Therapeutic options: what's new in the pipeline ?

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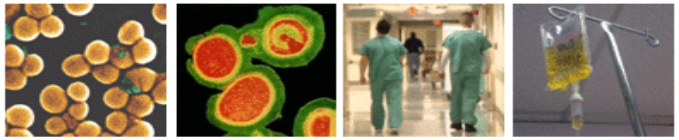
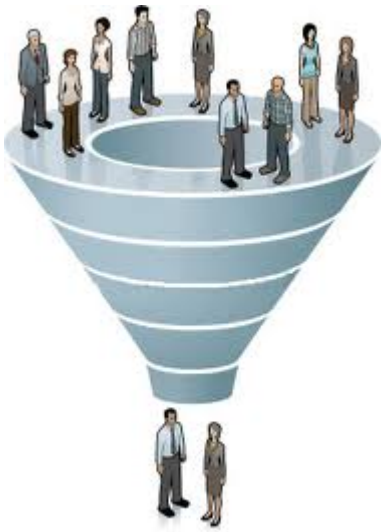


***Staphylococcus aureus* : from basic science to clinical applications**
FRIDAY October 5, 2012
Université catholique de Louvain – Université libre de Bruxelles

What its all about ?

- What is the clinical problem ? …
  - ➔ Resistance ?
  - ➔ Persistence ?
  - ➔ Difficult-to-reach foci ?
  - ➔ Wrong target ?
- Is the pipeline really dry ?
  - ➔ Semi-old drugs
  - ➔ Drugs at the corner of the street
  - ➔ Dugs of the future ?
- But why not in Belgium ?

Do we really have a drying pipeline ?



research

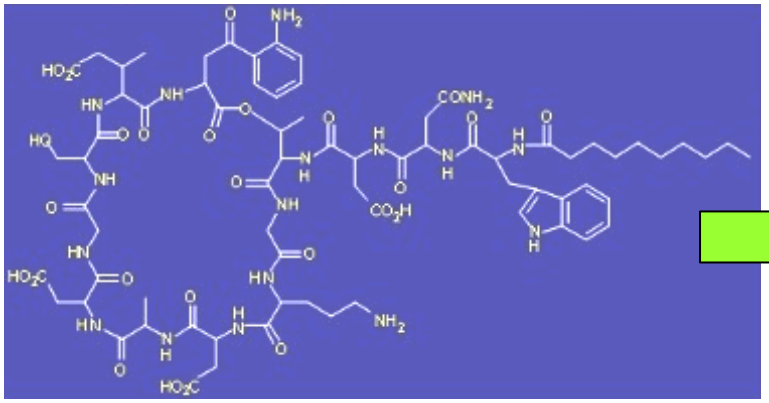
results

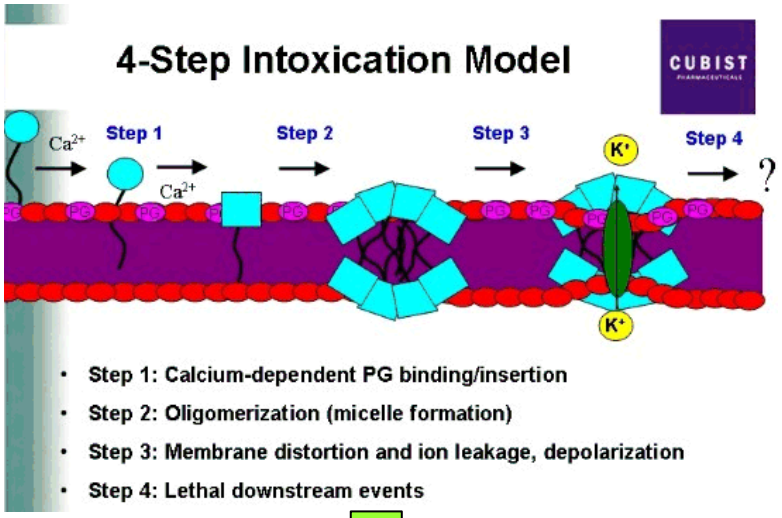
Drugs registered in EU since long …

- **Synercid®** (quinupristin/dalfopristin)
  - No longer available in Europe
  - Available from Pfizer in the US (acquisition of King Pharmaceuticals)
- **Tygecycline**
  - Available in Belgium but limited use
  - Indication (concerning *S. aureus*)
    "Infections compliquées de la peau et des tissus mous, à l'exclusion des infections du pied chez les patients diabétiques"
- **Daptomycin**
  - Largely used in the US
  - Registered in EU for
    - *Complicated skin and soft-tissue infections (cSSTI).*
    - *Right-sided infective endocarditis (RIE)*
    - *Staphylococcus aureus bacteraemia (SAB) associated with RIE or with cSSTI.*
  - Costly (125 €/day) and sparingly used in Europe
  - Not reimbursed and therefore not available in Belgium …

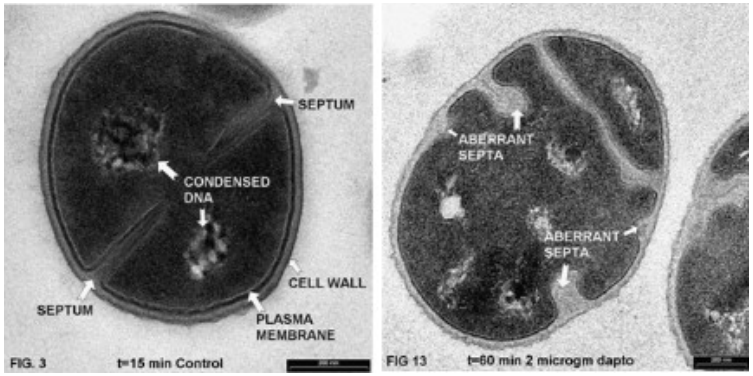
The story of daptomycin…

- Original molecule with a novel mode of action !





- **very bactericidal (membrane destabilization; no need of proteinaceous receptor !) and potent (MIC *S. aureus* = 0.5mg/L)**
- **spare eucaryotic cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes**



What the registration studies showed…

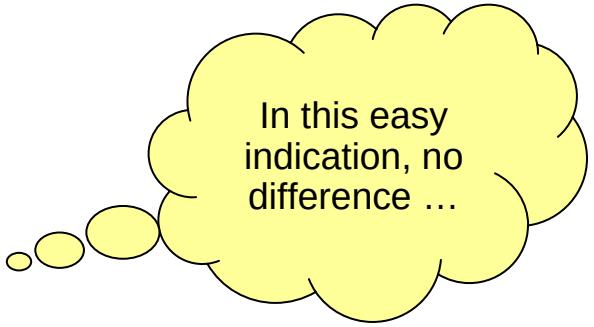
- Phase III studies : 1. skin & skin structures infections

Table 12. Clinical Success Rates by Infecting Pathogen in the cSSSI Trials (Population: Microbiologically Evaluable)

Pathogen	Success Rate n/N (%)	
	CUBICIN	Comparator*
Methicillin-susceptible *Staphylococcus aureus* (MSSA)†	170/198 (86%)	180/207 (87%)
Methicillin-resistant *Staphylococcus aureus* (MRSA)†	21/28 (75%)	25/36 (69%)
Streptococcus pyogenes	79/84 (94%)	80/88 (91%)
Streptococcus agalactiae	23/27 (85%)	22/29 (76%)
Streptococcus dysgalactiae subsp. *equisimilis*	8/8 (100%)	9/11 (82%)
Enterococcus faecalis (vancomycin-susceptible only)	27/37 (73%)	40/53 (76%)

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

† As determined by the central laboratory.



Daptomycin: what the registration studies showed…

- Look at the phase III studies : 2. endocarditis

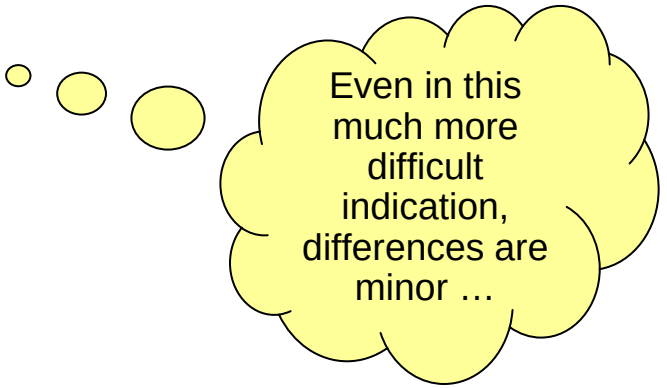
Table 13. Success Rates at Test of Cure in the *S. aureus* Bacteremia/Endocarditis (ITT)

Population	Success Rate n/N (%)		Difference: CUBICIN – Comparator (Confidence Interval)
	CUBICIN 6 mg/kg	Comparator*	
Overall	53/120 (44%)	48/115 (42%)	2.4% (–10.2, 15.1)†
Baseline Pathogen			
Methicillin-susceptible *S. aureus*	33/74 (45%)	34/70 (49%)	–4.0% (–22.6, 14.6)‡
Methicillin-resistant *S. aureus*	20/45 (44%)	14/44 (32%)	12.6% (–10.2, 35.5)‡
Entry Diagnosis§			
Definite or Possible Infective Endocarditis	41/90 (46%)	37/91 (41%)	4.9% (–11.6, 21.4)‡
Not Infective Endocarditis	12/30 (40%)	11/24 (46%)	–5.8% (–36.2, 24.5)‡
Final Diagnosis			
Uncomplicated Bacteremia	18/32 (56%)	16/29 (55%)	1.1% (–31.7, 33.9)¶
Complicated Bacteremia	26/60 (43%)	23/61 (38%)	5.6% (–17.3, 28.6)¶
Right-Sided Infective Endocarditis	8/19 (42%)	7/16 (44%)	–1.6% (–44.9, 41.6)¶
Uncomplicated Right-Sided Infective Endocarditis	3/6 (50%)	1/4 (25%)	25.0% (–51.6, 100.0)¶
Complicated Right-Sided Infective Endocarditis	5/13 (39%)	6/12 (50%)	–11.5% (–62.4, 39.4)¶
Left-Sided Infective Endocarditis	1/9 (11%)	2/9 (22%)	–11.1% (–55.9, 33.6)¶

* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

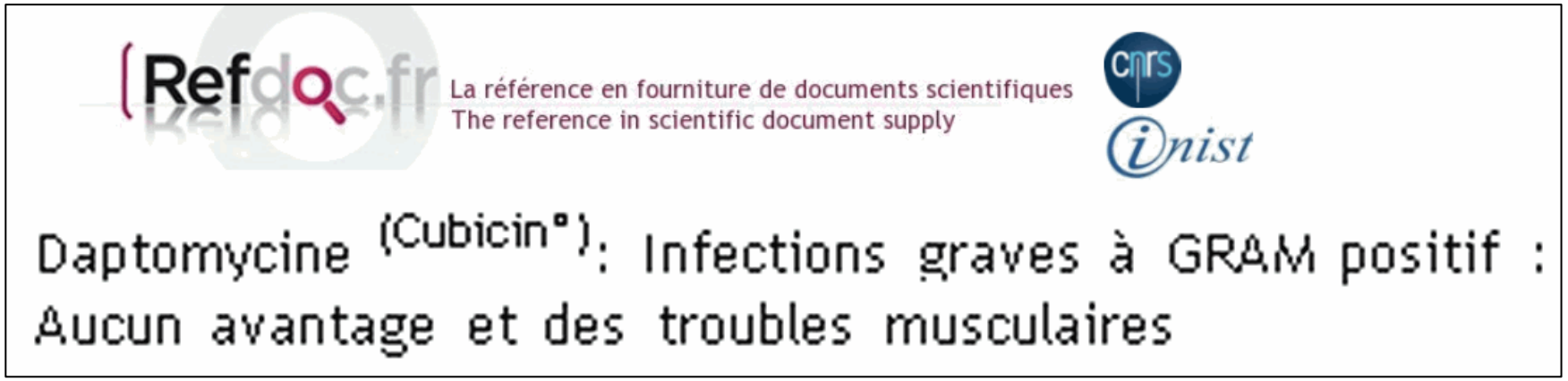
† 95% Confidence Interval ‡ 97.5% Confidence Interval (adjusted for multiplicity)

§ According to the modified Duke criteria[4] ¶ 99% Confidence Interval (adjusted for multiplicity)



But viewed from Europe…

- As a result, in a major EU country …



Is this what discovery was promising ?

The current situation with daptomycin

- **Higher doses (8 to 10 mg/kg/d) → higher price/day …**
  - Safety seems acceptable [1] but with limits
    - severe rhabdomyolysis (symptomatic, CPK > 1000 UI/L, stop)
    - higher risk in obese patients ?

- Resistance is developing [2]
  (sequential mutations → lead to stepwise reduction in susceptibility)
  - *mprF* (membrane synthesis)—less binding of daptomycin through Ca++
  - *yycG* (sensor histidine kinase)—may be another daptomycin target
  - *rpoB*
  - *rpoC* ? Alter transcription of key genes
  - *dlt* operon* (+surface charge)

- Failure to control VISA strains makes replacement of vancomycin uncertain

1. Figueroa et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis. 2009; 49:177-8
2. Gould IM. Clinical activity of anti-Gram-positive agents against methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother. 2011; Suppl 4:iv17-iv21

Drugs more recently registered in EU …

- **Telavancin**
  - Dual mode of action and highly bactericidal !
  - **VISA: 0.5-1 mg/L**; **VRSA: 2-4 mg/L…**
    - Breakpoints EUCAST: S ≤ 1 - R > 1
  - Approved in US **for skin infections** … and not for HAP so far
    - Warnings for renal insufficiency and potential teratogenic effects
  - Approved in EU **for HAP** … and not for skin infections
    - *VIBATIV® is indicated for the treatment of adults with nosocomial pneumonia (NP) including ventilator associated pneumonia, known or suspected to be caused by methicillin-resistant Staphylococcus aureus (MRSA).*
    - *VIBATIV® should be used only in situations where it is known or suspected that other alternatives are not suitable*
  - Marketing Authorization withdrawn in 2012 because of negative FDA, MHRA and AFSSAPS inspections at the site of production
    → uncertain status

Talavancin marketing authorization suspended !

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report for Vibativ

25 May 2012
EMA/303395/2012

The European Medicines Agency (EMA) was made aware on 10 November 2011 of the cessation of manufacture at Ben Venue Laboratories as a result of findings by the Supervisory Authorities of United Kingdom (MHRA) and France (AFSSAPS) and by US FDA inspectors during a Good Manufacturing Practice (GMP) inspection of Ben Venue Laboratories, Inc. (BVL) manufacturing site conducted jointly from 6 to 11 November 2011. This cessation included manufacturing operations in the three operational parts of the facility, North Complex, South Complex and Phase IV.

Telavancin marketing authorization suspended !

EUROPEAN MEDICINES
SCIENCE MEDICINES

Assessment report fo

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Ben Venue Laboratories

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Established in 1938, Ben Venue Laboratories is the manufacturi
Boehringer Ingelheim Company. Ben Venue Laboratories' manu
the largest sterile injectable capacities in world, with aseptic filli
manufacturing capabilities. The site also supports the developm
products.

Ben Venue Laboratories announced its decision to exit the contract manufacturing business in August 2011. As such, the company is no longer accepting new contract manufacturing business.

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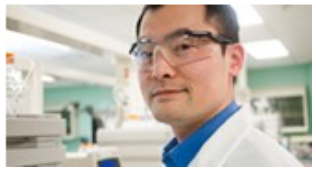
Jobs at Boehringer Ingelheir



Drugs more recently registered in EU …

- **Ceftaroline**
  - One of the several anti-MRSA cephalosporins with low MICs
  - Binds to PBP2a → conformational change imposed by its side chain
  - Registered in both the US and the EU
    - **EMA:** Zinforo® is indicated in adults for the treatment of
      - **complicated skin and soft tissue infections** (cSSTI)
      - **Community-acquired pneumonia** (CAP)
    - **FDA:** Teflaro® is indicated in adults for the treatment od
      - **Acute Bacterial Skin and Skin Structures Infections** (ABSSSI)
      - **Community-acquired bacterial pneumonia** (CABP)

Ceftaroline in Europe …

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to ceftaroline *in vitro*.

Complicated skin and soft tissue infections

Gram-positive micro-organisms

- *Staphylococcus aureus* (including methicillin-resistant strains)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)
- *Streptococcus dysgalactiae*

Gram-negative micro-organisms

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Morganella morganii*

Community-acquired pneumonia

No cases of CAP due to MRSA were enrolled into the studies. The available clinical data cannot substantiate efficacy against penicillin non-susceptible strains of *S. pneumoniae*.

Gram-positive micro-organisms

- *Streptococcus pneumoniae*
- *Staphylococcus aureus* (methicillin-susceptible strains only)

Gram-negative micro-organisms

- *Escherichia coli*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella pneumoniae*

Ceftaroline in Europe …

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

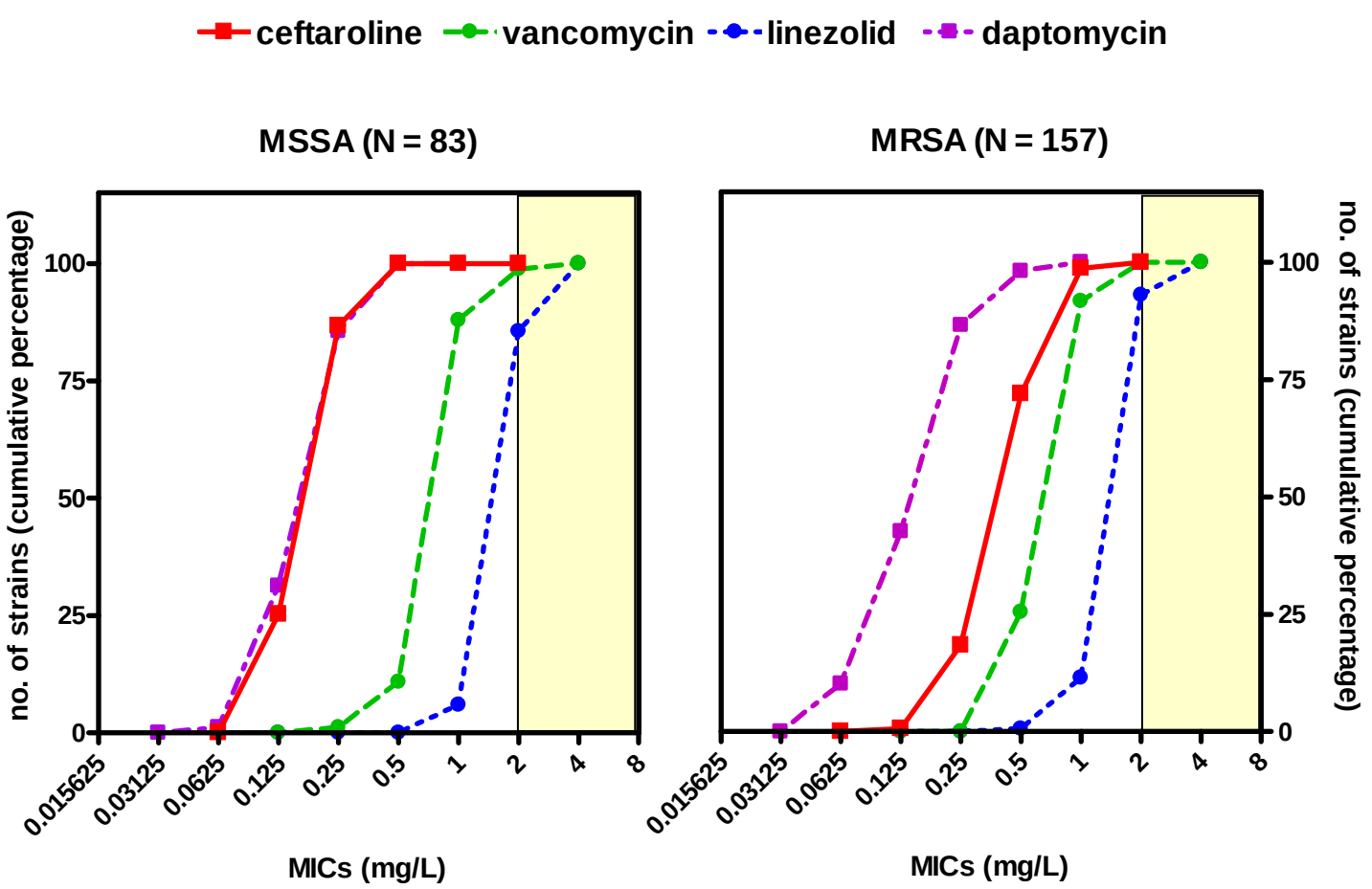
Breakpoints for ceftaroline from EUCAST and EMA

Addendum (September 2012) to EUCAST breakpoint tables v. 2.0
Breakpoints to be included in EUCAST breakpoint tables v 3.0, January 2013

Organisms	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Enterobacteriaceae	0.5	0.5		Note[3]	Note[3]
Staphylococcus aureus	1	1		Note[3]	Note[3]
Streptococcus Groups A, B, C, G	Note[1]	Note[1]		Note[3]	Note[3]
Streptococcus pneumoniae	0.25	0.25		Note[3]	Note[3]
Haemophilus influenzae	0.03	0.03		Note[3]	Note[3]
Pk/Pd (non-species related) breakpoints[2]	0.5	0.5		-	-

1. Infer susceptibility from susceptibility to benzylpenicillin.
2. Based on Pk/Pd target for Gram-negative organisms.
3. Disk diffusion breakpoints corresponding to the MIC breakpoints are currently being established. Breakpoints for *S.aureus* will be available by 1 October 2012.

Ceftaroline in Belgium …



MIC_{90} = 0.25

at 0.5 mg/L = 100 %

MIC_{90} = 1

at 1 mg/L = 98.7 %

Lemaire *et al.* in preparation

Ceftaroline:

vs

Table 2. *In vitro* activity of ceftaroline against select Gram-positive bacteria[13]

	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)
S. aureus (MS), *n*=1554	0.25	0.25	≤0.008–1.0
S. aureus (MR), *n*=1237	1.0	1.0	0.25–2.0
Viridans streptococci (PS), *n*=190	0.03	0.06	≤0.008–1.0
Viridans streptococci (PR), *n*=42	0.03	0.5	≤0.008–1.0

MS, methicillin susceptible; MR, methicillin resistant; PS, penicillin susceptible; PR, penicillin resistant.

MSSA MIC_{90} = 0.25

at 0.5 mg/L = 100 %

MRSA MIC_{90} = 1

at 1 mg/L = 98.7 %

13. Zhanel et al. Ceftaroline: a novel broad-spectrum cephalosporin with activity against meticillin-resistant *Staphylococcus aureus.* Drugs 2009; 69: 809–31.

Ceftaroline: target attainment rate

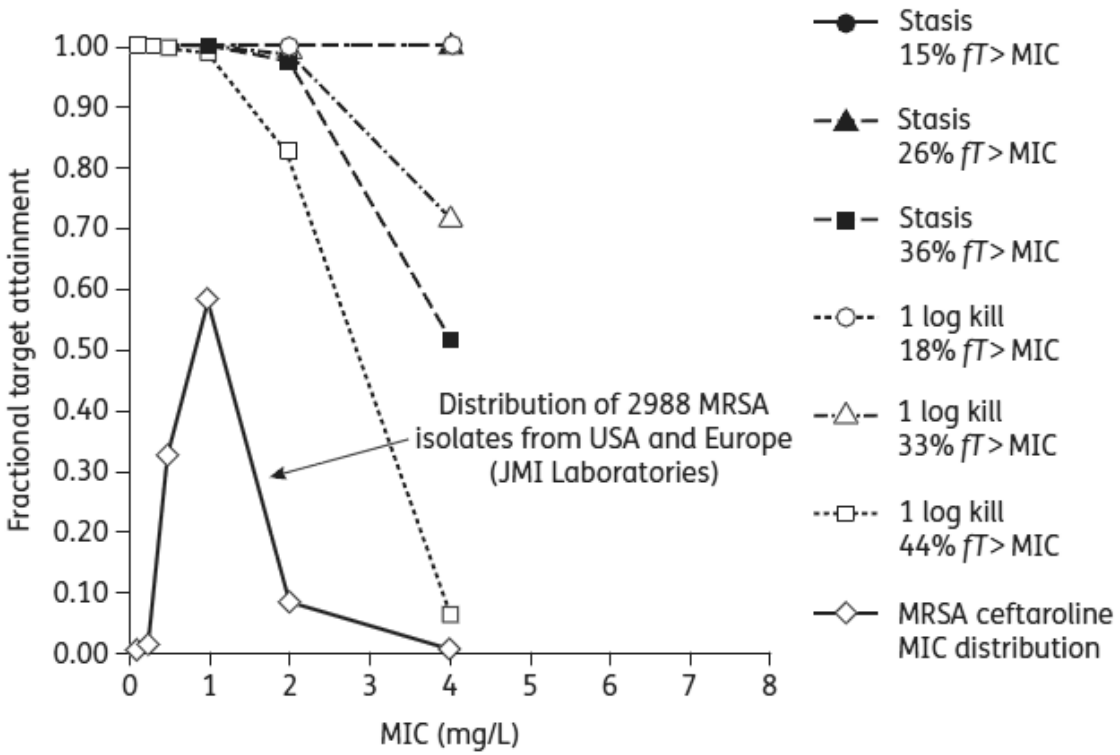


Figure 4. Target attainment for 600 mg of ceftaroline fosamil every 12 h against MRSA with different free drug $T>$MIC targets. The listed targets are the highest, lowest and mean free drug $T>$MIC targets for four *S. aureus* isolates evaluated in a mouse thigh infection model. $fT>$MIC, free drug time above the MIC.

Ceftaroline: target attainment rate

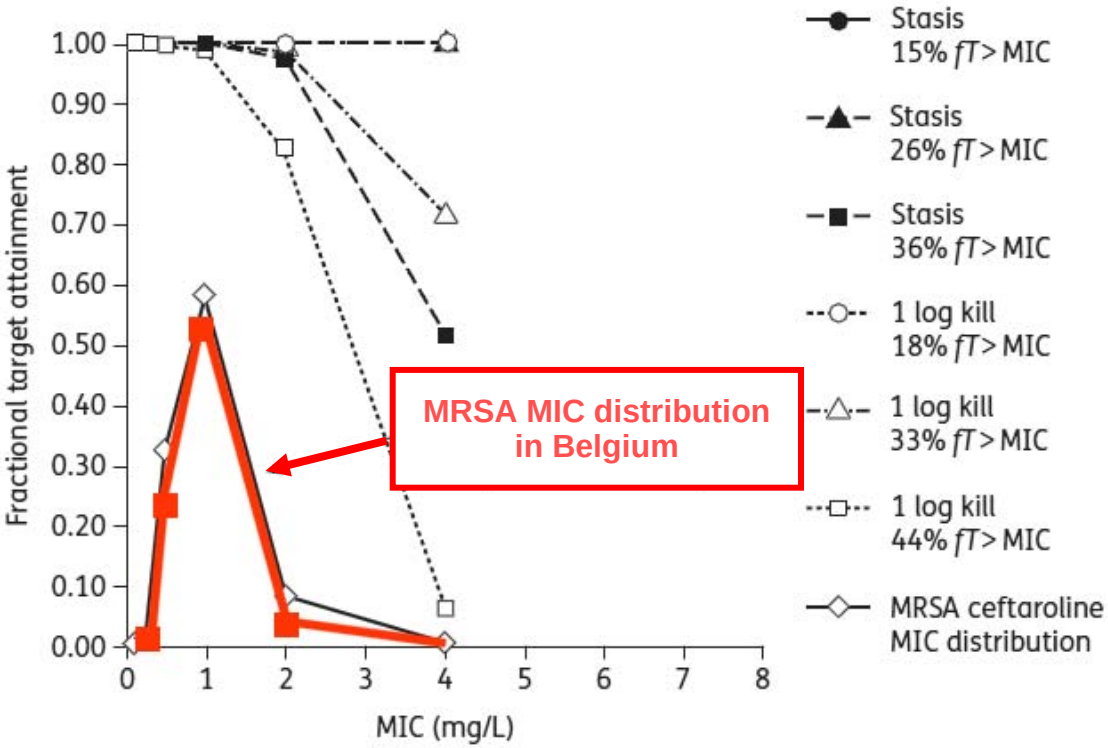


Figure 4. Target attainment for 600 mg of ceftaroline fosamil every 12 h against MRSA with different free drug $T>MIC$ targets. The listed targets are the highest, lowest and mean free drug $T>MIC$ targets for four *S. aureus* isolates evaluated in a mouse thigh infection model. $fT>MIC$, free drug time above the MIC.

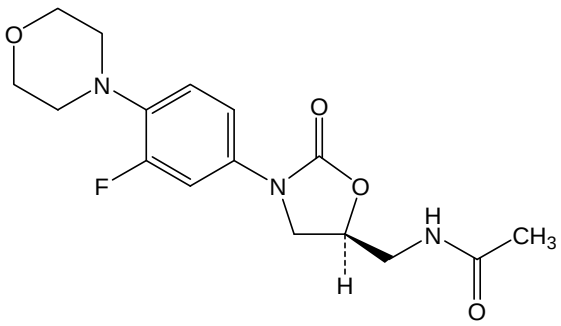
Which are the other "future" drugs ?

- **β-lactams**
  - **Ceftobiprole**
    - former Roche compound developed to phase II by Basilea
    - rejected by the FDA and the EMA for "data integrity problems" during phase III trials (coordinated by J&J)
    - returned by J&J to Basilea and prepared for resubmission after data cleaning
- **Glycopeptides**
  - **Oritavancin**
    - former Eli Lilly compound
    - similar to telavancin (highly bactericidal) + active against VRSA + longer half-life
    - rejected by the FDA and withdrawn from EMA due to "insusufficient phase III"
    - redevelopped as a "front-dose drug" by The Medicines Company (phase III)
  - **Dalbavancin**
    - former Lepetit/Verscor compound as a super teicoplanin
    - VERY long half-life (R_x once a week !) but not active against VRSA
    - Acquired by Pfizer but transferred to Durata (currently in phase III)

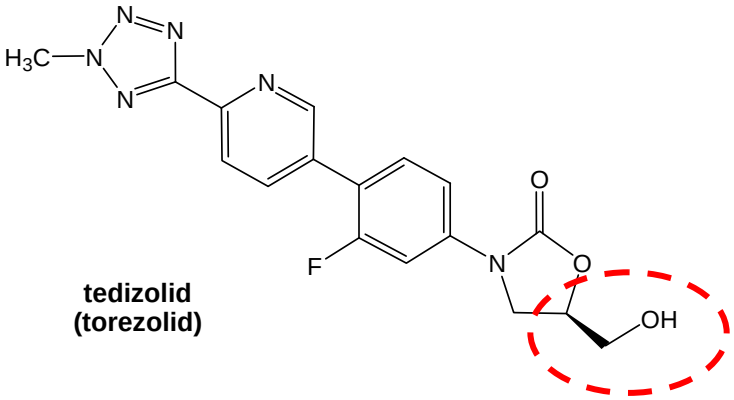
Which are the other "future" drugs ?

- **Oxazolidinones (beyond linezolid)**
  - **Radezolid**
    (RibX [potential discussions with Sanofi])
  - **Tedizolid**
    (Trius with agreement with Bayer for Asia and other "emerging markets)

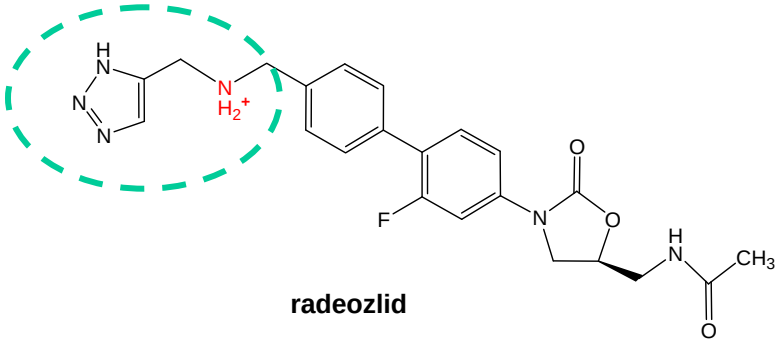
Phases II / III



linezolid



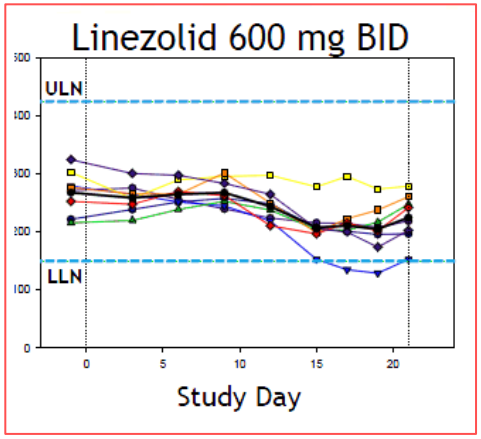
tedizolid (torezolid)

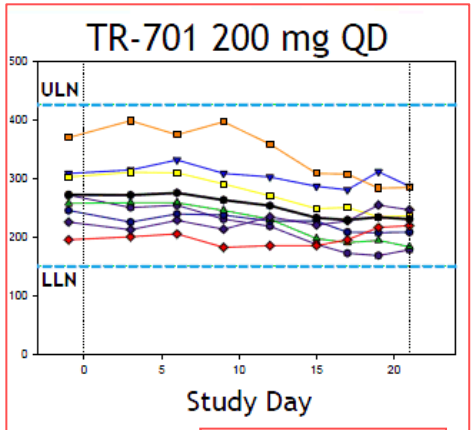


radeozlid

New oxazolidinones ?

- More active than linezolid (MICs 4-8-fold lower)
- Active against linezolid-resistant strains
  - *cfr* + (methylation) : retain activity
  - ribosomal mutation: loses activity but MICs remain low
- Decreased potential for MAO interferences (prodrug for tedizolid)
- Decreased potential for myelosuppression (lower doses)





Tedizolid phase I studies

Table 1. Susceptibility of the strains of *S. aureus*, *L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

Species, phenotype and strain no.		MIC (mg/L)[a] linezolid	torezolid
Staphylococcus aureus			
MSSA	ATCC 25923[b]	2	0.25
HA-MRSA	ATCC 33591[b]	1	0.125–0.25
	SA 238[c]	2	0.25–0.5
	CM 05[d]	8	0.25–0.5
	SA 238L (LZD^R after drug exposure)[c]	16	1
CA-MRSA	NRS 192[e]	2	0.125–0.25
	NRS 384 (US300)[e]	2	0.25
VISA	NRS 52[e]	2	0.125
VRSA	VRS 1[e]	1–2	0.125–0.25
	VRS 2[e]	1–2	0.25
animal MRSA	N7112046[f]	2	0.125
Listeria monocytogenes			
	EGD[g]	1–2	0.125
Legionella pneumophila			
	ATCC 33153[b]	4–8	0.25–0.5

LZD^R, resistant to linezolid.
[a]Representative values of at least two determinations.
[b]From the American Tissue Culture Collection (Manassas, VA, USA).
[c]Provided by P. C. Appelbaum.[36]
[d]Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
[e]From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN272200700055C); details on each strain are available at http://www.narsa.net/content/home.jsp.
[f]Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
[g]Provided by P. Berche, Hôpital Necker, Paris, France.[28]

Lemaire et al. JAC 2010; 64:1035–1043

New fluoroquinolones ?

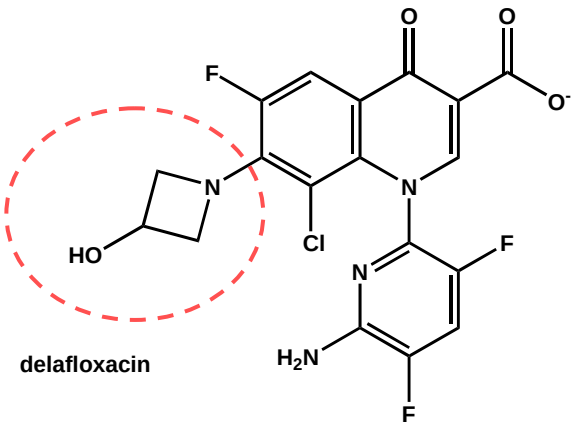
- Delafloxacin
- Nadifloxacin

} non zwitterionic

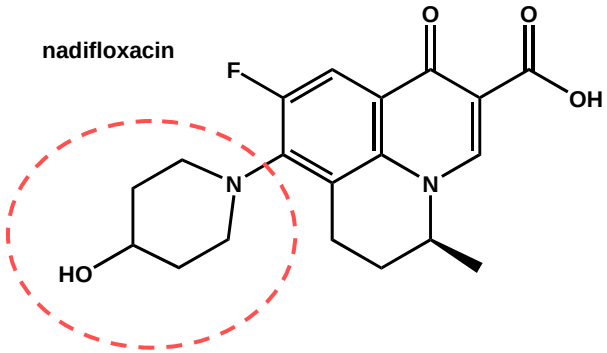
- Finafloxacin

8-cyano-"moxifloxacin"

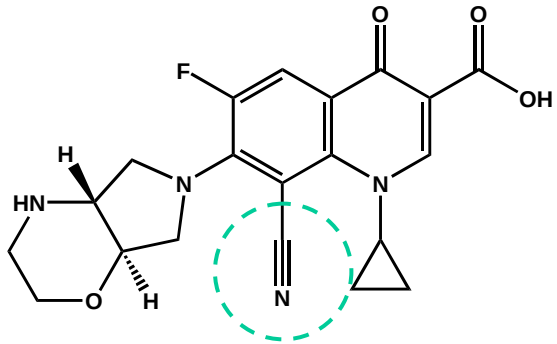
- …



delafloxacin



nadifloxacin

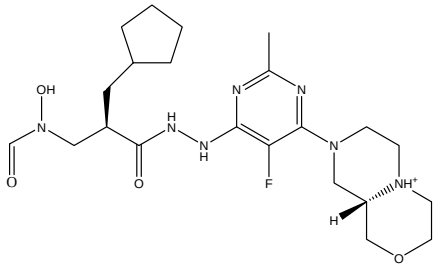


finafloxacin

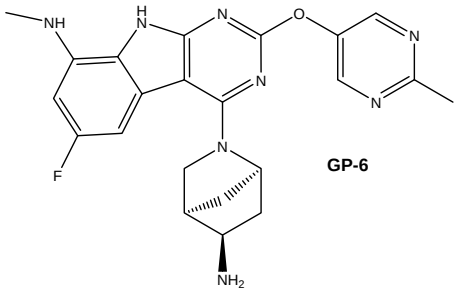
- Very low MICs especially at acid pH (down to 0.00006 mg/liter at pH 5.5 for delafloxacin
- Usually insensitive to NorA efflux transporters (*S. aureus* CIP^{R})
- Animal safety data similar to other fluoroquinolones but scarce human data

And several other compounds… (examples)

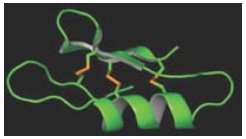
- Deformylase inhibitors
  - GSK1322322



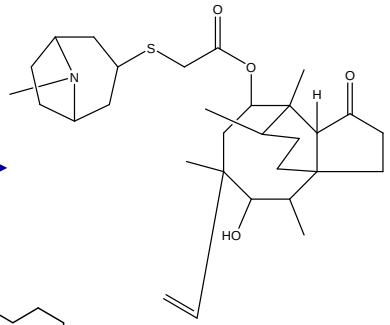
- Novel gyrase inhibitors
  - Trius GyrB/ParE inhibitors



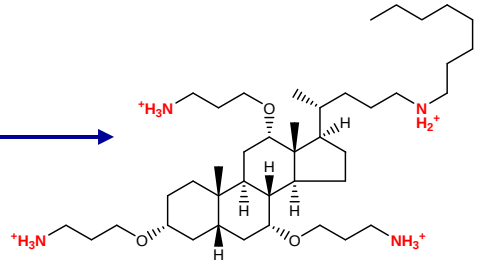
- Cationic peptidic antibiotics (and analogues)
  - Plectasin and analogues …



- Pleuromutilins
  - Retapamulin (developed as topical antibiotic)
  - Other compounds for systemic use



- Ceragenins
  - CSA-13 (developed as anti-biofilm)



Where does the money come from ?

- Discovery !
  - Large efforts are made by both public and private funding

Today, several new antibiotic programs are financed by the US Department of Defense…

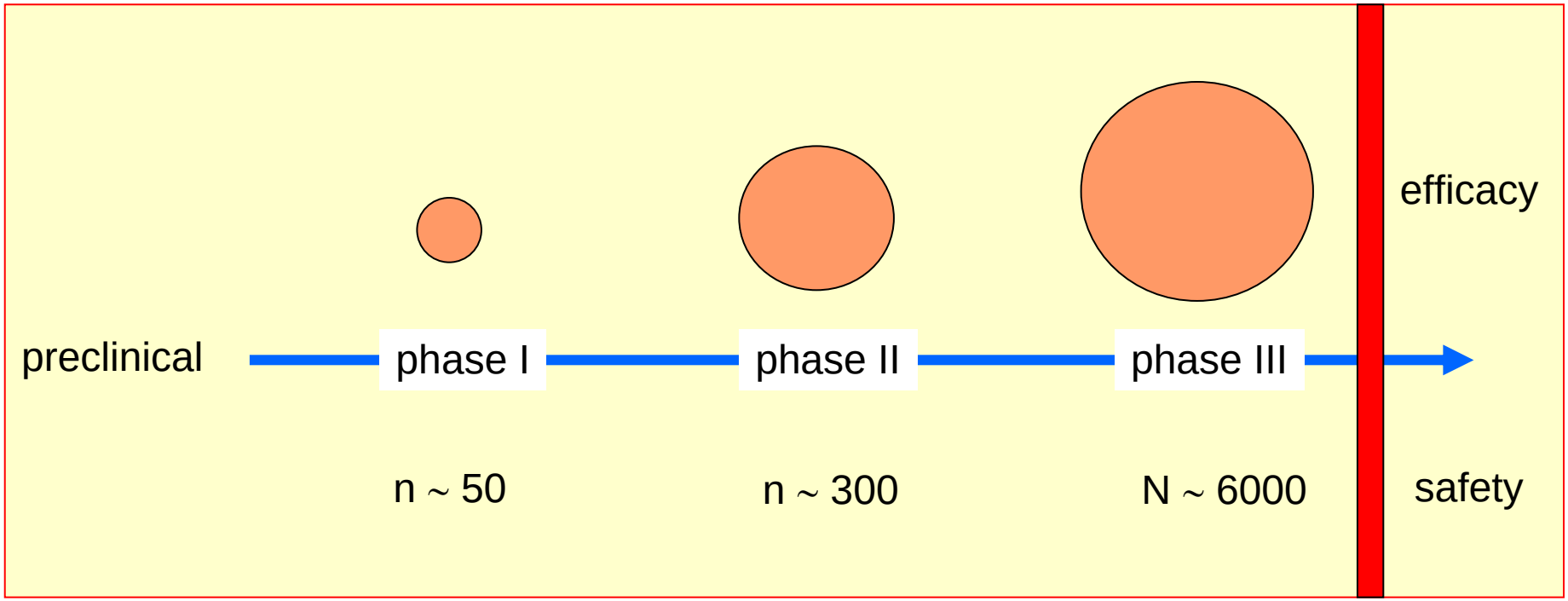
But NIH (and EU…) programs are catching up…

Solving the problem of "uninteresting phase III studies" ?

- Address a real problem … and look for the **correct target** (the bacteria)
  - Look for infections caused by multi-resistant RESISTANT organisms (or organisms you cannot fight with available antibiotics)
    (infections need NOT be necessarily severe…)
- Run the study in a **non-controlled fashion**
  - By definition, you cannot have a comparator if you aim at resistant organisms
- Target your study for non-inferiority against **historical controls**
  - Control = same type of infection caused by the same organisms but when it was still susceptible to the best-in-class antibiotic at that time
- By definition, **you will be superior** since the "control antibiotic" will not longer be acceptable.

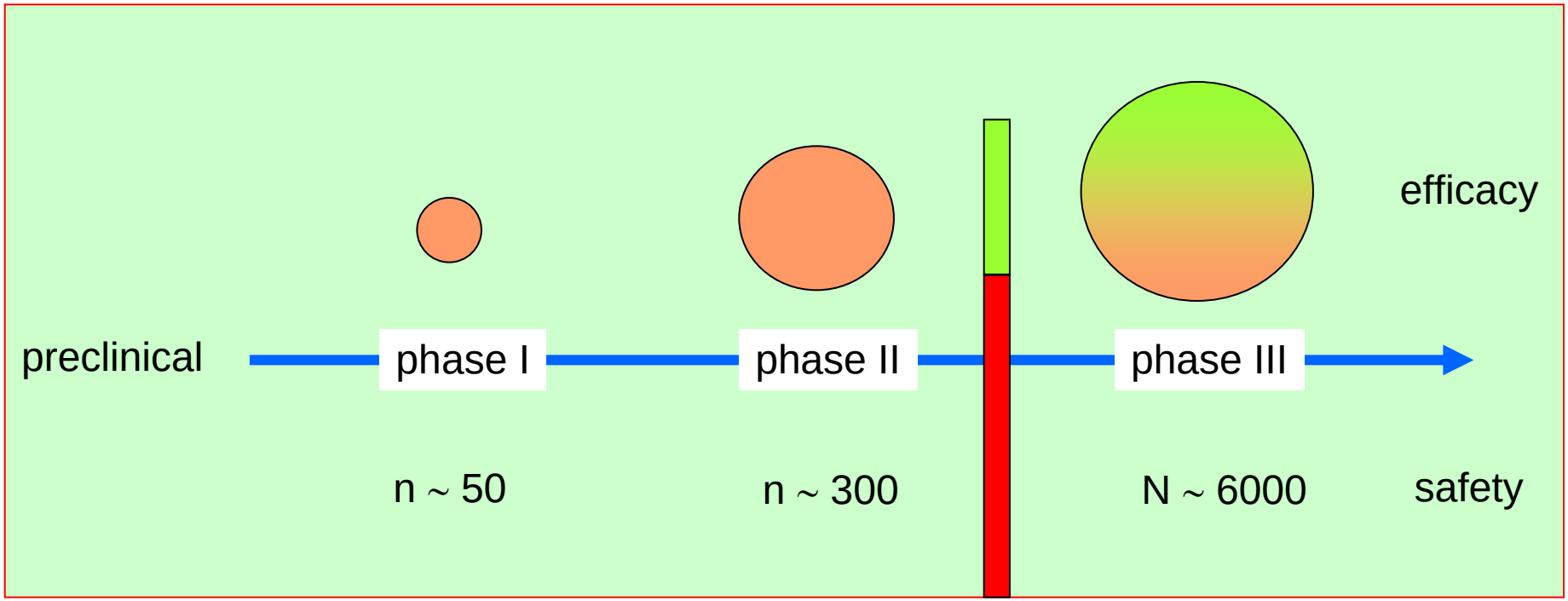
What about safety ?

- Registration : old scheme
  - Progression through phase I – II - III …
  - Until reaching the number of patients required for safety …



How to combine this with safety ?

- Registration: proposed new scheme
  - Provisional registration at phase II level (solving the unmet medical need)
  - Continue evaluation through commercialization until reaching a number of patients equivalent to a phase III to get full registration



But there us still another problem ?

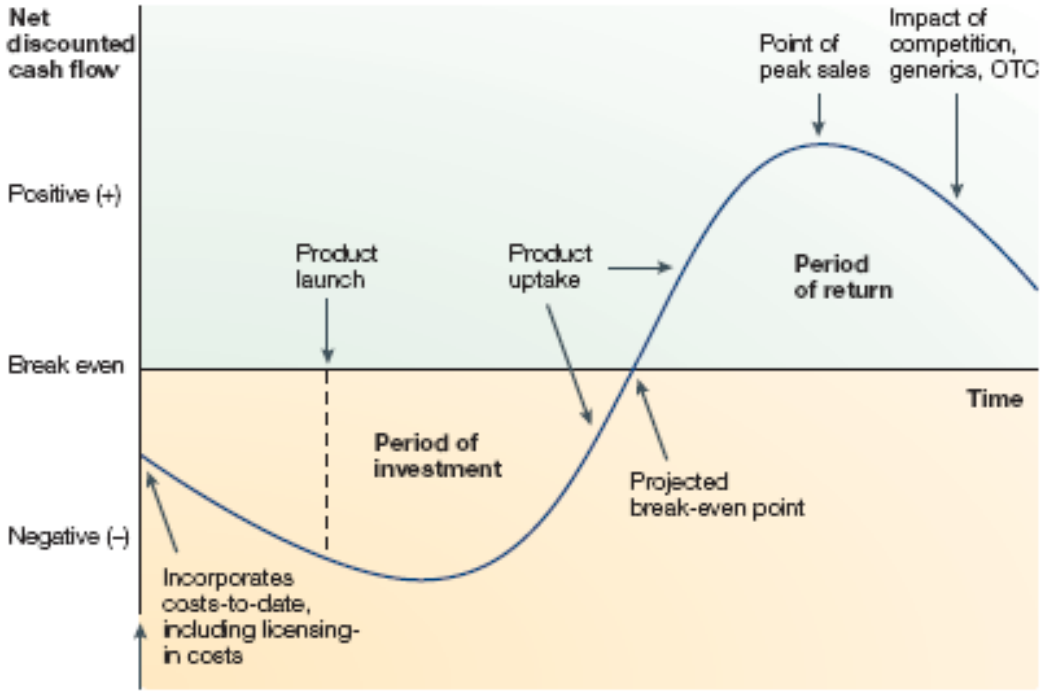
- Discovery **IS** difficult…
- Preclinical development **IS** challenging…
- Clinical development and registration are **not easy …**
- **But, will you recoup your investment ?**

This is a main part of the problem (in our current situation)

Why is economy important ?

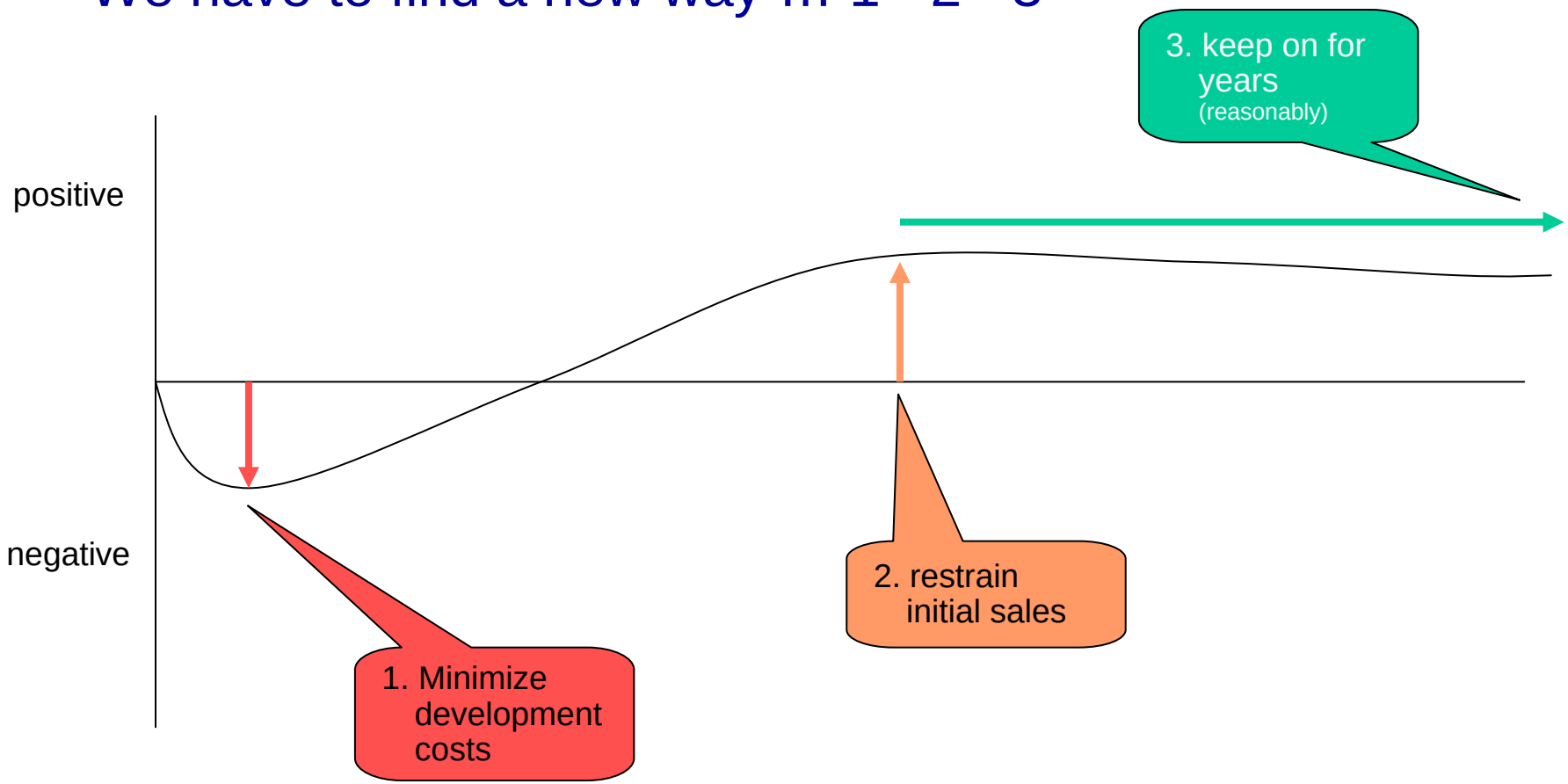
- Can you work without support ? …
  - You need investors
  - Those will ask some return at some point…
  - And none ignores what is a ROI

This is what every economist will tell you
(and you know it !)



Can you modify economy ?

- We have to find a new way … 1 - 2 - 3



Food for thought…

- The pipeline is not really dry …
- But the final delivery is disappointing…
- Real targets need to be clearly defined and pursued actively…
- The registration process needs to be modified for allowing true novel compounds to get through
  - to reach those patients who need them
  - but with clear view of the potential risks
- The business model of bringing drugs to the market (trying to flood it in a short time) may need to be revisited
- The current "minimizing drug acquisition costs" approach may also need to be reexamined.