Technology of drugs department

Discipline "*Biopharmacy*"

Biopharmaceutics role in the development of new drugs. Influence of technological factors on the rate of release of active pharmaceutical ingredients and the stability of drugs.

LECTURE FOR ENGLISH SPEAKING STUDENTS OF SPECIALTY «PHARMACY»

Lecturer: ***ass. prof. Herasimova I.V.***

Plan of the lecture

1. ***DEFINITIONS***
2. ***BIOEQUIVALENCE STUDY***
3. ***BIOPHARMACEUTICS ROLE IN THE DEVELOPMENT OF NEW DRUGS***

Questions for individual work

- ***Methods for determining the stability of drugs.***
- ***Tests for determining the solubility of tablets "in vitro".***

Recommended Books

- **Biopharmaceutics. Practical handbook for English students of the 5th year, speciality "Pharmacy": a handbook for the work of students / Edited by acad. A.I. Tikhonov. - Kh.: PH of NUPh, 2011. – 68 p.**
- **British Pharmacopoeia. – London: The Stationery Office, Vol. III, 2009. – P. 7533-7614. European Pharmacopoeia. Sixth edition. – Strasbourg: Council of Europe, Vol.1., 2008. – P. 1063-1084.**
- **Shargel, L. Applied Biopharmaceutics & Pharmacokinetics / L. Shargel, A. Yu, S. Wu-Pong. – 6 ed. – New-York: McGraw-Hill Medical, 2012. – 811 p. Mark P. Mathieu. PAREXEL Biopharmaceutical R&D Statistical Source-book 2014-2015 / Mark P. Mathieu. – Parexel Intl Corp., 2014. – 421 p.**
- **www.tl.nuph.edu.ua – site of Drugs Technology Department.**
- **Training portal http://pharmel.kharkiv.edu – distance learning center of NUPh.**
- **http://dspace.nuphedu.ua – electronic archive of NUPh.**

DEFINITIONS

Bio waiver

procedure of the generic drugs registration based on biopharmaceutical classification system and the results of comparative studies in vitro using test "Dissolution“ for solid medicinal forms

Bioavailability

the active ingredient rate and extent of absorption from the dosage forms and becomes available at the site of action

Bioequivalence

Two drugs are bioequivalent if they are pharmaceutically equivalent or pharmaceutically alternative and if their bioavailability after administration in the same dose are similar to such an extent that the effects of these drugs on the efficacy and safety, will be essentially the same.

DEFINITIONS

Generic drugs

pharmaceutically equivalent or pharmaceutically alternative drug that can be therapeutically equivalent or not equivalent therapeutically.
Generic drugs that are therapeutically equivalent are interchangeable

Biopharmaceutical classification system (BCS)

Scientific classification system active compounds based on their solubility in aqueous solutions and the degree of intestinal penetration

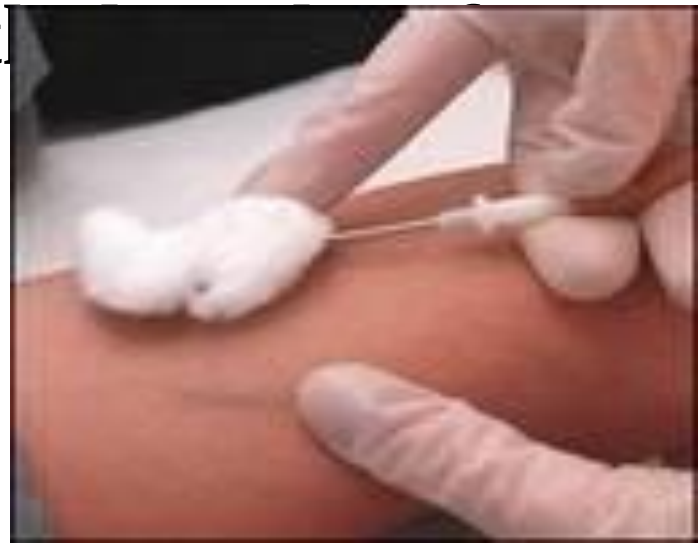
BIOEQUIVALENCE STUDY

The main objective in assessing BE - quantitative calculation of the difference between the reference and test drug and evidence that any clinically significant difference is unlikely.

BIOEQUIVALENCE STUDY

All procedures should be carried out in accordance with pre-defined standard operating procedures (SOPs).

Test drug used in biological studies must be conducted in accordance wit
GMP.



BIOEQUIVALENCE STUDY

Bioequivalence studies, are a comparative bioavailability study designed to determine the equivalence investigated and reference product.

Study on bioequivalence should be conducted according to the protocol agreed and signed by the investigator and the applicant (sponsor). Protocol should contain: the purpose of the study; procedures to be used; causes of testing involving human; nature and degree of any known risks; assessment methods, and so on.

CONDUCTING RESEARCH *in vitro*

Researchers must have relevant experience, qualifications and competence to conduct research.

Research equivalence in vitro - are comprehensive studies, based on the classification of the active substance according to the BCS and dissolved drug and include comparison of dissolution profiles of the generic and reference drugs in three environments with values of pH 1.2, pH 4.5 and pH 6.

CONDUCTING RESEARCH *in vivo*

Equivalence research carried out in vivo used if a risk of bioavailability differences is possible.

For example:

Oral drugs for system effects of traditional release, if they used one or more of the following criteria:

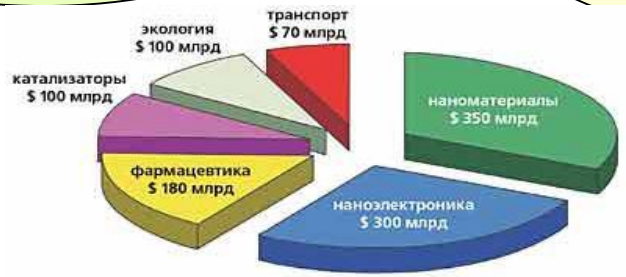
- The use of the drug for emergency care;

- Narrow range of therapeutic action (limits the effectiveness / safety), steep slope of the dose-response, and so on;

Production of medicines develops in such directions:

Development of new medicines – *new quality in pharmacotherapy*

Development of copies and its modification (*decrease of medicine's cost*)



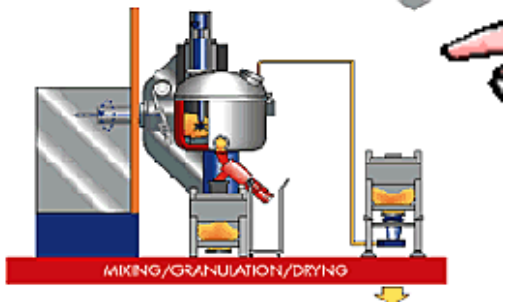
1. Different requirements to registrational documents and procedure of registration!!!

2. For copies: *aim* –

decrease of safety and growth of

Modified generics: drugs of 2 – 4 -th generations

***Rational pharmacokinetics* at optimal therapeutic concentration of MS**



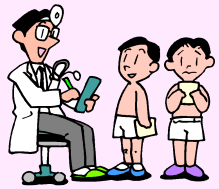
Base of 3-rd level of medical aid – are modern medical technologies and appropriate material base;

RATIONAL PHARMACOTHERAPY depends from 3 factors:

1. ***QUALITY OF DRUG;***
2. ***ADEQUATE ACTIONS OF A DOCTOR:***

- ***Adequate choice of MS and dosing regime,competibility of MS, etc.***
- ***Account of individual features of a patient***

  (question of age pharmacology, pharmacogenetics, state of patient's bodies and systems, his nutritiment);



- ***Placebo dependance*** ***- patient should believe,***
- ***that he obtains the best medicine for him.***

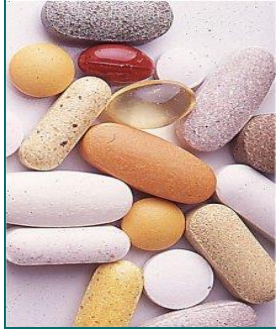
3. Actions of patient:

- ***clarity of fulfilment of doctor's recommendations;***
- ***Self-treatment.***

GUIDANCES FOR CONDUCTING ASSESSMENT OF EQUIVALENCE

- ***FDA – Guidance for Industry. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based an a Biopharmaceutics Classification System, 2000***
- ***Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms, Japan, 14.02.2000***
- ***CPMP/EWP/QWP/1401/98 Note for Guidance on the Investigation of Bioavailability and Bioequivalence, 2001***
- ***WHO Technical Report Series 937. WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006***
- ***Order of Ministry of Health of Ukraine from 17.04.2007 № 190***

INTERCHANGEABILITY OF BREND AND GENERIC MEDICINES



Generic medicines should meet the same standards of quality, effectiveness, and safety, as innovative drugs, and also must be presented convincing evidences of their equivalence, i.e. therapeutic interchangeability.

Innovative drug

equivalent

Interchengeable in therapeutic mean

Generic

Providing system of quality of medicines covers accurate rules and procedures as for the questions:

GMP, GLP, GCP, GXP

1. *Development of medicine (pharmaceutical development and production of medicines' series for testing by technology, which should be recreated for series production of this medicine);*
2. *Testing,volume and requirements to which sets Ministry of Health;*
3. *Preparing of registration of medicine;*
4. *Registration file's examination of and state registration of medicine;*

GMP

5. *Requirements to manufacture of medicines and set for production of MS, based on the above principles;*
6. *Inspection and licensing of production of MS;*
7. *Observance of requirements to medicine, declared in registration documents during series' production;*
8. *After-registration changes and control;*
9. *Observance of rules and conditions of medicines' storage during dispensing and application time, determined under its state registration.*

GPP GDP

*WHAT IS **QUALITY OF MEDICINE**, WHERE IS IT ESTIMATED, HOW TO SET IT, CONTROL AND GUARANTEE?*

***Art. 2 Law of Ukraine «About medicines (MS)»:** Quality of MS – is a set of properties, which make MS able to saticfy users in accordance to its assignment and **correspond the requirements, set by legislation** (**Pharmacopeia** **+ Instruction for medical use - art12**)*

THE QUALITY OF MEDICINE IS INDICATED BY:

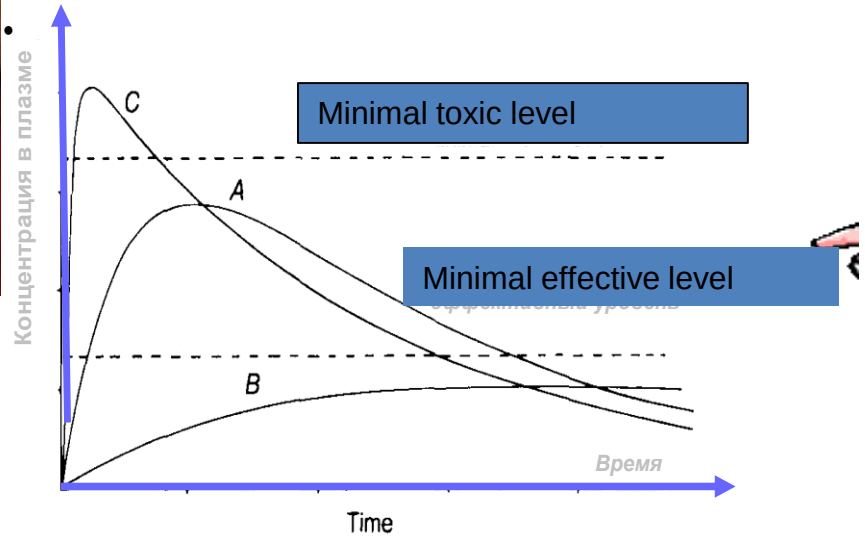
***QUALITY CERTIFICATE* + ITS APPEARANCE IN HOSPITAL**

- **EFFECTIVENESS;**
- **SAFETY;**
- **QUALITY OF MEDICINE.**

THERE IS FUNCTION FROM DOSE

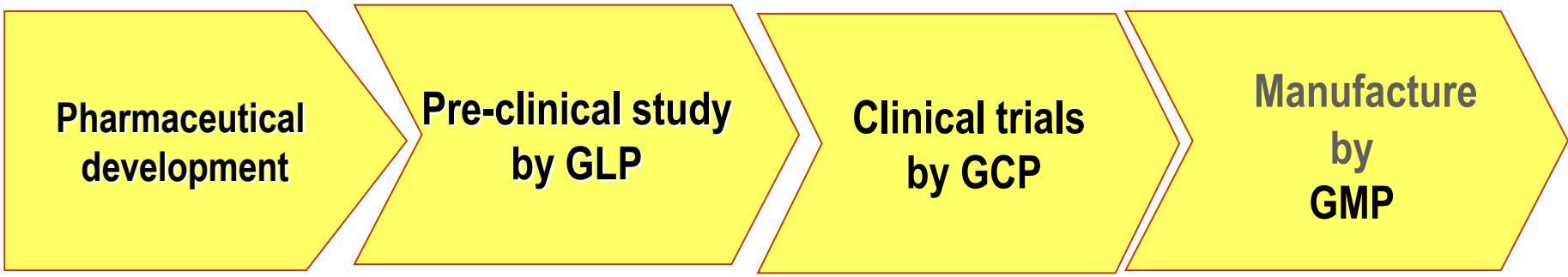
OR concentration of MS in blood C???

DOSE = C (WHO, *№ 937, 2006*)

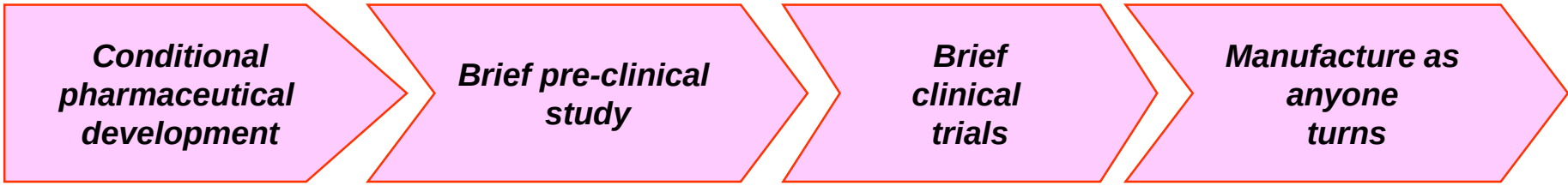


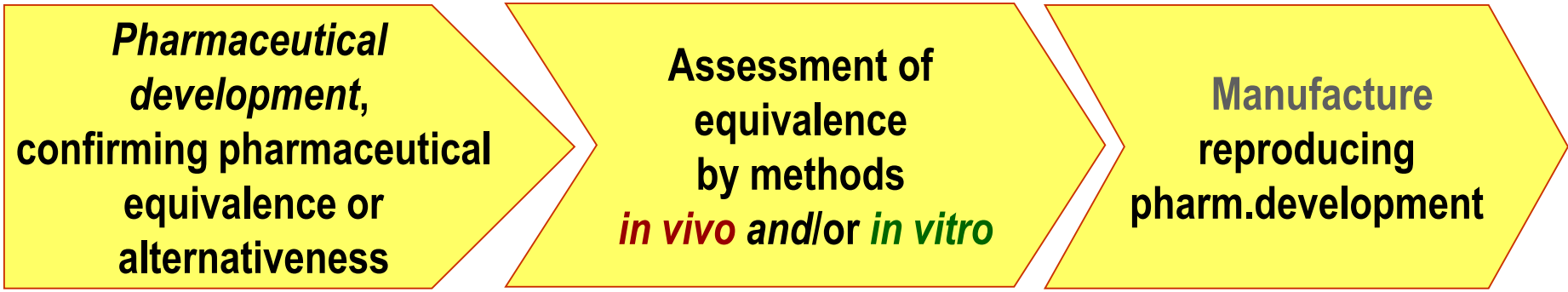
ORDER MH of UKRAINE 17.04.2007 № 190

INNOVATIVE MEDICINE



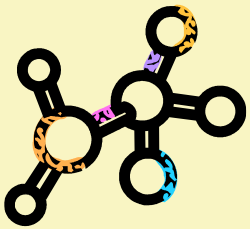
GENERIC MEDICINE

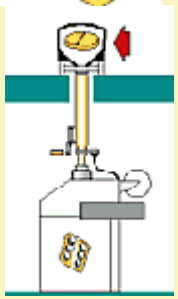


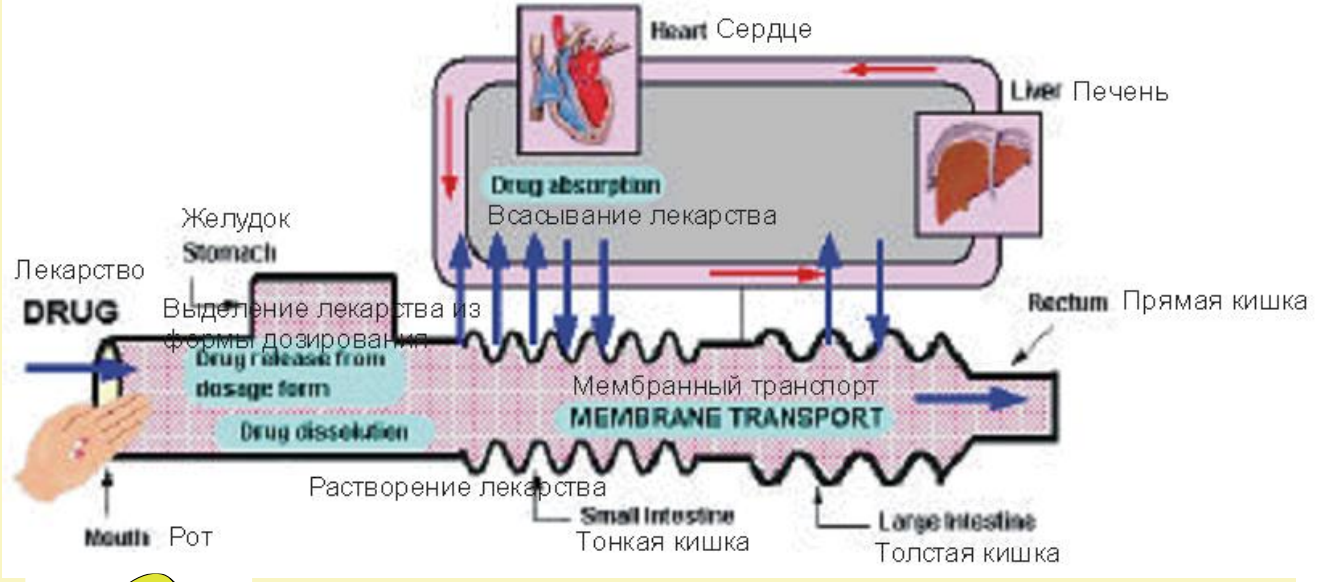


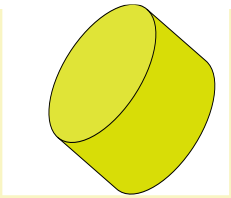
«Medicine – necessary molecule of certain structure, should get to the blood:

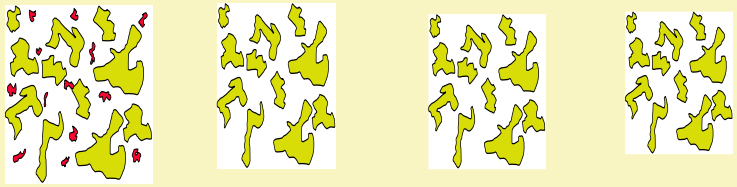
- **At the right time;**
- **In the right concentration and in certain place of the gastro-intestinal tract»**











Besides, patient should believe, that he obtained the best and effective medicine

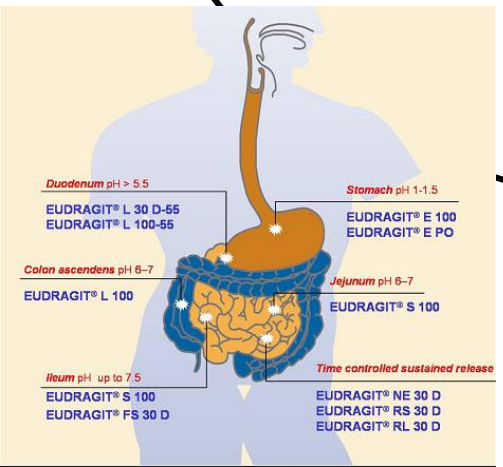
Generic is a copy of brend (interchangeability!?)

Instruction for medical use as the brend has !?

1. Physical-chemical properties of the substance

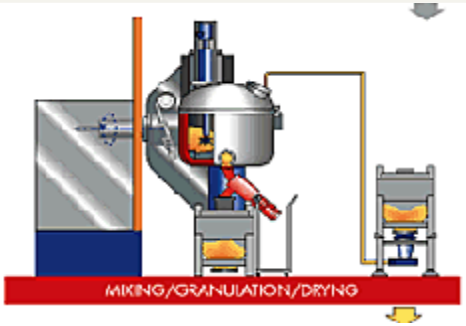
2. Impurity profile

3. Medicinal form



4. Auxiliary substances, which supply with target functions of medicine

5. Technology of producing medicines, which supply with target functions of medicine



6. Pharmaceutical development as a result of which is formed quality for medicines and requirements to manufacture process, that provides reproducible properties of medicines (п 1 – 5)

Order of Ministry of Health of Ukraine № 426 of 28.06.2005

General technical document for licensing of medicines in EU

Chapter «PHARMACEUTICAL DEVELOPMENT»

«*Chapter* «pharmaceutical development» should contain information about *researches for development, that have been conducted for establishing the fact, that medicinal form, composition, manufacturing process, packaging, microbiological characteristics and instruction for medical use corresponds to the objection, indicated in a application»*.

DOSE – should correspond to the expected effect!!!

Based on the fundamental principle of the effect / dose, we can have:

DOSE IS, BUT EFFECT IS NOT PRESENT, IT'S RATHER IS, BUT each time is DIFFERENT!?

PRDER OF MINISTRY OF HEALTH OF 17.04.2007 № 190

MEDICINES, THAT ARE NOT INVESTIGATED FOR BIOEQIVALENCEЯ, *because*
interchangeability is guaranteed by the proof of accordance to pharmacopeian specifications (**pharmaceutical equivalence**)

- **Parenteral medicnes**
- **Solutions for oral application**
- **Powders for preparing solutions**
- **Gases**
- **Eye, ear medicines in the solution form**
- **Medicinal remedies of local action in the form of water solutions**
- **Nasal spreys nad inhalation medicines in the form of water solutions**

Nation	***60%***
Foreign	***40%***

ORDER OF MINISTRY OF HEALTH OF 17.04.2007 № 190

NECESSARY CIRCUMSTANCES FOR VERIFICATION OF EQIVALENCE ***are argument of an accordance to pharmacopeian specifications***

- **Identity of active substances**
- **Identity of CONCENTRATION**
- **The same medicinal form**

- **Identity or similarity of qualitative and quantitative composition of auxiliary substances**
- **Similar way of application**
- **Accordance of quality specifications (profile of admixtures)**
- **Implementation of requirements to manufacture, set by legislation of Ukraine and international norms**

Reseaches of *bioavailability* by methods **in vitro**
Biopharmaceutical classification system
Order of *МН № 426 of 28.06.2005/№ 95 - 01.03.2006, № 190 of 17.04.07.*

Class 1 – High solubility, high permeability

It is possible to reject from studying bioavailability

Class 2 – Low solubility, high permeability

it is possible to reject from studying bioavailability under such circumstances:

if active substance *is a weak acid and generic is dissolved ≥ 85% of sub-ce under pH 6.8 for ≤ 30 min. and its solubility profile is similar to profile of the reference medicine under pH 1.2, 4.5, 6.8;*

Class 3 – High solubility, *low permeability*

it is possible to reject from studying of bioequivalence under such circumstances: if generic and reference medicine are rapidly soluble ≥ *85% of sub-ce for ≤ 15 min. under pH 1.2, 4.5, 6.8*

Class 4 – Low solubility, *low permeability*

Study of bioavailability in vivo are carried out always!!!

CRITERIA FOR EVALUATION OF THE METHOD OF EQUIVALENCE (INTERCHANGEABILITY)

- ***Researches in vitro are conducted for medicines in a solid dosing form of immediate release of systemic effect***

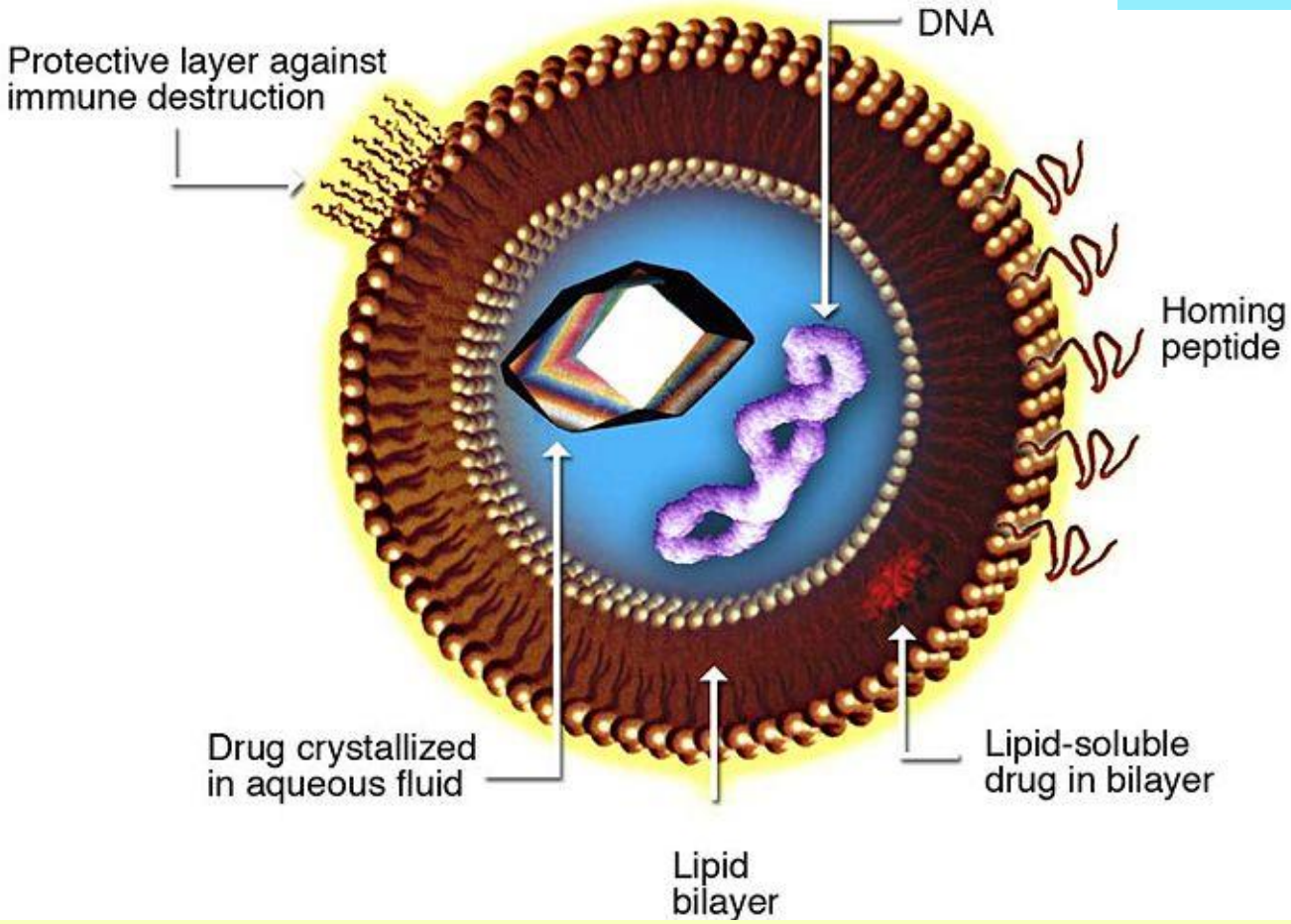
- ***Pharmacodynamic tests carry out for medicines, which concentration of active substance cannot be determined in biological fluids, but is possible to evaluate significant pharmacodynamic data, caused by medicinal preparation***

- ***Pharmacokinetic tests carry out for medicines of systemic effect, which concentration of active substance can be determined in biological fluids***

- ***Comparative clinical trials carry out for medicines, for which is impossible to determine pharmacokinetic parametres or obtain corresponding pharmacodynamic points***

Liposome for Drug Delivery

Taken from Solovjev A.I.



LIPOSOME – ***nanoparticle (nanosome) with lygands for target cells, situated at its' surface and permitting to fasten and accumulate in the focus of inflammation process***

Guarantee of quality is a constant process, which supplies accordance of established standards

SAFETY AND EFFECTIVENESS OF MEDICINES

▪***Information obtained by the post-marketing phase, i.e after registration, can significantly affect the application of the drug in the clinic, including generic because: :***

results of experimental investigations at the animals can't be always used in the same way to the human,

•a small number of patients, involved in clinical trials, doesn't allow to make correct conclusions about safety and effectiveness of MS,

• groups of patients, suffering from concomitant diseases, are not included in trials.

In short, objective information about the effectiveness and development of side effects can only be obtained when medicine is taken by hundreds of thousands of patients

Conclusions

- The discovery & development of new medicines is a long completed process.
- Research based pharmaceutical companies are committed to advancing science & bringing new medicines to patients.
- Increased support from govt & organisation may helps in development safer & cost effective medicines.

Thank for your attention!