

# Intelektualno vlasništvo u znanstvenim istraživanjima, inovacije i projekti

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**Verbanac, Donotella**

**Conference presentation / Izlaganje na skupu**

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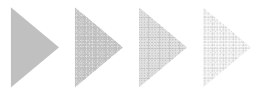


# Intelektualno vlasništvo u istraživanju lijekova i biomedicini



**Donatella Verbanac**

Centar za translacijska i klinička istraživanja  
Sveučilište u Zagrebu Medicinski fakultet



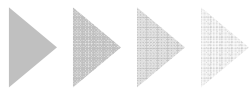
## Trenutno stanje u farmaceutskoj industriji



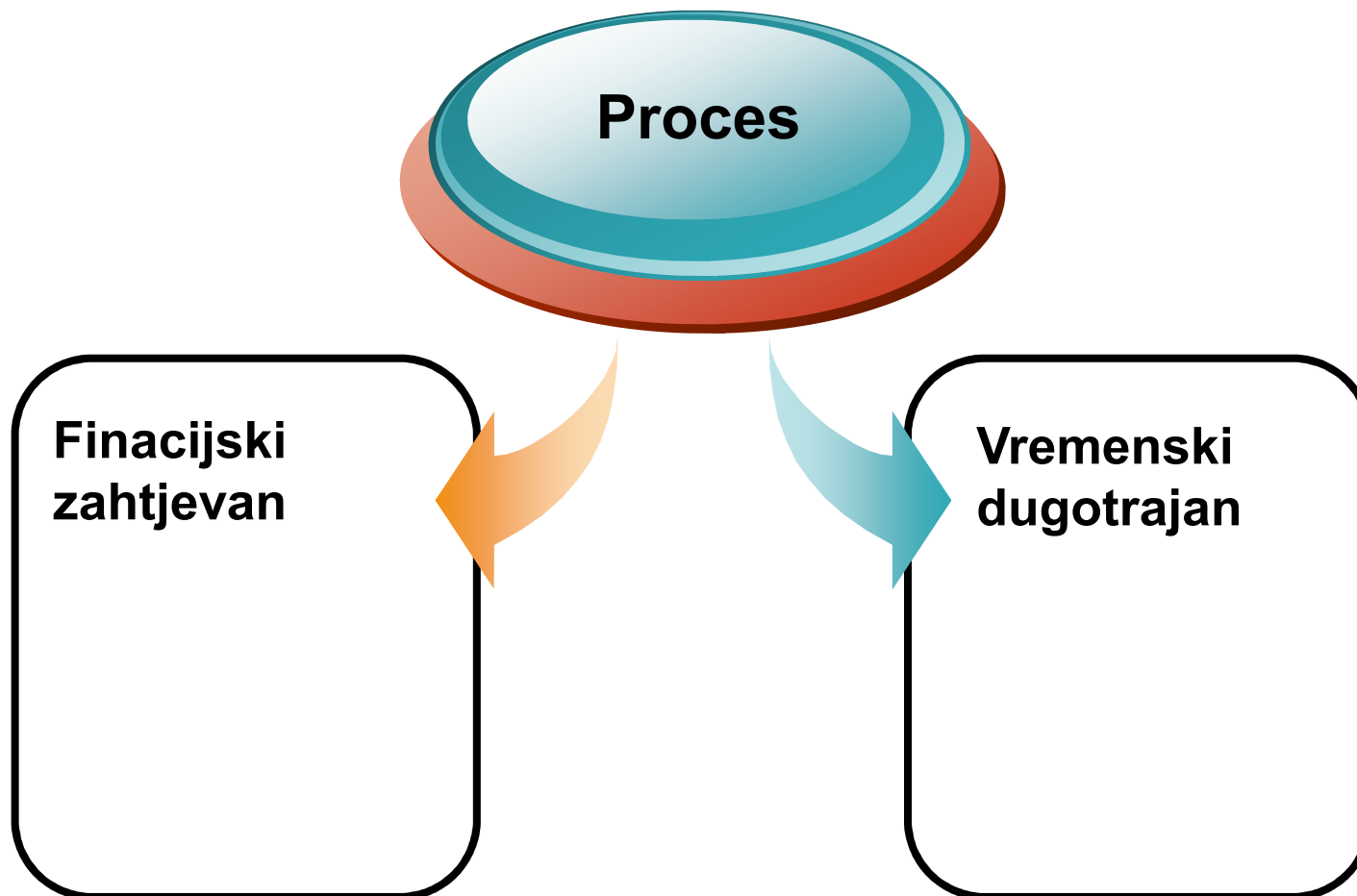
Uspjeh se mjeri po broju lijekova koji zarađuju >\$1 milijarde

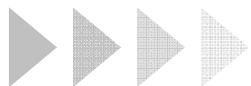
Pritisak je povećan radi očekivanja investitora i povećane konkurencije

Lijekovi koji su nekad predstavljali osnovu profita (tzv. *blockbusters*) više nisu dovoljni za očuvanje poslovanja zbog gubitka prava intelektualnog vlasništva



# Istraživanje lijekova





## Visoki troškovi razvoja pojedinih ideja



Novi avion	€ 50 Mrd.
Novi automobil	€ 3 - 6 Mrd.
Novi kompjuterski chip	€ 1 Mrd.
Novi lijek	€ 0,8 – 1,2 Mrd.

**1,000,000,000** CHF investment  
**7,000,874** hours of work  
**6,587** experiments  
**423** researchers  
**1** medicine



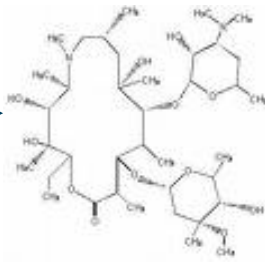
### Razvoj proizvoda

Skup proces i relativno podložan kopiranju - **visok rizik (piratskog) preuzimanja** -  
1/10 - 1/100 troškova ukupnog razvoja proizvoda

# Put nastanka novog lijeka



Osnivanje projektnog tima i definiranje ciljeva



Sinteza novih spojeva ili selekcija iz postojeće baze spojeva



Spojevi testirani *in vitro* i *in vivo* - rezultati upotrijebljeni za selekciju najboljeg kandidata



Formulacija, stabilitet «scale-up» sinteza, dodatno testiranje neškodljivosti u životinja



Lijek odobren za marketing i prodaju

**Cjelokupan razvoj traje 10-15 godina**

Tvrtka podnosi zahtjev za IND (Investigational New Drug) ili IMPD (Investigational Medicinal Product Dossier)



Regulatorne agencije



Tvrtka podnosi zahtjev za NDA (New Drug Application)



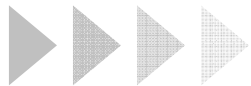
Faza III: velika klinička ispitivanja na mnogo pacijenata



Faza II: studije na pacijentima (učinkovitost)



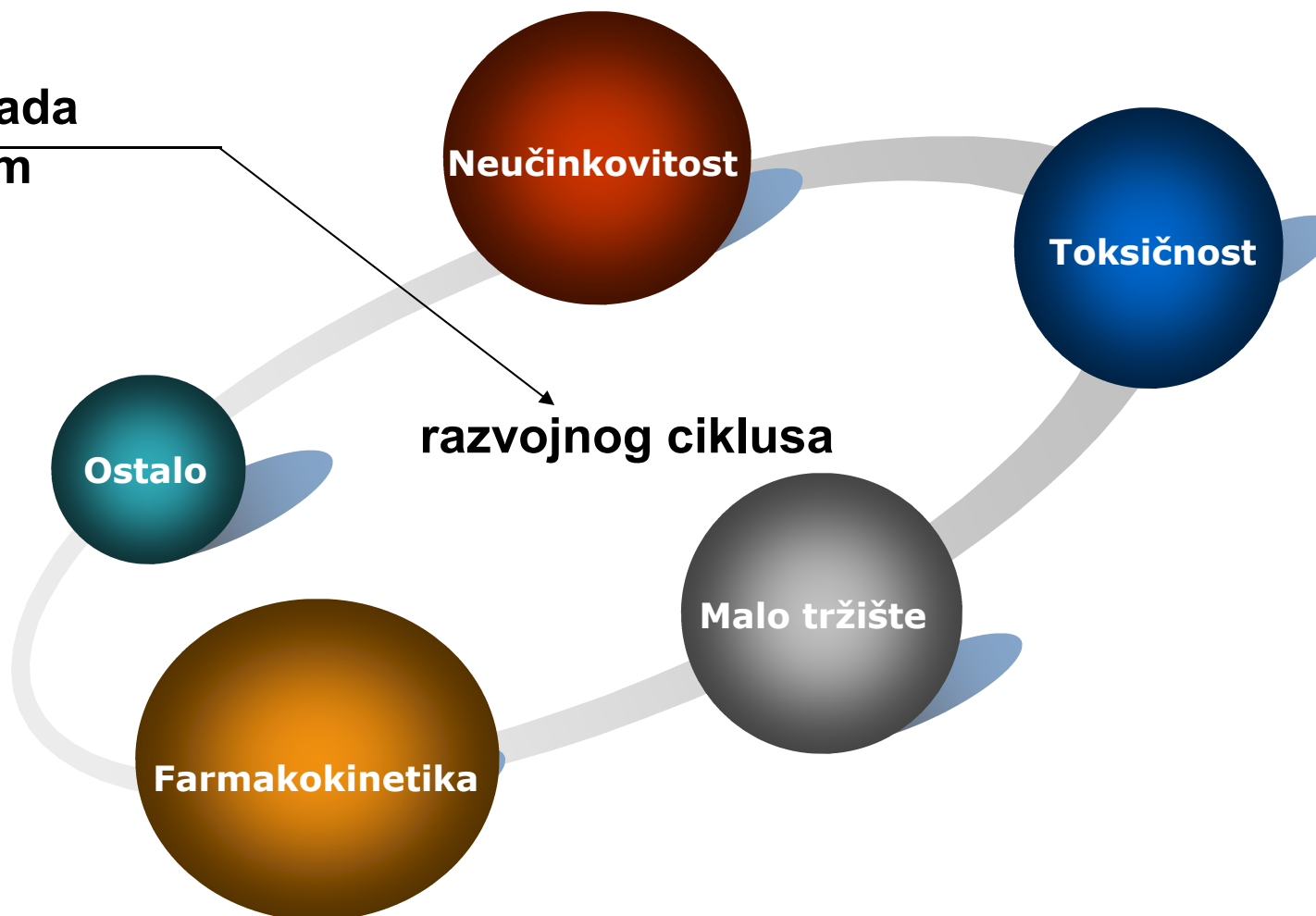
Faza I: studije na zdravim dobrovoljcima (tolerancija i doza)



# Razlozi prekida razvoja nekog lijeka



Bilo kada  
tijekom





## Reasons for Attrition During Drug Development



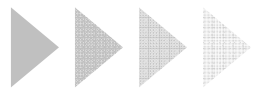
1990



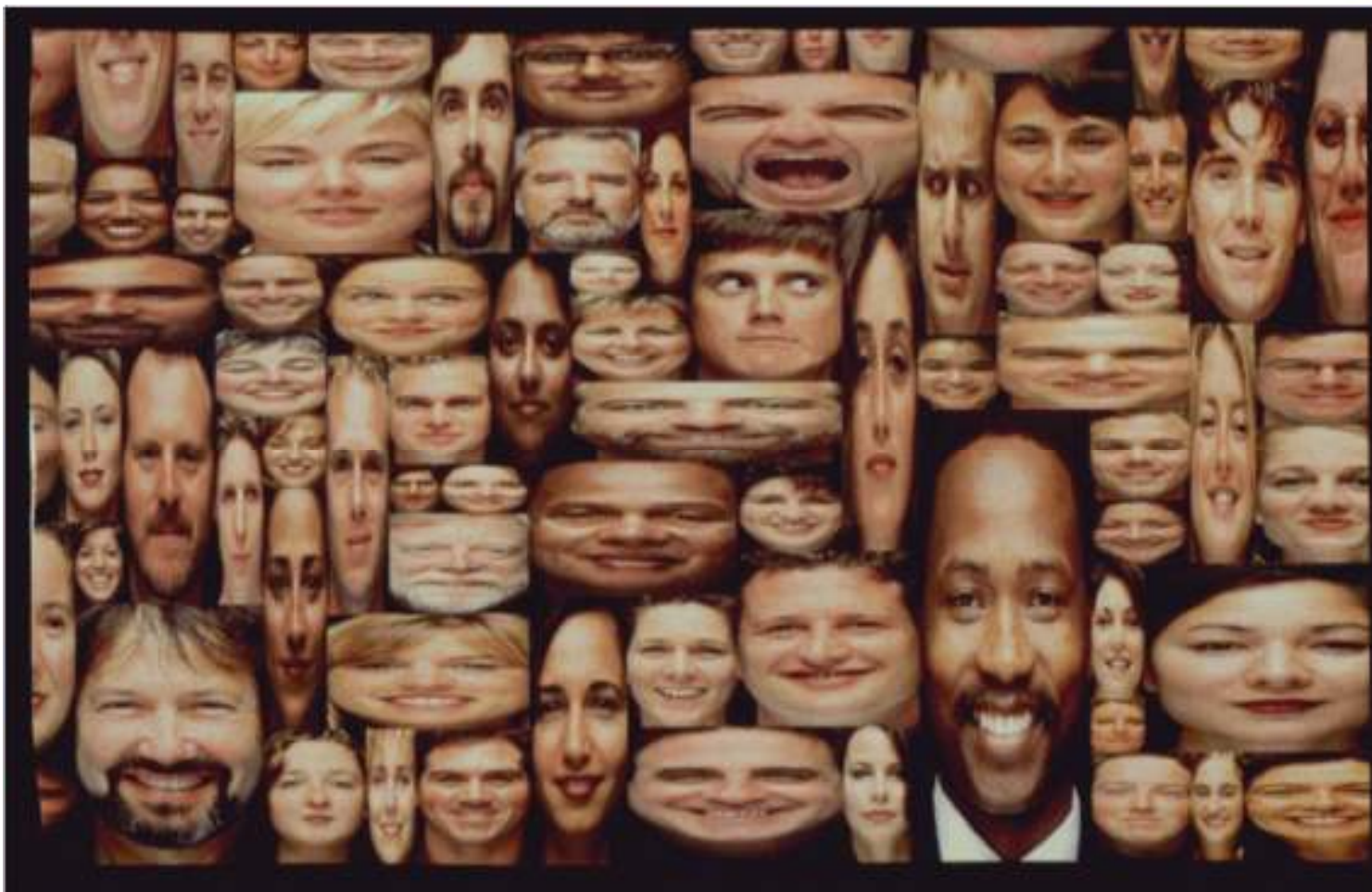
2000-2010

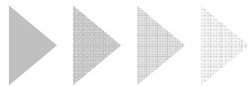
- PK/bioavailability
- Clinical safety
- Efficacy
- Commercial
- Toxicology
- Miscellaneous



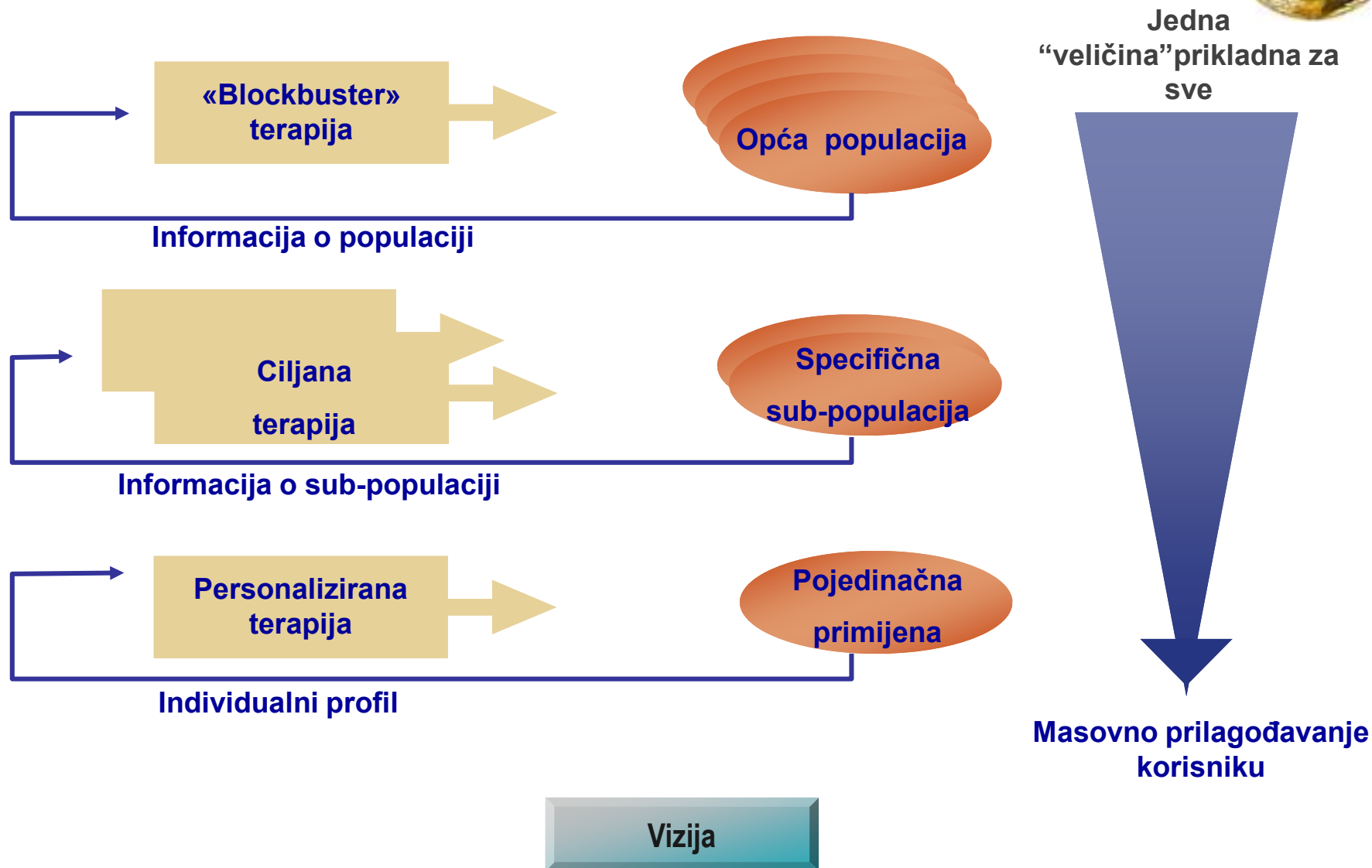


# Krajnji korisnici su ljudi



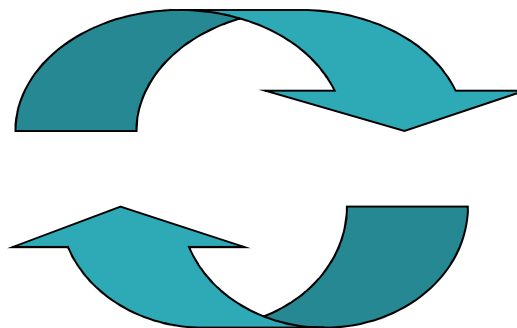


# Novi pristup razvoju lijekova





# Translacijska istraživanja



- ❖ Omogućuju dvosmjernu komunikaciju između bazičnih istraživača i medicinskih djelatnika na klinici i u praksi
- ❖ Omogućuju primjenu eksperimentalnih podataka preko kliničkih ispitivanja do konačnog korisnika – pacijenta
- ❖ Omogućuju povratnu informaciju dobivenu iz iskustvenih podataka i opažanja s klinike, te dobivanje uzoraka za rad bazičnih istraživača



Biomedicina i industrija lijekova

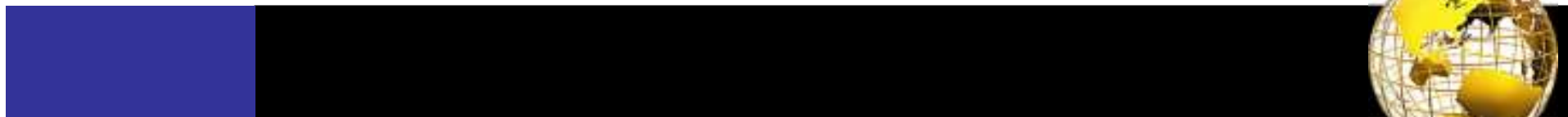
# **VAŽNOST PATENTA**



# Aspirin



- ❖ U antičkoj Grčkoj Hipokrat je ženi tijekom poroda dao čaj lista vrbe kako bi joj umanjio osjećaj boli
- ❖ 1823 - iz vrbe je izolirana aktivan tvar i nazvana **salicin**
- ❖ 1859: Njemački kemičar Hermann Kolbe sintetizira salicilnu kiselinu
- ❖ 1897: Patent - *Synthesis of acetyl salicylic acid/aspirin* – izumitelj – kemičar i farmaceut **Felix Hoffmann** Odjel *Farbenfabriken* - Elberfeld, Njemačka)
- ❖ 1899: Aspirin® registracija naziva pri Kaiserliches Patentamt u Berlin
- ❖ 1950: Guinness Book, 1969 Apollo 11, 1971 MOA farmakolog Sir J.R.Vane



**Lijepi primjer...dobrog patenta**



# Izumitelji - Azitromicina



**Gabrijela Kobrehel  
Slobodan Đokić  
Gorjana Lazarevski  
Zrinka Tamburašev**





# Azythromycin - Zythromax



United States Patent [19]

[11] Patent Number: 4,517,359

Kobrehel et al.

[45] Date of Patent: May 14, 1985

[54] 11-METHYL-11-AZA-4-O-CLADINOSYL-6-O-DESOSAMINYL-15-ETHYL-7,13,14-TRIHYDROXY-3,5,7,9,12,14-HEXAMETHYLOXACYCLOPENTADECANE-2-ONE AND DERIVATIVES THEREOF

[75] Inventors: **Gabrijela Kobrehel; Slobodan Djokic**, both of Zagreb, Yugoslavia

[73] Assignee: **Sour Pliva farmaceutska, kemijska prehrambena i kozmeticka industrija, n.sol.o.**, Zagreb, Yugoslavia

[21] Appl. No.: 304,481

[22] Filed: Sep. 22, 1981

[30] Foreign Application Priority Data

Mar. 6, 1981 [YU] Yugoslavia ..... 592/81

[51] Int. Cl.<sup>3</sup> ..... C07H 17/08

[52] U.S. Cl. .... 536/7.4

[58] Field of Search ..... 536/9, 7.4

[56] References Cited

U.S. PATENT DOCUMENTS

4,283,527 8/1981 Sciavolino ..... 536/7.4

4,328,334 5/1982 Kobrehel et al. .... 536/7.4

Primary Examiner—Nicky Chan

Attorney, Agent, or Firm—Pollock, Vande Sande & Priddy

[57] ABSTRACT

11-Methyl-11-aza-4-0-cladinosyl-6-0-desosaminy-15-ethyl-7,13,14-trihydroxy-3,5,7,9,12,14-hexamethyl-oxacyclopentadecane-2-one and derivatives thereof, such as the 13,14-carbonate and C<sub>1</sub>-C<sub>3</sub>-alkanoyl derivatives thereof. The compounds exhibit antibacterial activity.

1 Claim, No Drawings

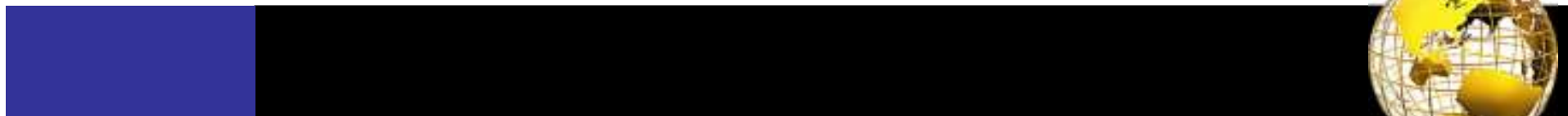
What is claimed is:

❖ **Tvrdnja/Claim:**

1. N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A.

\* \* \* \* \*





**Lijepi primjer...učinkovitog patenta**



US008197840B2

The Director of the United States Patent and Trademark Office

The United States

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

(12) United States Patent Vukicevic et al.

(10) Patent No.: US 8,197,840 B2 (45) Date of Patent: Jun. 12, 2012

(54) WHOLE BLOOD-DERIVED COAGULUM DEVICE FOR TREATING BONE DEFECTS

Asahina et al., Human Osteogenic Protein-1 Induces Chondroblastic, Osteoblastic and/or Adipocytic Differentiation of Clonal Murine Target Cells. *Exp. Cell Res.*, 222: 38-47 (1996).

(75) Invention: Shohadan Vukicevic, Zagreb (HR); Lavorka Grigorevic, Zagreb (HR); Hermann Oppermann, Melway, MA (US)

Chen et al., Three-dimensional structure of recombinant human osteogenic protein 1: Structural paradigm for the transforming growth factor (superfamily). *Proc. Natl. Acad. Sci. USA*, 93: 878-883 (1996).

(73) Assignee: Genera Istraivanja d.o.o., Kufnerica (HR)

Hoffmann et al., Perspectives in the biological function, the technical and therapeutic applications of bone morphogenetic proteins. *Appl. Microbiol. Biotechnol.*, 57: 294-308 (2001).

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35

Jones et al., Osteogenic Protein-1 (OP-1) Expression and Processing in Chinese Hamster Ovary Cells: Isolation of a Soluble Complex Containing the Mature and Pro-Domains of OP-1. *Growth Factors*, 11: 215-225 (1994).

Kim et al., BMP6 in Healing of Bone Defect. *Tissue Med. Adv.*, 33(1): 56-63 (1992).

(12) United States Patent Vukicevic et al.

(10) Patent No.: US 8,197,840 B2 (45) Date of Patent: Jun. 12, 2012

(54) WHOLE BLOOD-DERIVED COAGULUM DEVICE FOR TREATING BONE DEFECTS

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or (c)(1), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b). See the Maintenance Fee Notice on the inside of the cover.

David J. Kappas

Director of the United States Patent and Trademark Office

(58) Field of Classification Search ..... None See application file for complete search history.

(50) References Cited

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4,968,591 A 11/1991 Kabacian et al. 5,661,891 A 6/1991 Oppermann et al. 5,171,579 A 12/1992 Kim et al. 5,385,882 A 1/1995 Yeo et al. 5,496,552 A 3/1996 Kabacian et al. 5,674,844 A 10/1997 Kabacian et al. 6,117,425 A \* 9/2000 MacPhail et al. 6,133,332 B1 12/2001 Kabacian et al. 20070014780 A1\* 1/2007 Wadsworth

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Applicant's Response to the Written Opinion as Filed for international application No. PCT/US2007/016601 on Jan. 6, 2009 International Search Report for international application No. PCT/US2007/016601 (Oct. 7, 2008). Written Opinion of the International Searching Authority for international application No. PCT/US2007/016601 (Oct. 7, 2008).

1995, CHEMIST, et al. (MAY 1995) UNIVERSITY MICROFILMS, 0096, pp. 94-95

Chen et al., "The Fusion Rate of Calcium Sulfate With Local Autologous Bone Compared With Autologous Ilac Bone Graft for Instrumented Short-Segment Spinal Fusion," *Spine*, 30(20): 2293-2297 (Oct. 15, 2005).

Debnath et al., "Periosteal Intramedullary Decompression, Curettage, and Grafting With Medical-Grade Calcium Sulfate Pellets for Unilateral Bone Cysts in Chickens: A New Minimally Invasive Technique," *J. Pediatr. Orthop.*, 25 (6): 804-811 (Nov.-Dec. 2005).

Gillespie et al., Chemistry, second edition, (Nahyn and Bacon, Inc., Boston, 1989), p. 218.

Isala et al., "Calcium Sulfate and Particle-Rich Plasma make a novel osteoconductive biomaterial for bone regeneration," *J. Translational Medicine*, 5:15 (2007); article available from: <http://www.translational-medicine.com/content/5/1/15>.

Marsell et al., "New Bone Induction by Bone Matrix and Recombinant Human Bone Morphogenetic Protein-2 in the Mouse," *Crit Care Med.*, 17(4): 237-244 (1989).

\* cited by examiner

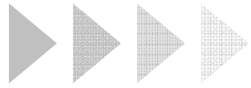
Primary Examiner: Suzanne M Noakes

(74) Attorney, Agent, or Firm: Thomas R. Berka; Leon R. Yankwich; Yankwich & Associates, P.C.

(57) ABSTRACT

Whole blood-derived coagulum devices are described for use in treating bone defects.

26 Claims, 9 Drawing Sheets



# OSTEOGROW FP7 Projekt



Akademik Slobodan Vukičević  
Izv.prof. dr.sc. Lovorka Grgurević  
Dr.sc. Hermann Oppermann, dr.med.

## Patent

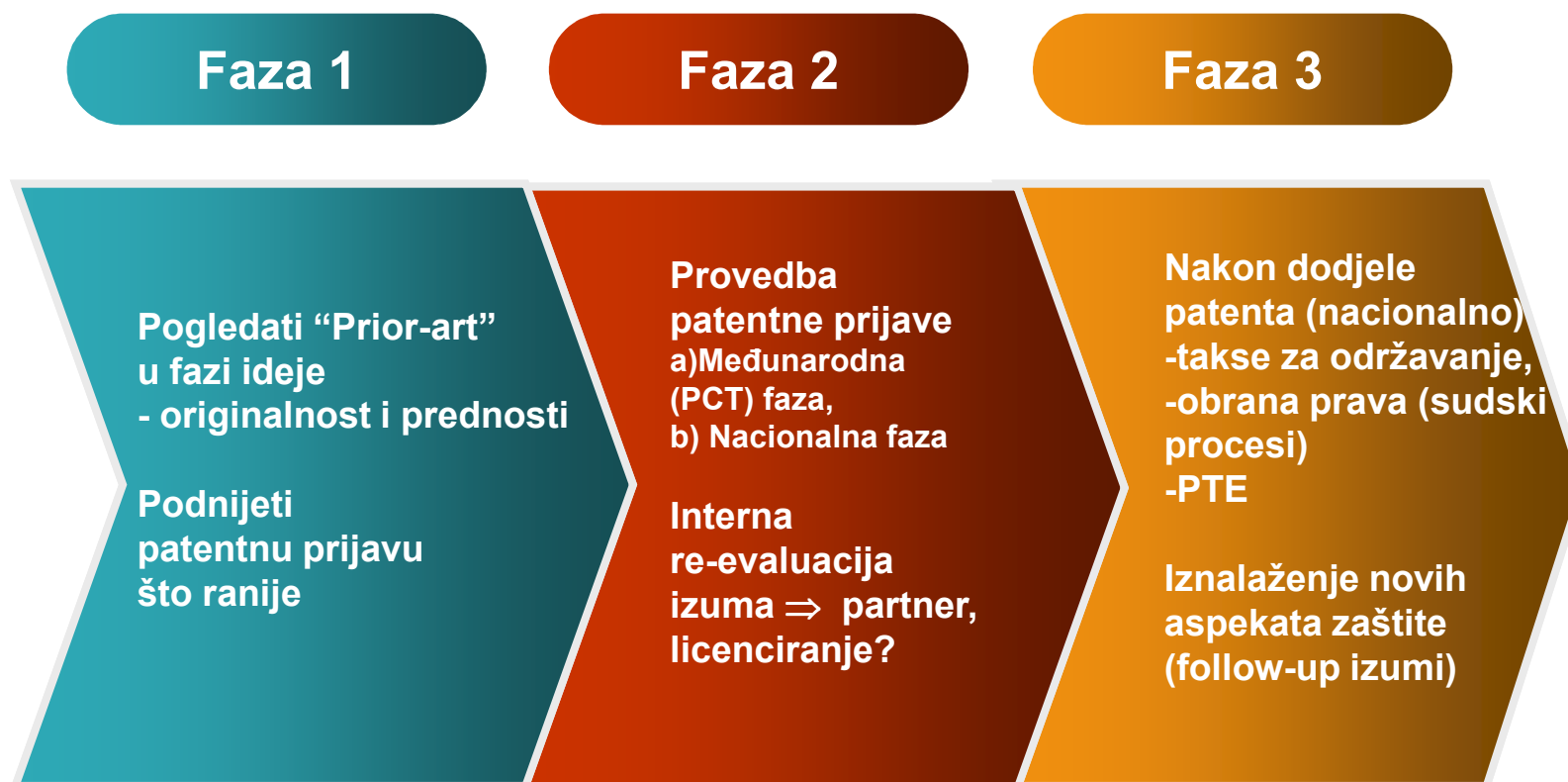
*„Whole blood-derived  
coagulum device for  
treating bone defects”*

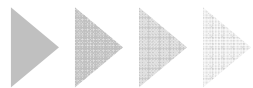
OSTEOGROW

OSTEOGROW is a **60-months SME-targeted Collaborative Project** and has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement No 279239.

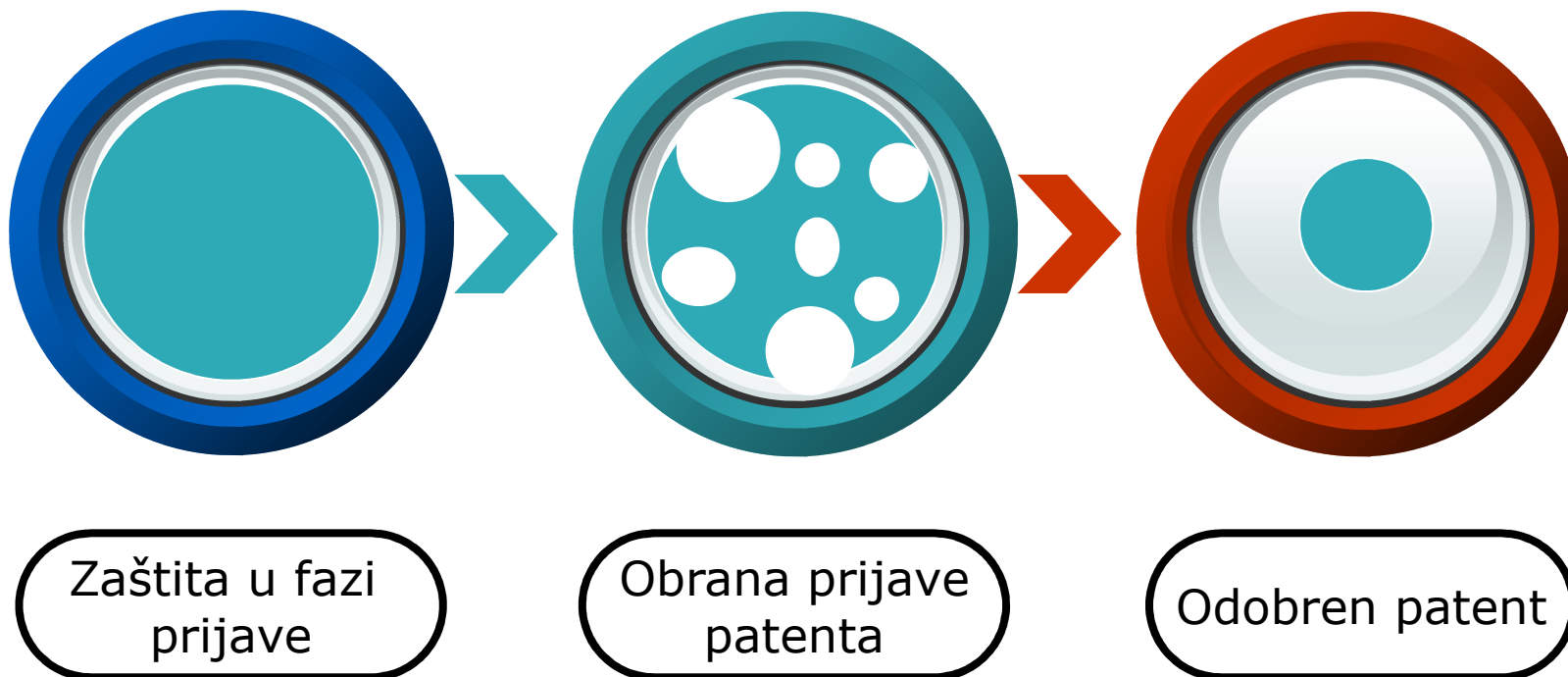


# Patentiranje u farmaceutskoj industriji





# Faze u dobivanju patenta

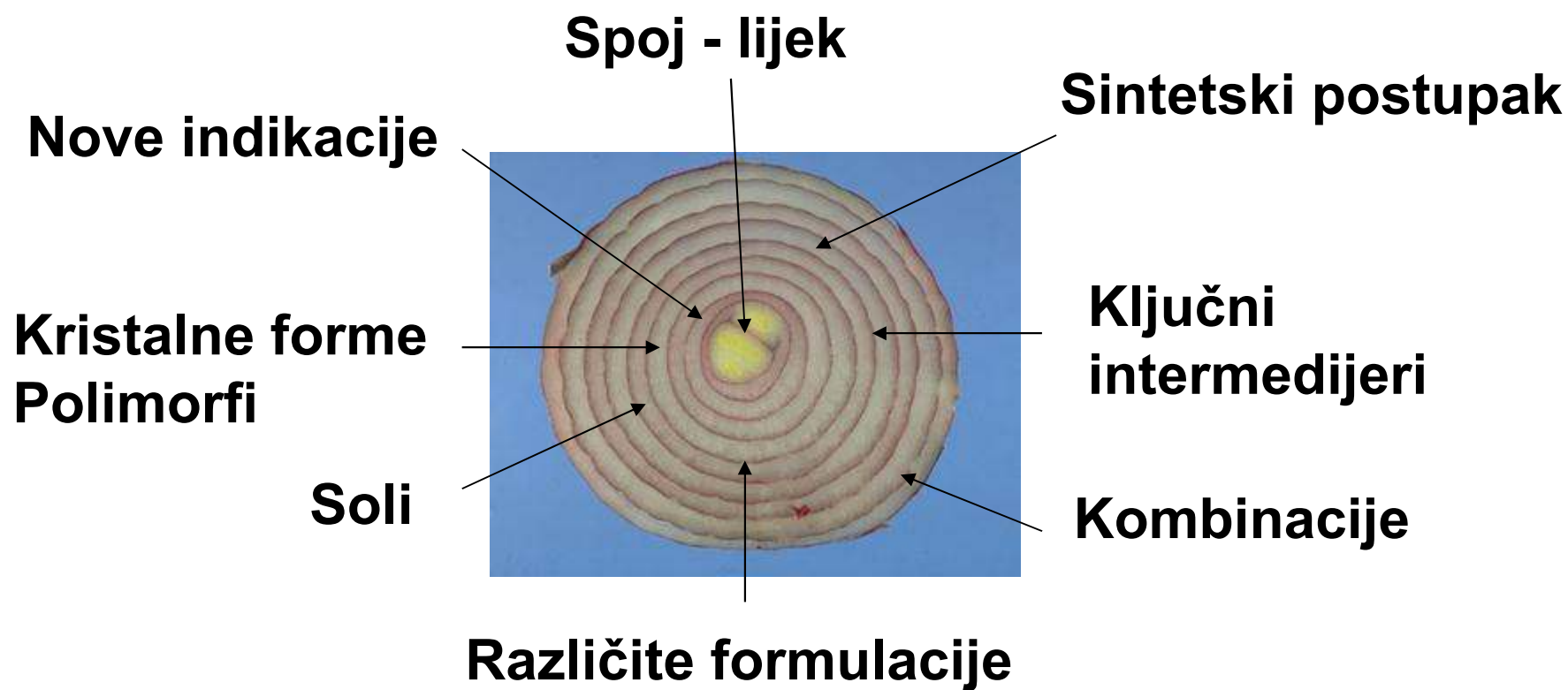




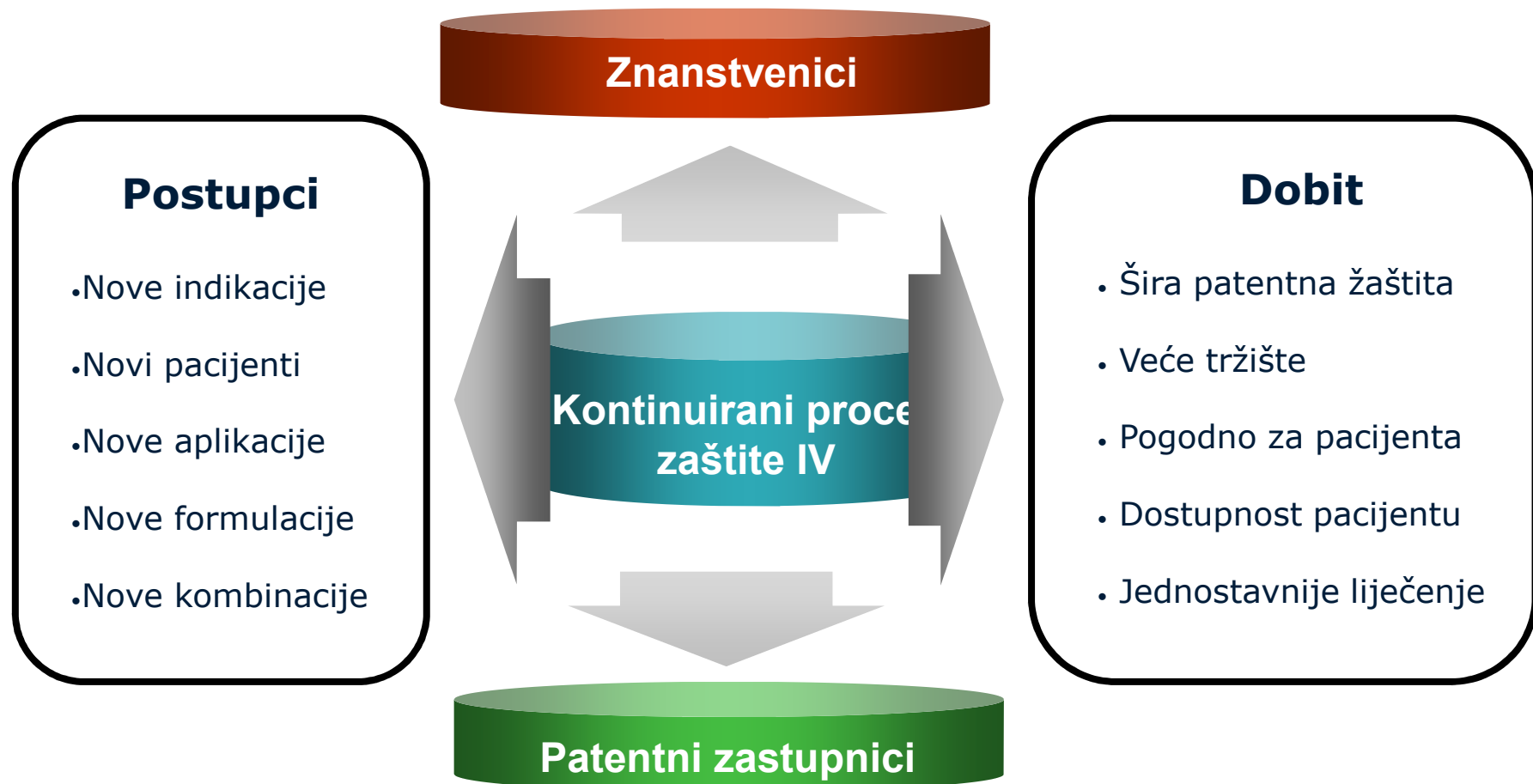
# Patenti u farmaceutskoj industriji

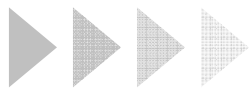


## “Onion” Approach



# Produljenje trajanja zaštite patenta nekog lijeka

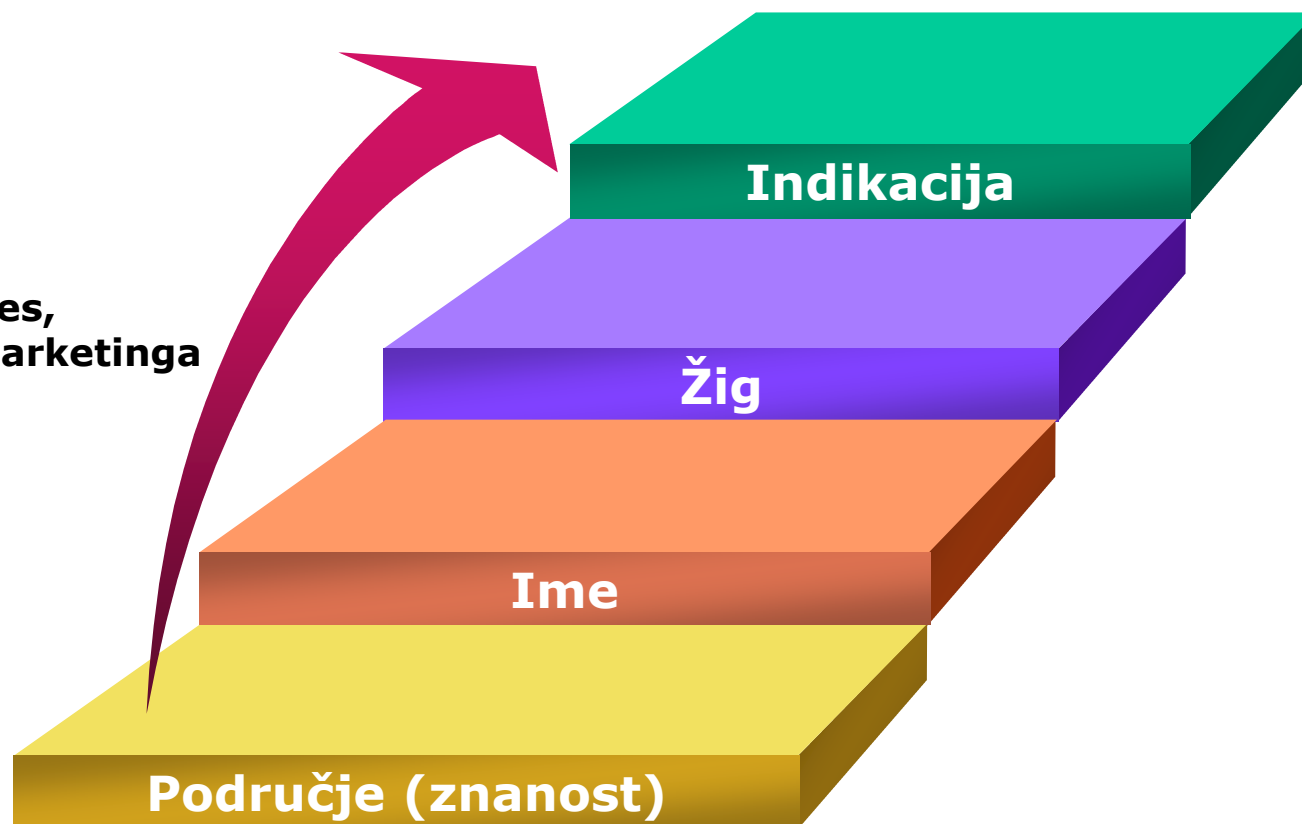




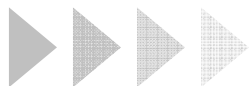
# Što se sve kod lijeka može zaštititi?



Kontinuiran proces,  
važna je uloga marketinga



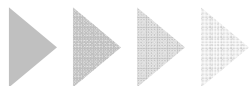




## Osnovna obilježja zaštite lijeka



- ❖ Odjel koji se bavi razvojem poslovanja morao bi raditi zajedno s patentnim zastupnicima kako bi već u fazi određivanja strategije razvoja mogao procijeniti u kojem području istraživanja postoji prostor za nove zaštite
- ❖ Već kod postupka prvih registracija lijeka treba znati kako će se štititi ime, te teritorijalno pravo žiga (žig je pravo, ali nije i obaveza)
- ❖ U postupku registracije lijek treba imati svoj naziv, potrebno je oko godinu dana da se naziv zaštiti
- ❖ Postoje baze zaštićenih imena lijekova koje je potrebno pretražiti kad se odabire ime za novi lijek

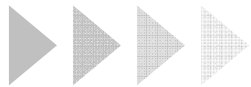


# Što s novim indikacijama i nazivima?



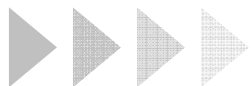
- ❖ Kod novih indikacije odabir novog imena ili zadržavanje starog naziva odluka je same tvrtke
- ❖ U pravilu bi za potrebe novih indikacija u **generičkom poslovanju** ime moralo biti za najmanje tri slova različito od originalnog
- ❖ Postoji i tzv. "Umbrella" zaštita naziva proizvoda pojedinih tvrtki (primjer PLIVA: **Plicet**, **Plibex**, **Plivadon**...)
  
- ❖ **Primjer I:**
  - Finasterid (generički naziv)
  - Lijek za prostatu - Prostide ("brand" ime)
  - Nova indikacija – alopecija – novi naziv (Propecia)
    - Može se odabrati i novo ime za neka nova tržišta (SAD i EU mogu imati različite "brand" nazive)
  
- ❖ **Primjer II:**
  - Sildenafil (generički naziv)
  - Lijek za plućnu arterijsku hipertenziju – Revatio
  - Lijek za erektilnu disfunkciju – Viagra (zaštićen i oblik tableta)
  
- ❖ **Primjer III:**
  - Azitromicin (generički naziv)
    - Teritorijalna zaštita imena
      - Sumamed
      - Zytromax
    - Isti nazivi koriste se sad i za razne indikacije





## Patent Term Extensions i pedijatrijska inicijativa

- ❖ Europa – **Supplementary Patent Certificates (SPC)**
  - Hrvatska je usvojila svjedodžbu o dodatnoj zaštiti za lijekove namijenjene ljudima ili životinjama i sredstva za zaštitu bilja; stupila je na snagu pola godine nakon ulaska Hrvatske u EU
- ❖ SAD – Hatch-Waxman Patent Term Extensions
- ❖ **SPC omogućuje maksimalno traje 5 godina i stupa na snagu odmah nakon isteka temeljnog patenta**
- ❖ Svjedodžba se izdaje na zahtjev nositelja patenta u roku od 6 mjeseci od datuma izdavanja odobrenja za stavljanje u promet, a ako je odobrenje izdano prije priznanja temeljnog patenta, u roku od 6 mjeseci od objave priznanja patenta
- ❖ U slučaju primjene u pedijatriji – **produljenje trajanja patenta za 6 mjeseci**



## Jedinstvenost podataka istraživanja i razvoja lijeka (*data/market exclusivity*)



- ❖ Administrativna mjera koju provode agencije za lijekove
  - Klinička istraživanja traju više godina i troše najviše sredstava;
  - Jedinstveni rezultat predstavlja čitav niz dokumenata/rezultata koji bivaju istraživani od regulatornih tijela kako bi se ishodile potrebne dozvole
  - Generičke tvrtke moraju ipak zasnivati svoja usporedna istraživanja na dobivenim rezultatima originatora
  
- ❖ Traje **8 godina**
  
- ❖ Razdoblje zaštite tržišta - nakon izdavanja prve dozvole za stavljanje na tržište originalni lijek u kome se generički lijek ne može staviti u promet
  - Traje **(2 (+1) god)**

# Pitanja !

