Registracija zdravil

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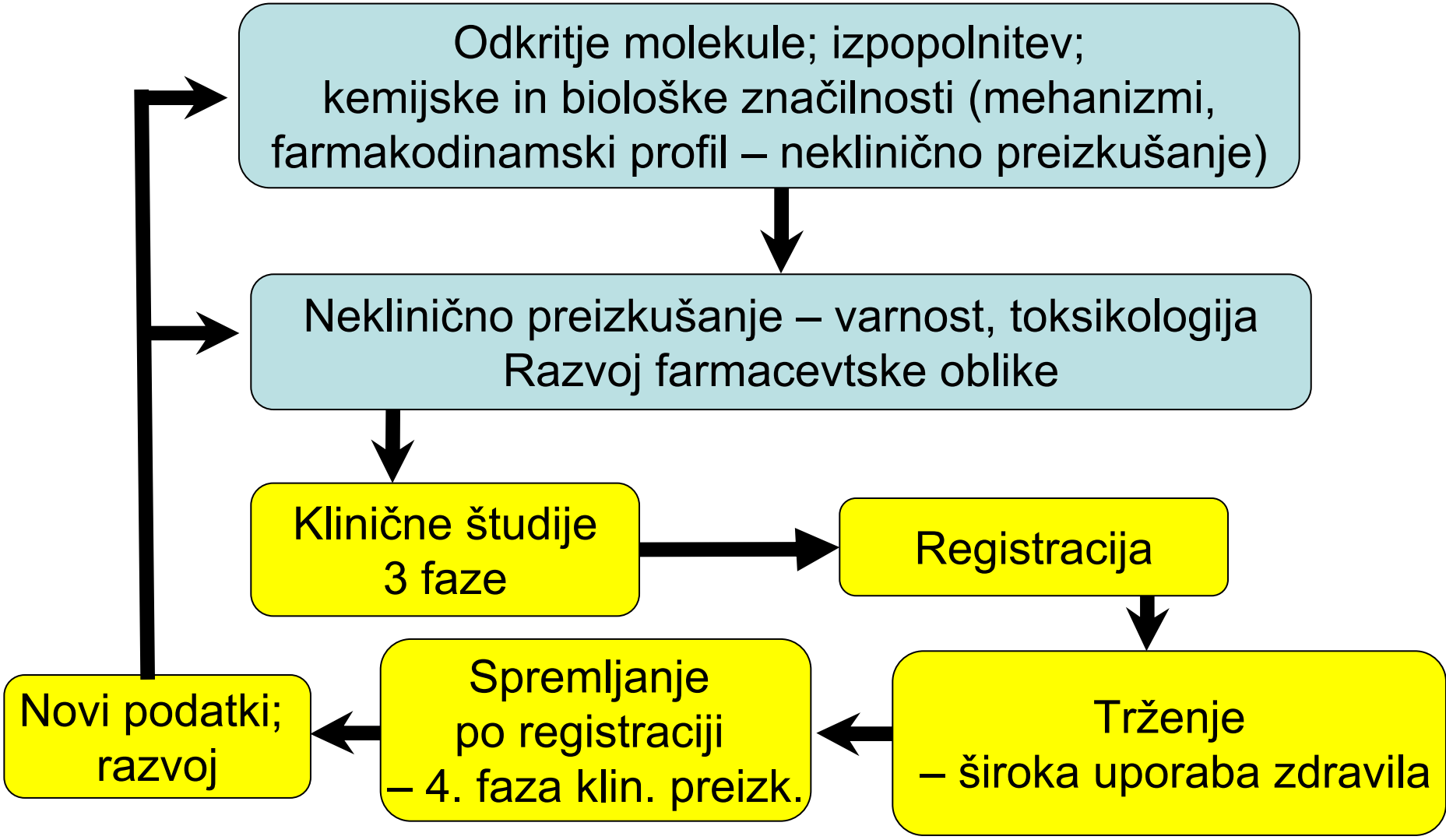
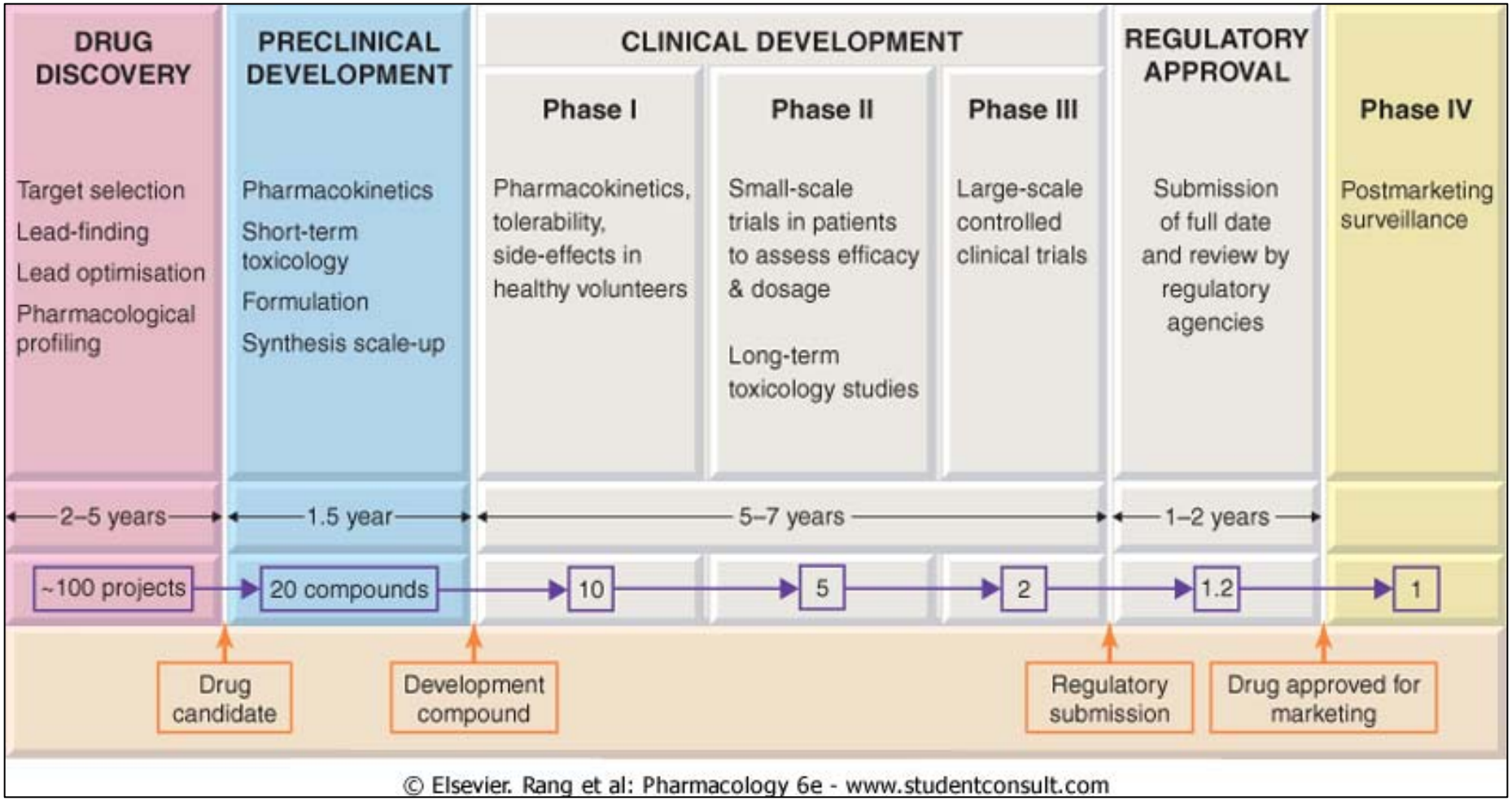
Faze razvoja novega zdravila



Trajanje različnih faz v razvoju zdravila



Clinical Testing

- {Phase 0 (non-clinical)}
- Phase 1 (volunteers)
- Phase 2 (patients)
- Phase 3 (large scale multi-centre)
- Phase 4 (post registration monitoring)

Phases can also be defined by the information you are trying to get out of the testing

Volunteer Studies (Phase I Trials)

- pharmacologists & employees (15-30 in number)
- Ethical approval
- Healthy
- Informed consent
- Full resuscitation + medical backup
- Monitor
- Single and repeat doses
- Increase dose levels

Volunteer Studies (Phase I Trials)

Objectives

- Metabolic and excretory pathways
- Variability between individuals; Effect of route; bioavailability
- Tolerated dose range
- Indication of therapeutic effects
- Indication of side effects

Patient Studies (Phase 2 Trials)

- 150-350 ill people; Informed consent.
- Maximum monitoring; Full resuscitation.
- Often patients where other treatment failed.
- **Objectives:**

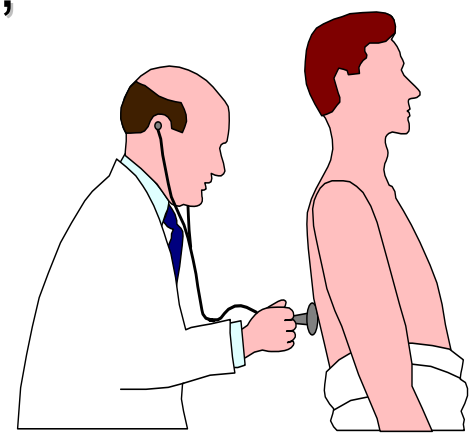
  Indication for use; Type of patient; Severity of disease;

  Dose range, schedule and increment;

  Pharmacokinetic studies in ill people;

  Nature of side effects and severity;

  Effects in special groups.



Patient Studies (Phase 3 Trials)

- 1500-3500 ill patients
- multicentric?
- More certain data for the objectives of phase 2 studies
- Interactions between drugs start to become measurable in the larger population
- Sub-groups start to be established
- Special features and problems show up

Clinical Trials I

Drug action depends on:

- Pharmacodynamics
- Pharmacokinetics and dose regimen
- Drug interactions
- Receptor sensitivity of patient

Clinical Trials II

Drug action depends on:

- Mood/personality of patient & doctor
- Patients expectations and past experience
- Social environment of patient
- Clinical state of patient

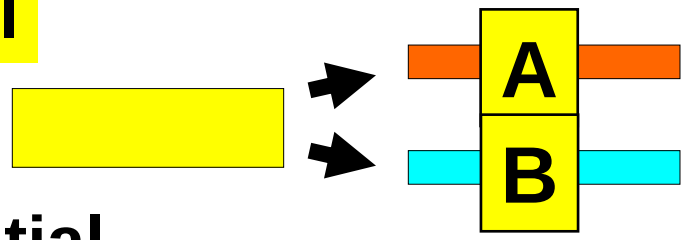
Clinical trial controls these variables and examines action of drug in defined set of circumstances

Clinical trials III

controlled or uncontrolled

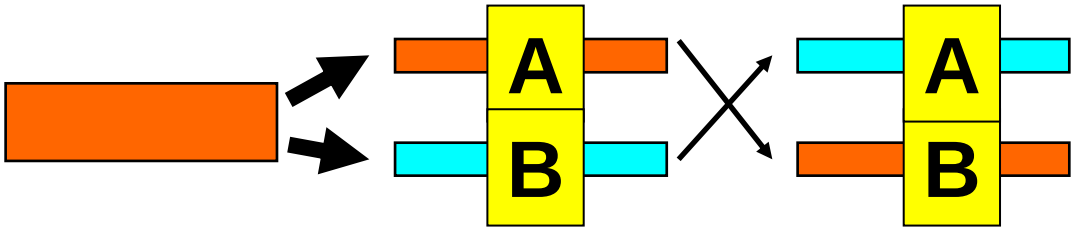
open or blind

parallel



sequential

cross-over



others: - matched pairs; combinations; ++

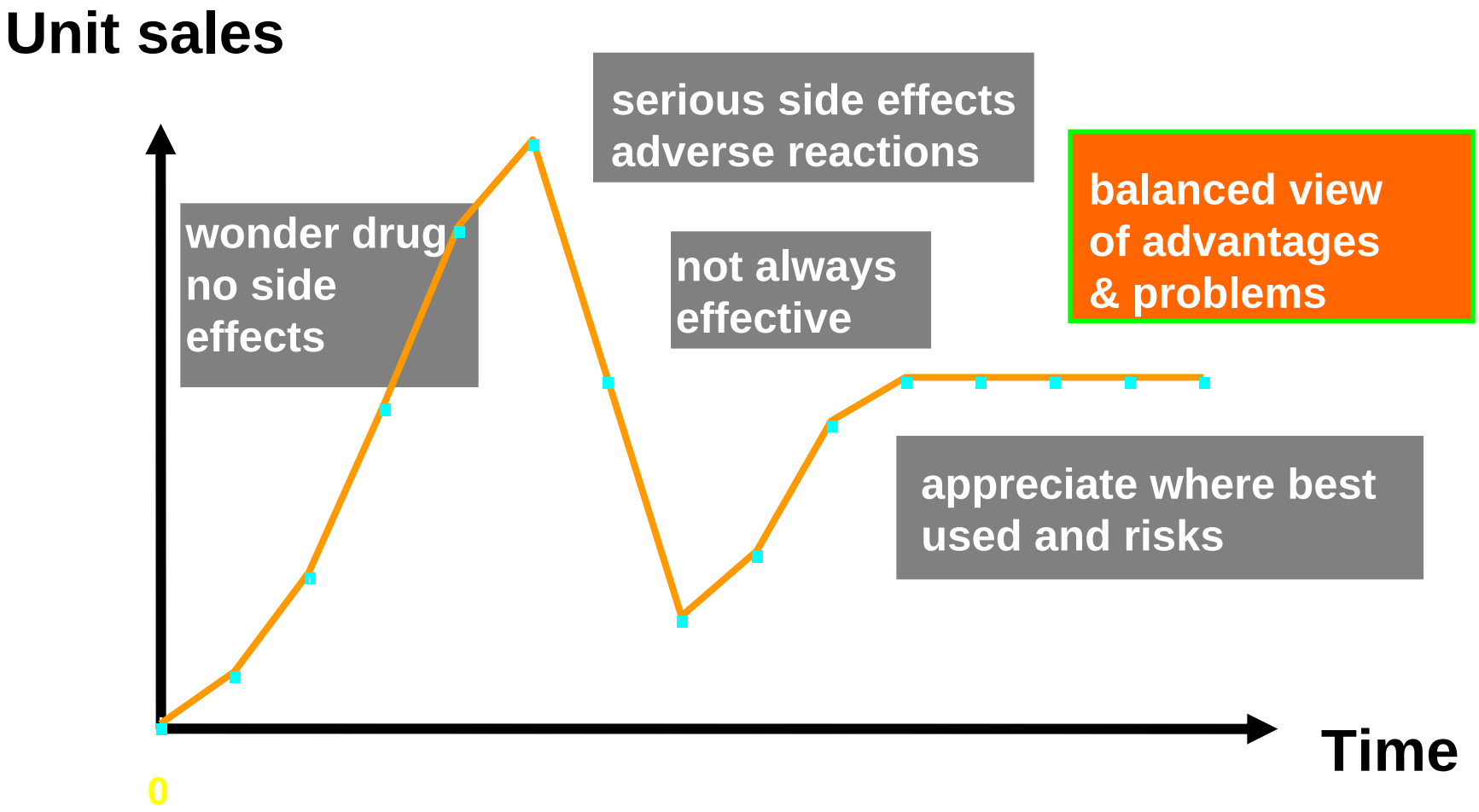
The Regulatory Process

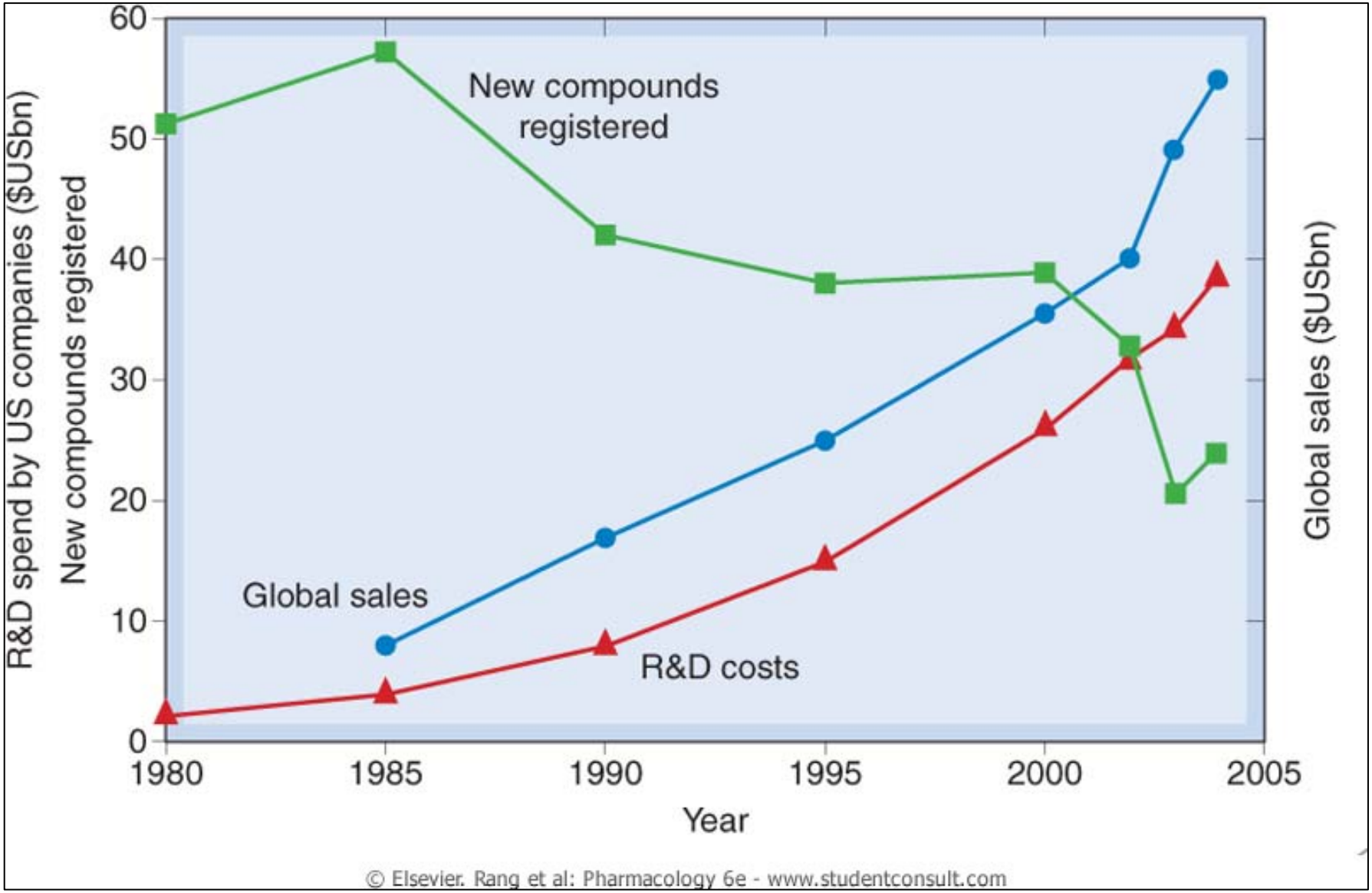
- Differs from country to country
- Demands safety and quality of product
- Encourages efficacy and need for product
- Grants clinical trials certificate if volunteer and animal data OK
- Approves protocols and examines data
- 50-400 volumes (30,000-150,000 pages)
- Original data available
- Two way process; Authority and company trying to produce a safe effective product
- Release for a specific purpose and use

Marketing

- Getting the product right (packaging; Formulation)
- Right therapeutic slot
- Information on new drug
- Information for honest comparison
- Reporting problems
- Reporting new indications
- Therapeutic trends

Classic Sales Curve





Post-registration Monitoring

- YELLOW CARD SYSTEM: voluntary reporting of adverse effects by GP to committee on safety of medicines; Easy; Effective?
- INTENSIVE MONITORING OF DEFINED GROUP: first 10,000; Administrative nightmare as patients move/die; Costly; Time-consuming.
- RESTRICTED RELEASE: only available to small group of GPs; Monitor their patients; Elitist.
- MONITOR INCIDENCE OF DISEASE PROBLEM: difficult to identify cause of change.

Lessons and Development

- Refine parts of treatment giving problems (dose interval? Side effects? Effective? Niche market?)
- Extend usage

  eg. PROPRANOLOL (beta adrenoceptor blocker)

  antidysrhythmic → antianginal → antihypertensive → relieve hyperthyroid symptoms → antihypertensive with diuretic → prolonged release formulation

Precipitate asthma attack → beta1 selective - ATENOLOL

The Future?

- 3rd world diseases?
- Orphan drugs with few users?
- Improve safety and efficacy records
- Reduce animal utilisation (cell lines; early human volunteers,)
- New diseases (AIDS; Alzheimer's; CJ disease; human BSE variant; obesity; cancer)
- New biology - (clone human receptors; disease model by gene changes)

Kdo vlaga prošnjo za registracijo zdravila ?

Registracija zdravila = izdaja dovoljenja za promet z zdravilom

- Proizvajalci zdravil
  - Farmacevtske firme
  - Laboratoriji lekarn

Potrebna dokumentacija

Dokazila o kvaliteti, učinkovitosti in varnosti zdravila.

- Farmacevtsko kemični del dokumentacije
- Farmakološko toksikološka dokumentacija
- Klinična dokumentacija

Vsak od delov dokumentacije vsebuje poleg originalnih dokumentov tudi poročilo eksperta o tem delu dokumentacije

Farmacevtsko kemična dokumentacija

Proizvodnja zdravila, sestava zdravila

- pokriva vse komponente zdravila
- sledljivost sestavin
- opis postopka proizvodnje, tolerančne meje ostankov postopka
- dokazila o usposobljenosti posameznih proizvajalcev (GMP certifikat)

Farmakološko toksikološka dokumentacija

Rezultati nekliničnega preizkušanja zdravil

- Farmakodinamske študije (mehanizem delovanja, farmakodinamski profil)
- Farmakokinetske študije
- Toksikološke študije

Klinična dokumentacija

Rezultati kliničnega preizkušanja zdravil – urejeni po fazah preizkušanja.

- Učinkovitost glede na kontrolno skupino
- Predlog indikacij za zdravilo
- Pregled stranskih (neželenih) učinkov zdravila

Dokumentacija, ki spremlja zdravilo

Vsebina se odobri ob registraciji

- Navodilo za uporabo zdravila (patient information leaflet – PIL)
  - Bolniku prijazen in razumljiv tekst
  - Vsebovati mora točno določena poglavja
- Povzetek osnovnih značilnosti zdravila (Summary of product characteristics – SPC oz. SmPC)
  - Namenjen zdravnikom
  - Vsebovati mora točno določena poglavja
  - Določene indikacije
  - Vsebovani izsledki kliničnih študij
  - Izsledki poročil o neželenih učinkih

Kdo in kako registrira zdravilo?

Odvisno od vloge (načini registracije – EC)

- Nacionalna registracija – nacionalne agencije za zdravila.
- Centraliziran postopek (CP)
- Postopek medsebojnega priznavanja (MRP)
- Decentraliziran postopek (DCP)

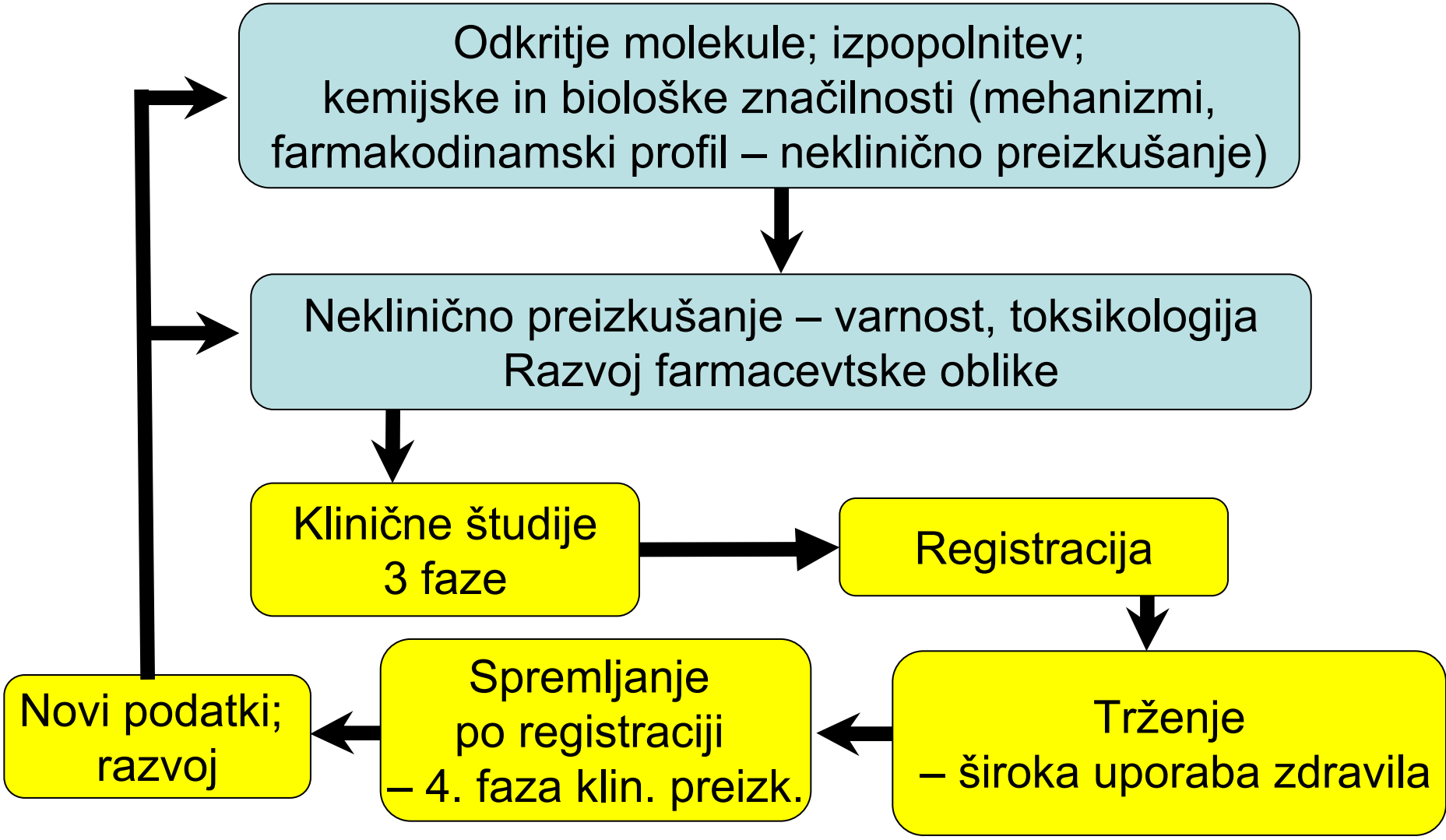
- Nacionalne agencije – SLO: Javna agencija Republike Slovenije za zdravila in medicinske pripomočke – JAZMP
- EC – European Medicines Agency – EMEA
- ZDA – Food and Drug Administration – FDA

Trajanje registracije

Registracija za določen čas – navadno 5 let

- Obnova registracije – poročila o stranskih učinkih zdravila (Periodic Safety Update Report – PSUR)
  - Ustrezne spremembe PIL in SPC
- Registracija sprememb
  - Spremembe v proizvodnem postopku
  - Spremembe oblike zdravila
  - Spremembe indikacij
  - Spremembe v doziranju
  - Druge spremembe

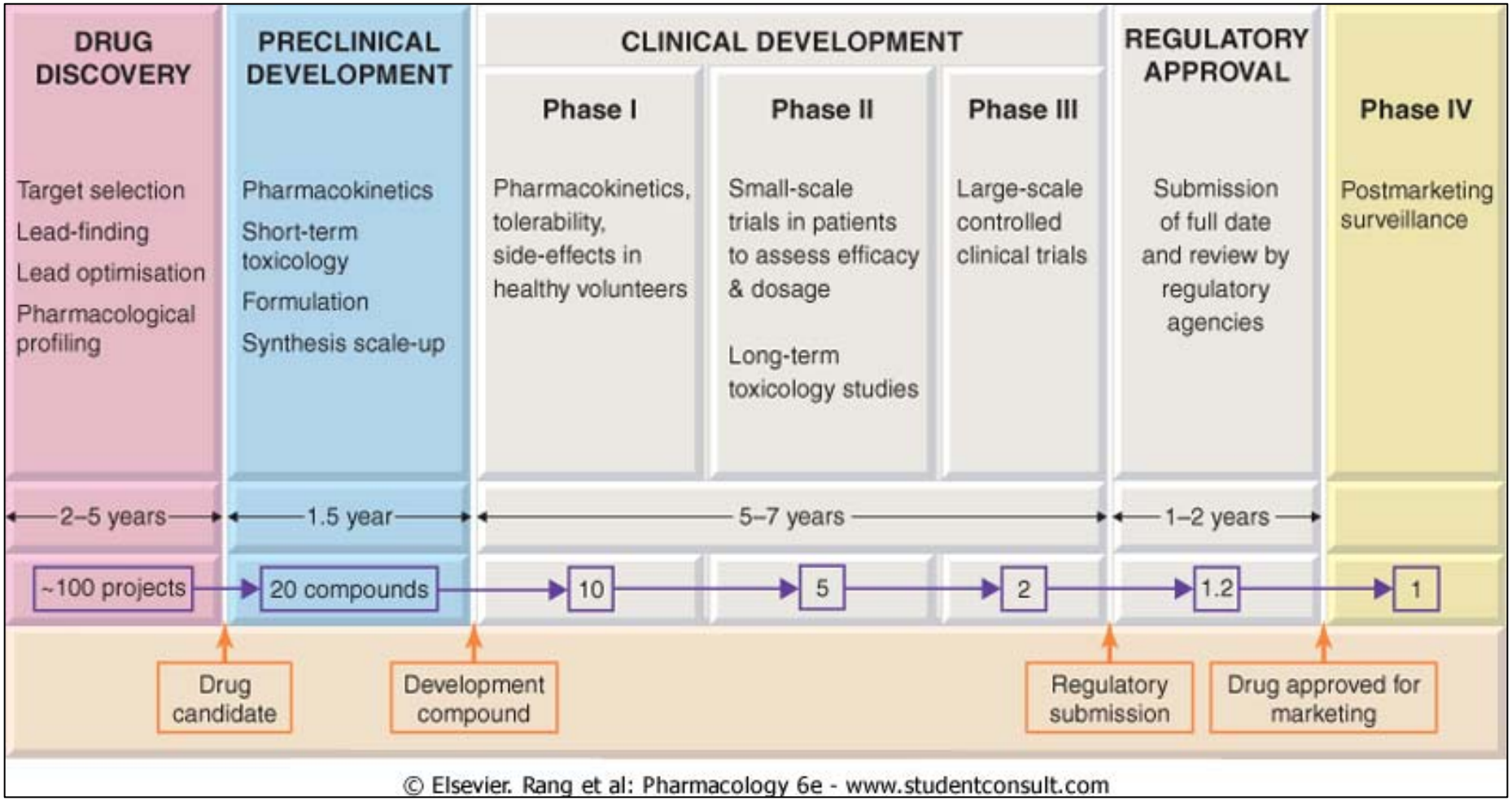
Faze razvoja novega zdravila



Proizvajalci zdravil

- Originatorji
- Generične firme – izdelava generikov (kopije zdravil po poteku patentne zaščite)

Faze v razvoju zdravil



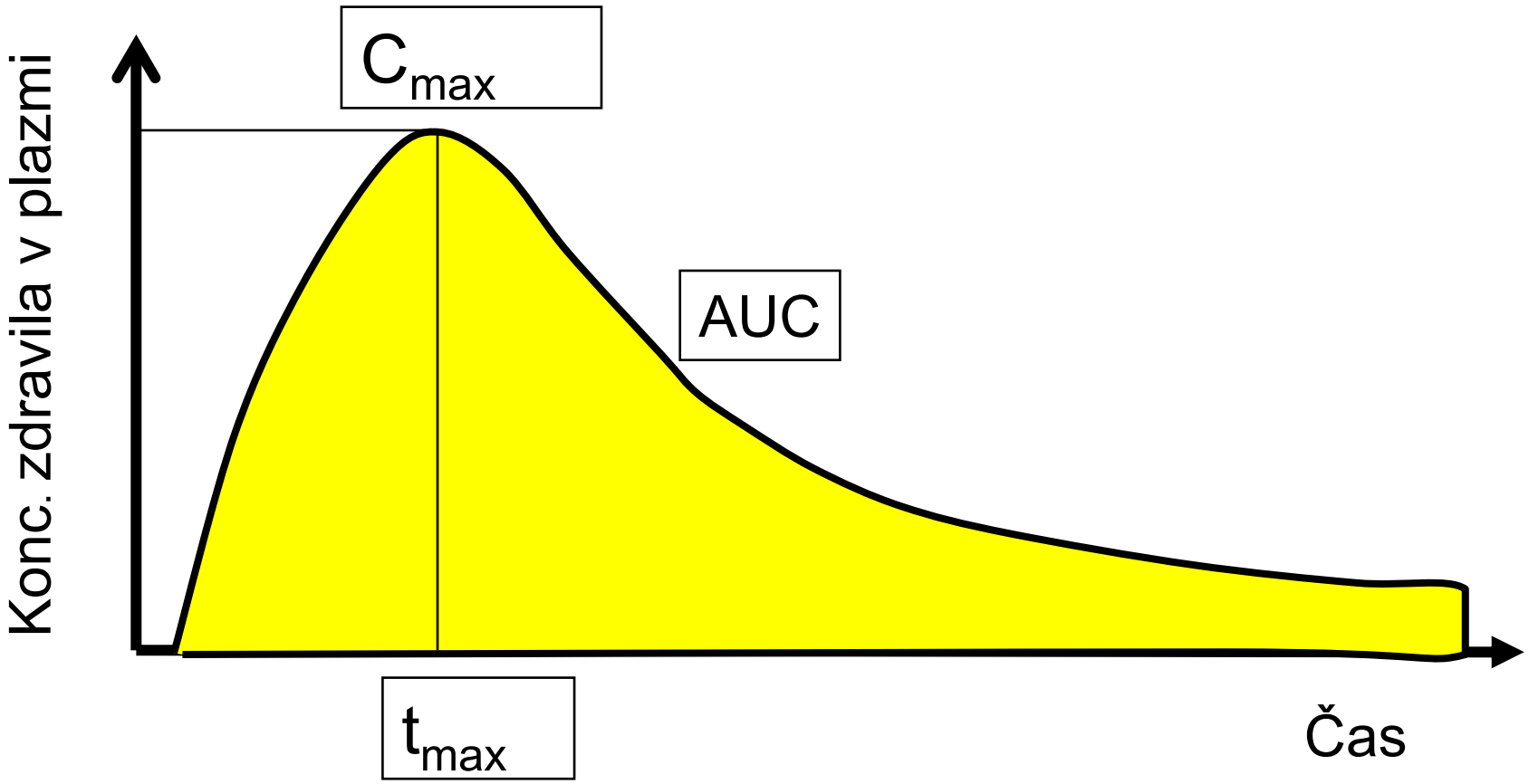
Registracija generikov

Zdravilo mora biti ‘bistveno podobno’ originalnemu zdravilu

- Enaka farmacevtska oblika zdravila
- Enak profil sproščanja (poskusi ‘in vitro’)
- Bioekvivalenca

Sklicevanje na dokumentacijo originatorja

Določanje bioekvivalence



Določanje bioekvivalence

- Parametri generika morajo biti ‘enaki’ originalnemu zdravilu (toleranca)
- Določanje bioekvivalence pri različnih odmerkih (linearnost farmakokinetskih parametrov)
- Določanje bioekvivalence ob jemanju s hrano in na tešče

Generična substitucija

- Kaj je?
- Cilji?
- Možnosti preprečitve – utemeljenost – razlaga

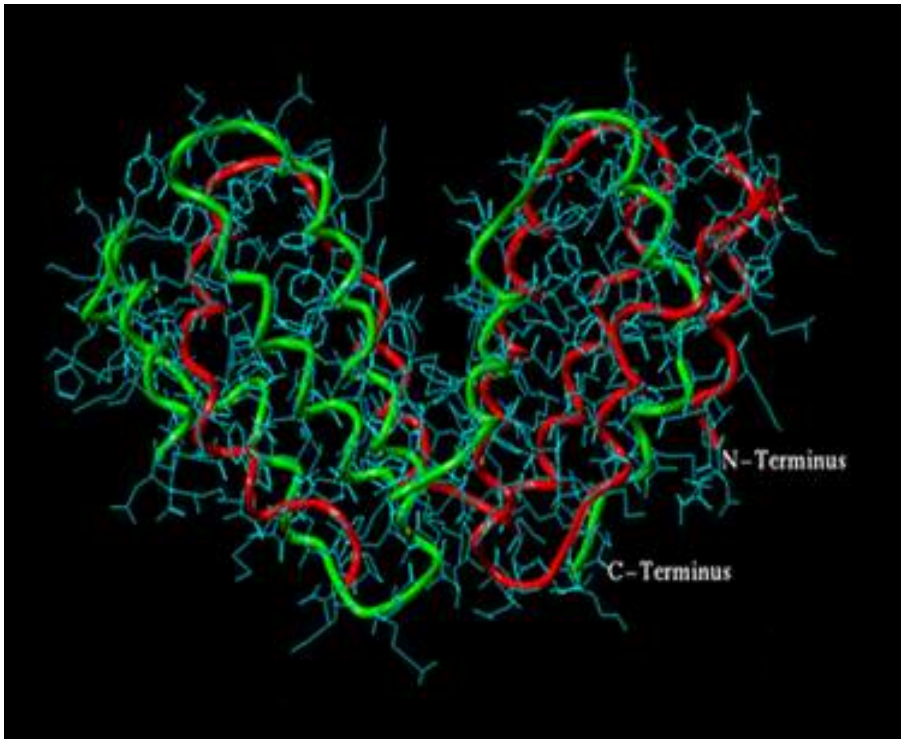
Problemi

- Ali so generiki lahko boljši od originalnih preparatov? (drugačna pot sinteze)
- Biološka zdravila – subtilne razlike v strukturi originalnega zdravila in posnetka $\Rightarrow$ razlike v učinku

Biološko podobna zdravila – biosimilars

- Pri bioloških zdravilih ne moremo govoriti o generikih
- Dokazi o bistveni podobnosti težko izvedljivi in nezadostni
- Potreba po dodatnih preizkušanjih biološko podobnih zdravil – sklicevanje na dokumentacijo originatorja ni mogoče

Example: Interferon Beta vs. Aspirin



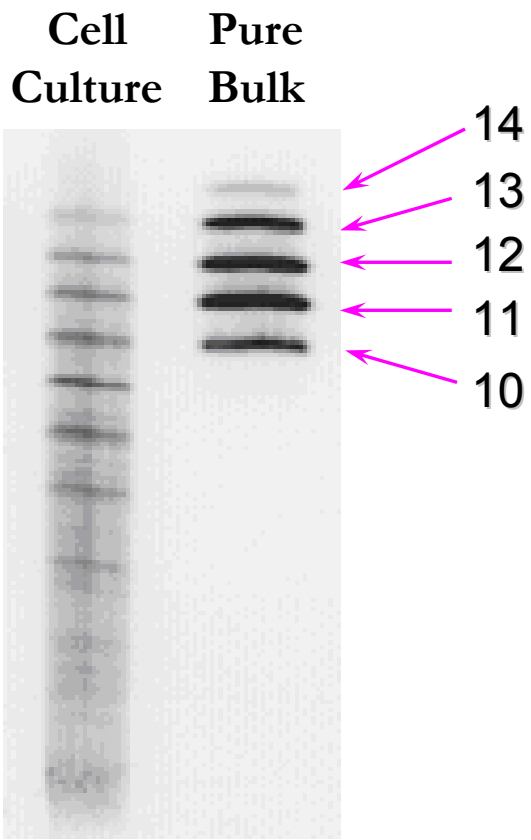
Interferon Beta
MW 19'000D

Aspirin:
MW 180D

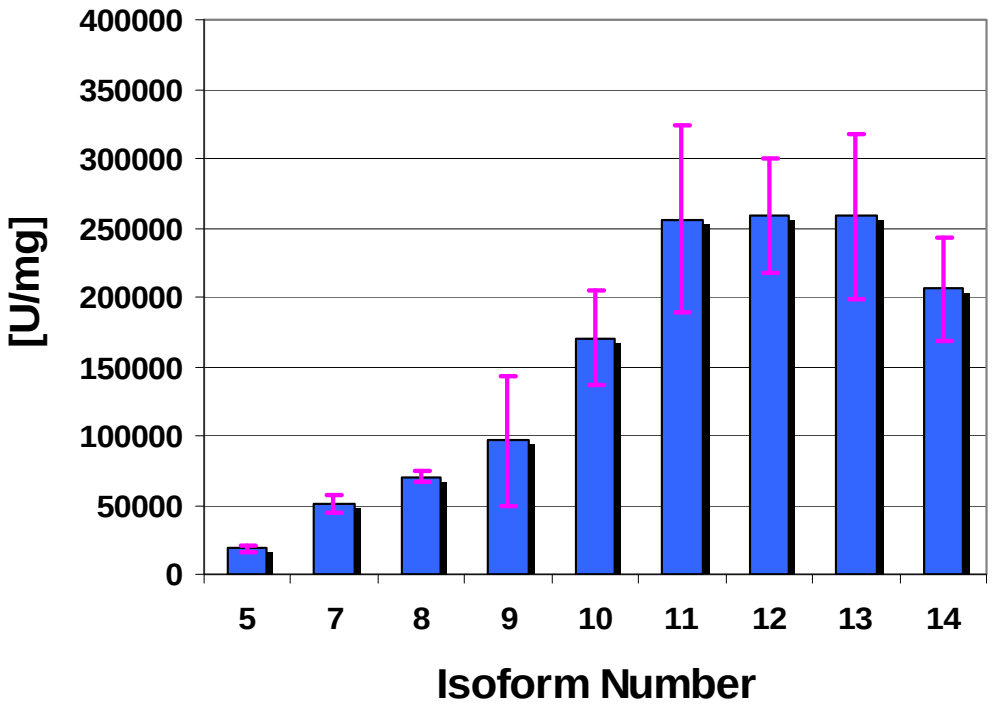
Source: Fraunhofer IGB (Interferon Beta)

Biotech medicines are not a single active ingredient, they are a heterogeneous mix of similar isoforms

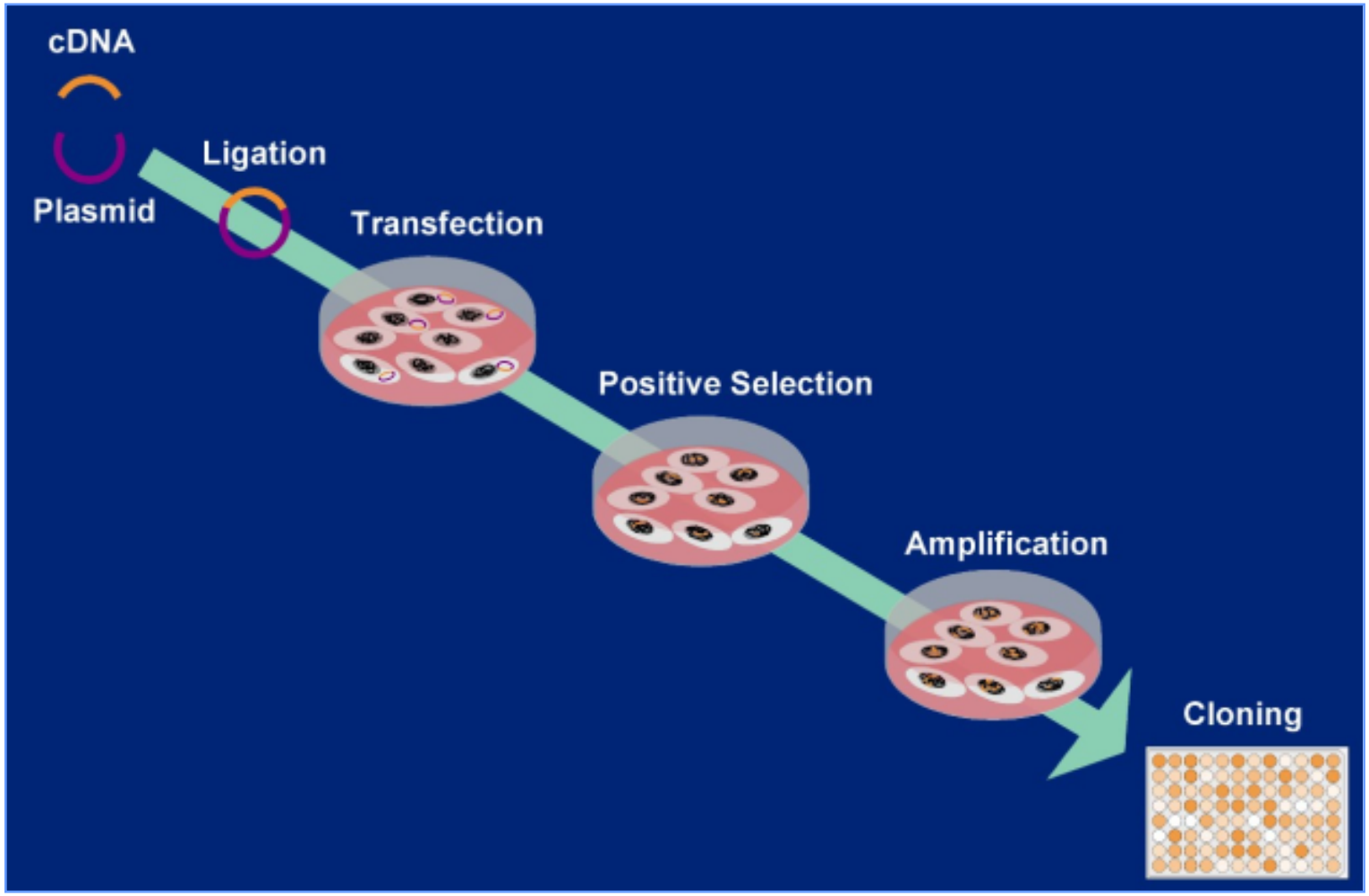
Isoelectric Focusing: epoetin alfa product is subfraction of cell culture isoforms



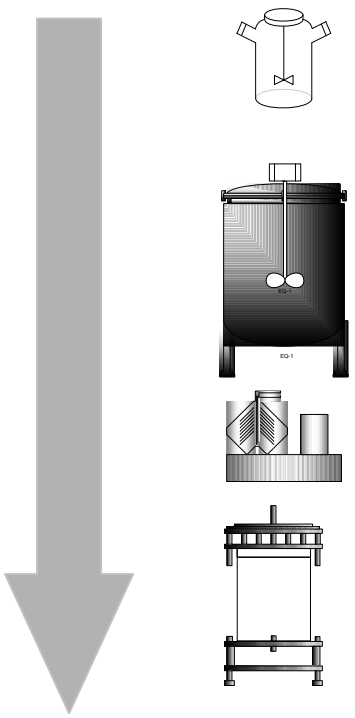
In-vivo Bioactivity



Each Manufacturer Must Make Their Own Unique Cell Line



The main manufacturing steps will be similar, but will not be identical between different manufacturers



Purified Bulk Drug

Unit Operation	Unique to each Manufacturer
Cell Expansion	Cell line, growth media, method of expansion
Cell Production in Bioreactors	Cell line, growth media, bioreactor conditions
Recover through filtration or centrifugation	Operating conditions
Purification through chromatography	Binding and elution conditions
Characterization and Stability	Methods, reagents, reference standards

Manufacturing

- The quality and consistency of the product are highly dependant on the manufacturing process
  - The process defines the product

- Minor differences in the biophysical characteristics of a biotech medicine can have clinical consequences

What Are Biosimilars?

- The expiry of patent protection and regulatory data protection for certain biotech medicines has led to the development of what are called biosimilars
- Biosimilars are products that claim to be a copy of the original, innovative biotech medicine
  - eg. epoetin, G-CSF, insulin, somatropin
- However, they are made with a different cell-line and a different manufacturing and purification process
- As they are made by a different manufacturing process
  - This will lead to biosimilars having similar, but not identical biophysical characteristics to the innovator biotech medicine

What Is The Principle Of Substitution?

Medicines are the same = therefore can be safely substituted

✓ Generics / chemical drugs

Substances are identical = therefore can be safely substituted

The principle behind substitution is that the medicines are identical and have the same therapeutic effect.

This applies to chemical medicines with generics as they are approved following a demonstration of bioequivalence, thus excluding any differences in bioavailability.

Principle Of Generic Substitution Does Not Apply To Biosimilars

Medicines are the same = therefore can be safely substituted

✓ Generics / chemical drugs

Substances are identical = therefore can be substituted

X Biosimilars/Biotech medicines are not identical

Can generic substitution rules be applied?

Therefore, with biotech medicines and biosimilars, the generic substitution rules do not apply