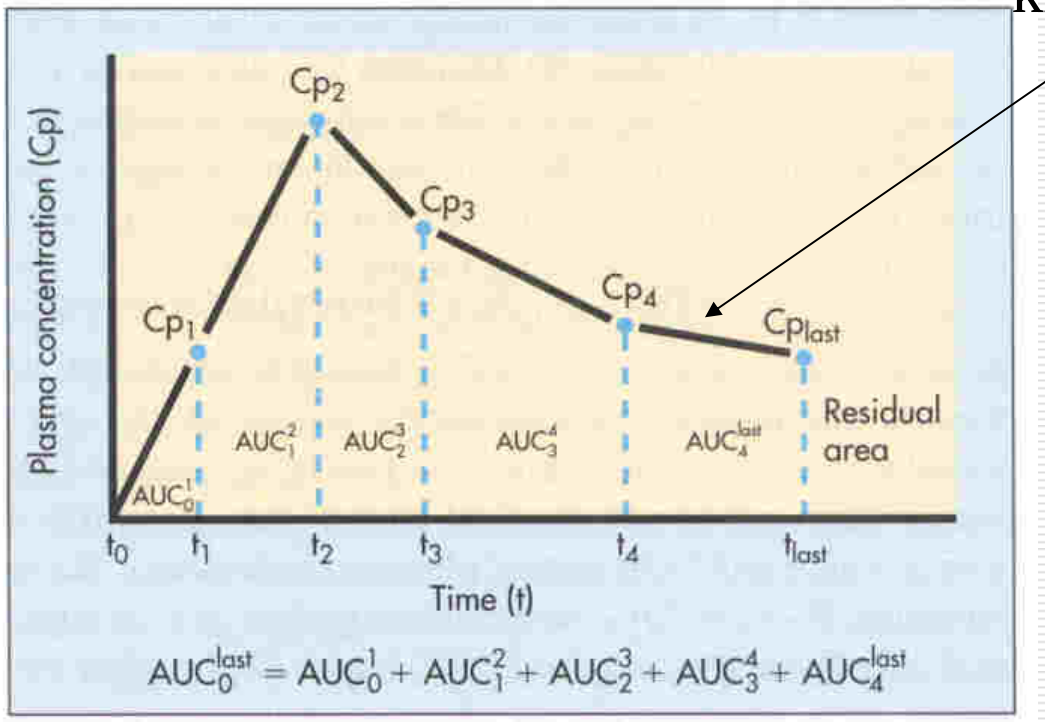
AUC


Conc (µg/ml)
Concentration (mg/L)
Time (hr)
Cp2
Cp3
t2
t3
0
20
40
60
80
100
0
2
4
6
8
10


Conc (µg/ml)
Concentration (µg/ml)
Time (hr)
?
?
0
20
40
60
80
100
0
2
4
6
8
10

Določanje AUC

β naklon termialnega dela krivulje



$$AUC_1^2 = \frac{Cp_1 + Cp_2}{2}(t_2 - t_1)$$

$$AUC_0^{\infty} = AUC_0^{last} + \frac{Cp_{last}}{\beta}$$

Bioekvivalenca
Bioaequivalence

EMEA, Note for guidance on the investigation of bioavailability and bioequivalence

2.4 Bioequivalence

Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Alternatively to classical bioavailability studies using pharmacokinetic end points to assess bioequivalence, other types of studies can be envisaged, e.g. human studies with clinical or pharmacodynamic end points, studies using animal models or in vitro studies as long as they are appropriately justified and/or validated.

Farmacevtska ekvivalenca /alternativa
Pharmaceutical equivalence / alternatives

EMEA, Note for guidance on the investigation of bioavailability and bioequivalence

2.1 Pharmaceutical equivalence

Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.

2.2 Pharmaceutical alternatives

Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength.

Bistvena podobnost
Essential similarity

EMEA, Note for guidance on the investigation of bioavailability and bioequivalence

2.5 Essentially similar products

The current EU definition for essentially similar products is as follows (see "The rules governing medicinal products in the European Union", Notice to Applicants, Vol. 2A in accordance with the December 1998 European Court of Justice ruling in the "Generics" case):

"A medicinal product is essentially similar to an original product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active substances, of having the same pharmaceutical form, and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original product as regards safety and efficacy".

By extension, it is generally considered that for immediate release products the concept of essential similarity also applies to different oral forms (tablets and capsules) with the same active substance.

Bistvena podobnost
Essential similarity

EMEA, Note for guidance on the investigation of bioavailability and bioequivalence

The need for a comparative bioavailability study to demonstrate bioequivalence is identified under 5.1. Concerns about differences in essentially similar medicinal products lie on the use of different excipients and methods of manufacture that ultimately might have an influence on safety and efficacy. A bioequivalence study is the widely accepted means of demonstrating that these differences have no impact on the performance of the formulation with respect to rate and extent of absorption, in the case of immediate release dosage forms. It is desirable that excipients must be devoid of any effect or their safe use is ensured by appropriate warning in the package label – see guideline on excipients in the label and package leaflet: "The Rules Governing Medicinal Products in the European Union", 1998, Vol. 3B, - and not interfere with either the release or the absorption process.

An essentially similar product can be used instead of its innovator product. An 'innovator' product is a medicinal product authorised and marketed on the basis of a full dossier i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. A 'Reference Product' must be an 'innovator' product (see 3.5).

Bistvena podobnost (Essential similarity)

bistvena podobnost zdravila je enaka kvalitativna in kvantitativna sestava učinkovine v enaki farmacevtski obliki (ali različne peroralne oblike s takojšnjim sproščanjem), z dokazano bioekvivalenco (če je potrebno), dokler se znanstveno ne dokaže pomembna razlika glede varnosti in učinkovitosti zdravil

Terapevtska ekvivalenca
Therapeutic equivalence

EMEA, Note for guidance on the investigation of bioavailability and bioequivalence

2.6 Therapeutic equivalence

A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically, shows the same efficacy and safety as that product, whose efficacy and safety has been established.

In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products, which are pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally recognised as not having an influence on safety and efficacy and comply with labelling requirements with respect to excipients. (see 2.5).

However, in some cases where similar extent of absorption but different rates of absorption are observed the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that differences in absorption rate are not therapeutically relevant will probably be necessary.

Načrt raziskave

In general, single dose studies will suffice, but there are situations in which steady-state studies

- may be required, e.g. in the case of
  - dose- or time-dependent pharmacokinetics,
  - some modified release products (in addition to single dose investigations),
- or can be considered, e.g.
  - if problems of sensitivity preclude sufficiently precise plasma concentration measurements after single dose administration.
  - if the 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.

In such steady-state studies the administration scheme should follow the usual dosage recommendations.

Bistvena podobnost (Essential similarity)

Bistvena podobnost zdravila je enaka kvalitativna in kvantitativna sestava učinkovine v enaki farmacevtski obliki (ali različne peroralne oblike s takojšnjim sproščanjem), z dokazano bioekvivalenco (če je potrebno), dokler se znanstveno ne dokaže pomembna razlika glede varnosti in učinkovitosti zdravil.

5.1 Bioequivalence studies

In vivo bioequivalence studies are needed when there is a risk that possible differences in bioavailability may result in therapeutic inequivalence.

The kind of studies to be performed may vary with the type of product, as follows.

5.1.1 Oral Immediate Release Forms with Systemic Action

This section pertains to dosage forms such as tablets, capsules and oral suspensions and takes into consideration criteria derived from the concepts underlying the Biopharmaceutics Classification System, i.e. high solubility, high permeability for the active substance and high dissolution rate for the medicinal product. These criteria, along with a non-critical therapeutic range should be primarily considered; therefore the following characteristics have to be taken into account in order to justify the request for exemption from in vivo bioequivalence studies. Hence data must be supplied to justify the absence of such studies.

a) Characteristics related to the active substance:

i - risk of therapeutic failure or adverse drug reactions:

this risk depends on the requirements of special precautions with respect to precision and accuracy of dosing of the active substance, e.g. the need for critical plasma concentrations;

ii - risk of bioinequivalence:

evidence of bioavailability problems or bioinequivalence exists for some specific active substances;

iii – solubility:

When the active substance is highly water soluble, the product could be in general exempted from bioquivalence studies unless, considering the other characteristics, the exemption could entail a potential risk. Polymorphism and particle size are major determinants of dissolution rate and special attention should be paid to these characteristics. An active substance is considered highly water soluble if the amount contained in the highest dose strength of an immediate release product is dissolved in 250 ml of each of three buffers within the range of pH 1-8 at 37ºC (preferably at or about pH 1.0, 4.6, 6.8);

iv - pharmacokinetic properties:

linear and complete absorption indicating high permeability reduces the possibility of an immediate release dosage form influencing the bioavailability.

b) Characteristics related to the medicinal product:

i - rapid dissolution

in case of exemption from bioequivalence studies, in vitro data should demonstrate the similarity of dissolution profile between the test product and the reference product in each of three buffers within the range of pH 1-8 at 37ºC (preferably at or about pH 1.0, 4.6, 6.8). However, in cases where more than 85% of the active substance are dissolved within 15 minutes, the similarity of dissolution profiles may be accepted as demonstrated (see appendix II);

ii – excipients

the excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected. In case of atypically large amounts of known excipients or new excipients being used, additional documentation has to be submitted;

iii – manufacture

the method of manufacture of the finished product in relation with critical physicochemical properties of the active substance (e.g. particle size, polymorphism) should be adequately addressed and documented in the development pharmaceutics section of the dossier.

5.2 In Vitro Dissolution

Dissolution studies are always necessary and consequently required. . In vitro dissolution testing forms a part of the assessment of a bioequivalence waiver request based on criteria as described in section 5.1. Dissolution studies must follow the guidance as laid out in Appendix II.

5.3 Variations

If a product has been reformulated from the formulation initially approved or the manufacturing method has been modified by the manufacturer in ways that could be considered to impact on the bioavailability, a bioequivalence study is required, unless otherwise justified. Any justification presented should be based upon general considerations, e.g. as per 5.1.1, or on whether an acceptable in vivo / in vitro correlation has been established.

5.4 Dose proportionality in immediate release oral dosage forms

If a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable. However the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. Furthermore all of the following conditions should be fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process;
- the drug input has been shown to be linear over the therapeutic dose range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used);
- the qualitative composition of the different strengths is the same;
- the ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar;
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

EMEA, Note for guidance on modified release oral and transdermal dosage forms (PK and clinical evaluation)

5.1 Prolonged release formulations

Prolonged release formulations can be assessed as bioequivalent on the basis of single and multiple dose studies which are designed to demonstrate that:

- the test formulation exhibits the claimed prolonged release characteristics of the reference;
- the active drug substance is not released unexpectantly from the test formulation (dose dumping);
- performance of the test and the reference formulation is equivalent after single dose and at steady state;
- the effect of food on the *in vivo* performance is comparable for both formulations when a single dose study is conducted comparing equal doses of the test formulation with those of the reference formulations administered immediately after a predefined high fat meal. This study should be conducted with the same strength as those of the pivotal bioequivalence studies.

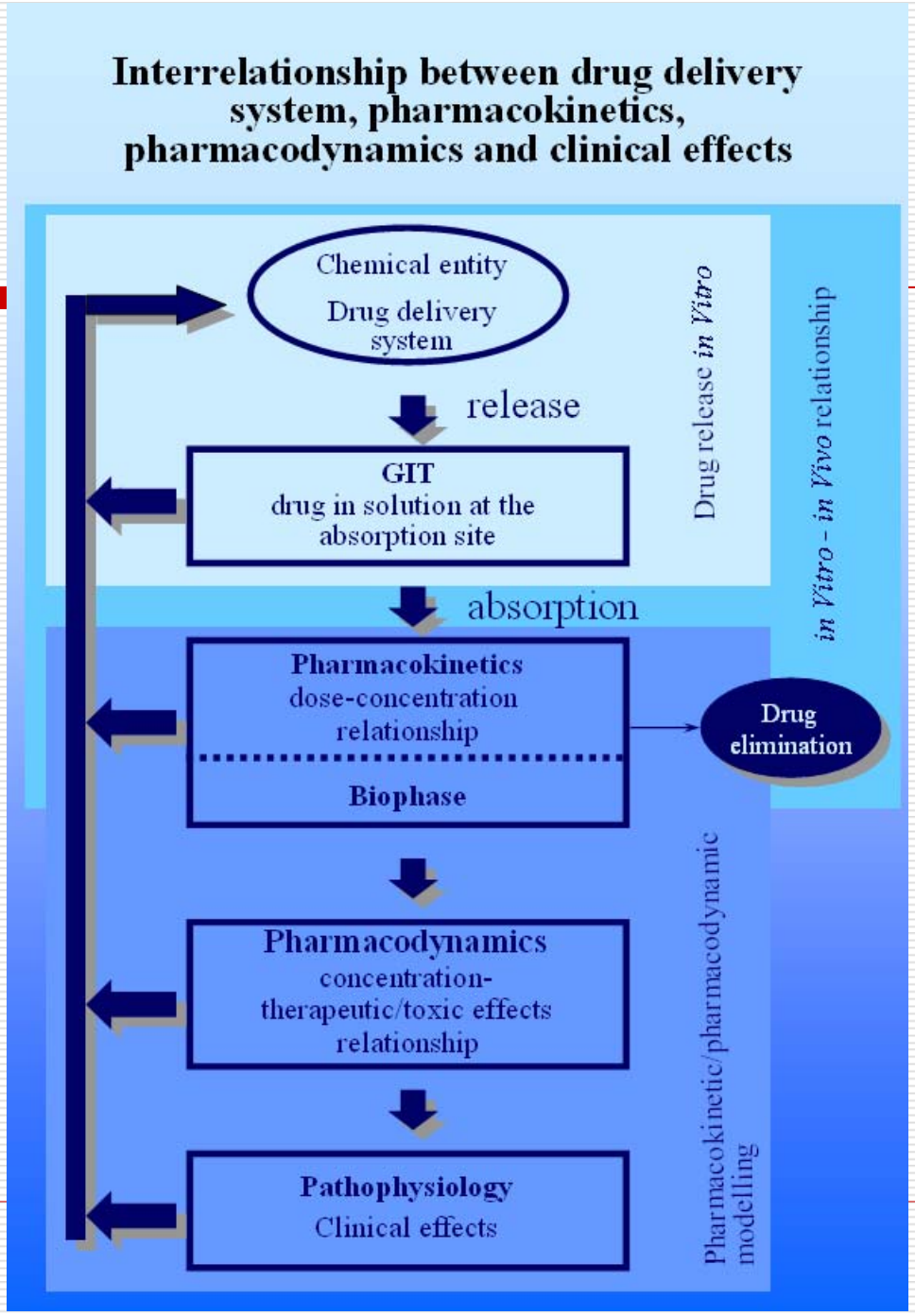
In case of prolonged release single unit formulations with multiple strengths, a single dose study under fasting conditions is required for each strength. Studies at steady state may be conducted with the highest strength only if the same criteria for extrapolating bioequivalence studies are fulfilled as described in the Note for Guidance for immediate release forms (linear pharmacokinetics, same qualitative composition ect.).

For multiple unit formulations of a medicinal product showing linear pharmacokinetics with multiple strengths a single dose study under fasting conditions on the highest strength is sufficient, provided that the compositions of the lower strengths are proportional to that of the highest strength, the formulations contain identical beads or pellets and the dissolution profiles are acceptable.

Assessment of bioequivalence will be based on AUC_{τ}, C_{max} and C_{min} applying similar statistical procedures as for the immediate release formulations.

Any widening of the acceptance criteria should be established prospectively in the clinical study protocols. They should be justified from a clinical point of view by the applicant.

Interrelationship between drug delivery system, pharmacokinetics, pharmacodynamics and clinical effects

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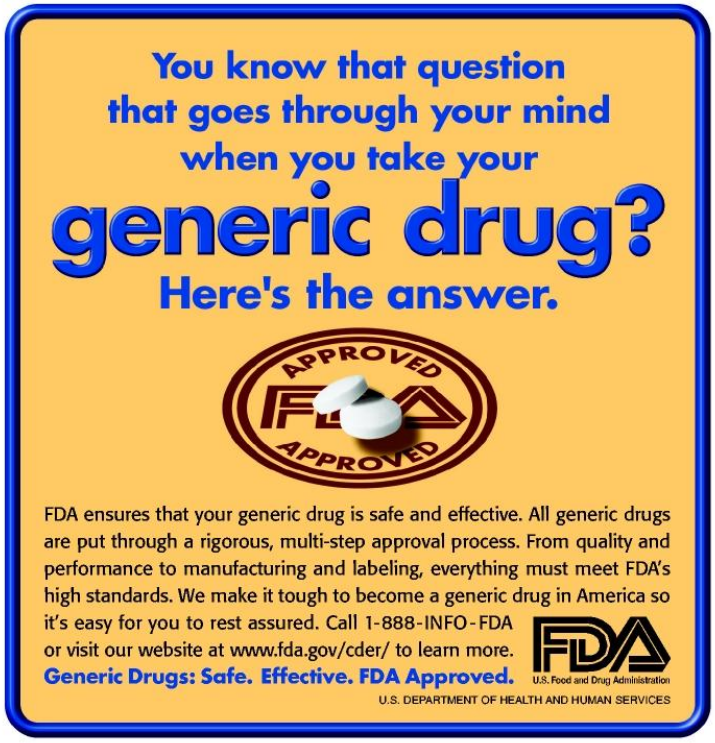
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that goes through your mind
when you take your
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Here's the answer.
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