New antibiotics: do we have them and how shall we pay for them ?

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Brussels, Belgium
http://www.facm.ucl.ac.be

Brussels, Belgium, 11 December 2015

This is an excerpt of public presentations …

- **The new antibiotics: useful improvement of our current armamentarium ... but can we pay for them?**
  Universitad de Antioquia (Faculty of Medicine), Medellin, Colombia, 1 December 2015 (this presentation is focused on the US Regsitration and breakpoints)
  PDF

- **The new antibiotics: useful improvement of our current armamentarium ... and can we pay for them?**
  Séminaire du service des soins intensifs, Cliniques universitaires St-Luc, Bruxelles, Belgium, 26 November 2015 (this presentation is focused on the European Registration and breakpoints)
  PDF

- **The European road map against antimicrobial resistance... (a changing paradigm for drug discovery and development ?)**
  2d International Conference on Polymyxins, La Jolla, CA, 22-24 September 2015
  PDF

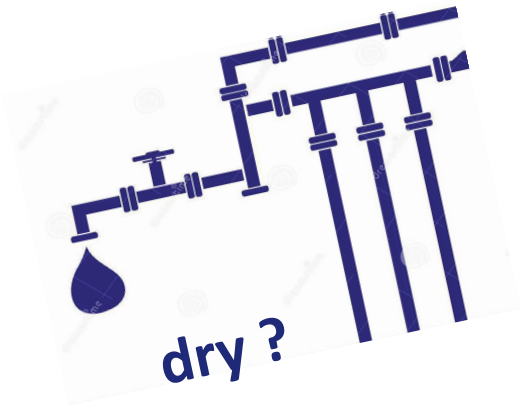
- **Antibiotic (accelerated) discovery and (more) rational use: a change in (accepted) paradigms based on economics ?**
  DRIVE-AB 2015 General Assembly Meeting, Uppsala, Sweden, October 15-16, 2015 (keynote introductory lecture)
  PDF

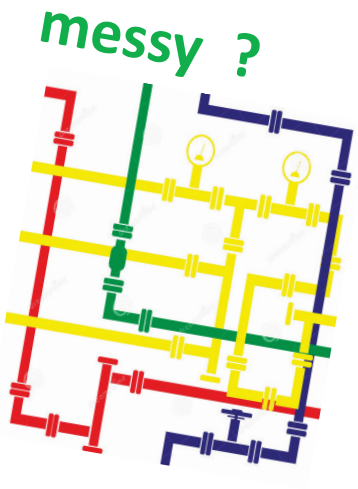
- **Antibiotic research and development in the age of 'superbugs'**
  Lunch meeting at the European Parliament, Brussels, 27 May 1015
  PDF

- **Drug pipeline for Gram-positive bacteria**
  25th European Congress of Clinical Microbiology and Infectious Diseases (Sympoisum: New antibacterail drugs), Copenhagen, Denmark, 25 April 2015
  PDF

Slides: http://www.facm.ucl.ac.be → Lectures

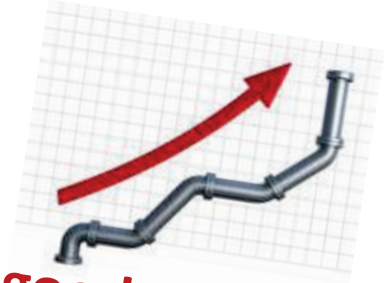
New antibiotics: what is your own view of the pipeline ?





of global concern?

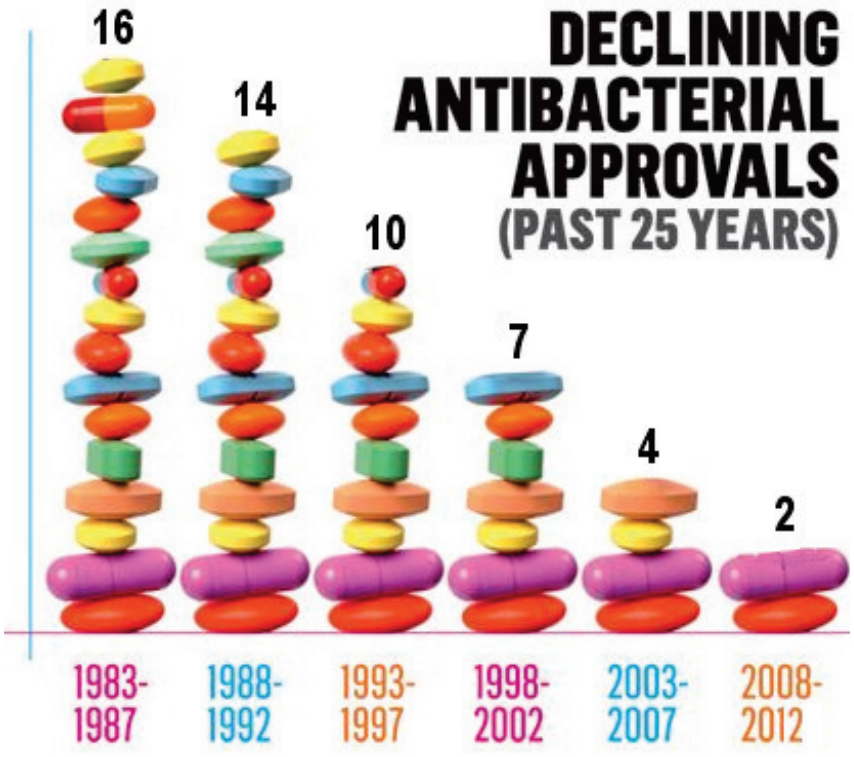
under repair?



in good shape ?

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



→ telavancin

→ ceftaroline

New antibiotics: where are we ?

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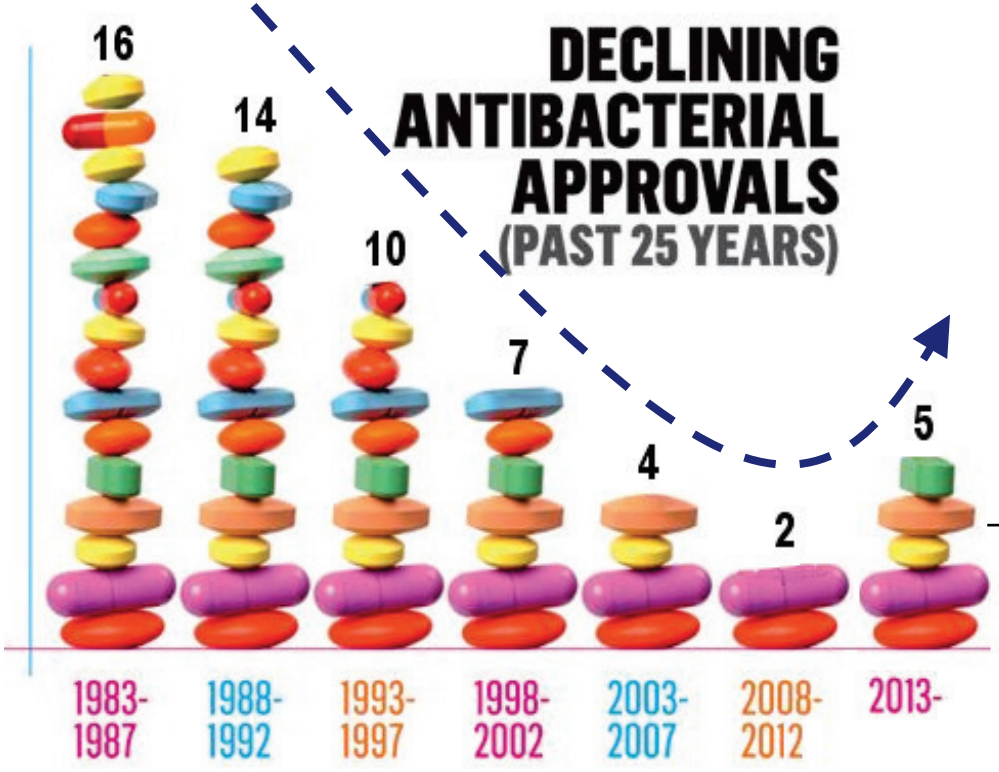

Shall we succeed ?

- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam *
- ceftolozane/tazobactam

FDA only so far

- telavancin
- ceftaroline

Our own pipeline (*)…

- in the good old time… (until 2000)

	papers	approval ?
– aminoglycosides		
• amikacin	28	worldwide
• netilimicin	13	worldwide
• ispepamicin	7	Japan
– macrolides		
• roxithromycin	5	worldwide
• azithromycin	25	worldwide
– fluoroquinolones		
• moxifloxacin	32	worldwide
• garenoxacin	5	failure

* new molecules approved by Regulatory Authorities that have been studied at the pre-clinical (translational) and/or clinical level in our laboratory

Our own pipeline (*)…

- and more recently … (2000-2015)

	papers	approval ?
– aminoglycosides		
• plazomycin	0	
– ketolides		
• solithromycin	4	
– lipoglycopeptides		
• telavancin	3	FDA / EMA
• oritavancin	14	FDA / EMA
– fluoroquinolones		
• finafloxacin	1	
• delafloxacin	3	
– oxazolidinones		
• tedizolid	3	FDA / EMA
• radezolid	2	
– β-lactams		
• ceftobiprole	2	UK → EU
• ceftaroline	1	FDA / EMA
• ceftazidime/avibactam	1	FDA
• doripenem	3	FDA / EMA

* new molecules submitted to or approved by Regulatory Authorities that have been studied at the pre-clinical (translational) and/or clinical level in our laboratory

As a result…

Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Current opinion | Published 31 July 2015, doi:10.4414/smw.2015.14167

Cite this as: Swiss Med Wkly. 2015;145:w14167

Development of new antibiotics: taking off finally?

Esther Bettiol[a], *Stephan Harbarth*[a,b]

[a] Infection Control Programme, Geneva University Hospitals and Faculty of Medicine, Switzerland

[b] Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Switzerland

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Development of new

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Table 2: Late-stage pipeline: systemic antibiotics recently approved, in registration or in phase III of clinical development.

Drug (brand name) - Company	Antibiotic class	Activity spectrum/resistant pathogens targeted	Phase and indication[1]	Regulatory status		
				US	European Union	Switzerland
Ceftazidime+ avibactam [44] (AvycazTM) – AstraZeneca/ Actavis	Cephalosporin + new BLI	Gram–, including MDR *P. aeruginosa*, ESBL-producing strains and KPC	Approved February 2015 for cIAI in combination with metronidazole, and for cUTI in patients who have limited or no alternative treatment options, in phase III for HAP/VAP and cIAI	Approved February 2015	Not submitted yet	Not submitted yet
Ceftolozane+ tazobactam [41] (ZerbaxaTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Cephalosporin + BLI	Gram–, including carbapenem, piperacillin+tazobactam and ceftazidime-resistant *Pseudomonas aeruginosa*, ESBL-producing strains	Approved for cUTI and cIAI, in phase III for VAP and phase I for paediatric use	Approved December 2014	Under review since August 2014	Under review since September 2014[2]
Ceftobiprole medocaril [45] (Zevtera®/Mabelio®) – Basilea Pharmaceutica/Quintiles	Cephalosporin	Gram+ and –, including MRSA, VRSA, penicillin- and ceftriaxone-resistant *Streptococcus pneumoniae*, *Enterobacteriaceae*, *P. aeruginosa*	Approved for CABP and HAP, excluding VAP	Not submitted (additional phase III data required	Approved October 2013	Approved December 2014
Oritavancin [42] (OrbactivTM) – The Medicines Company	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase I for paediatric use	Approved August 2014	Approved May 2015	Under review[2]
Tedizolid phosphate [43] (SivextroTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Oxazolidinone	Gram+, including MRSA and linezolid-resistant MRSA	Approved for ABSSSI, in phase III for HAP/VAP and for ABSSSI in adolescents	Approved June 2014	Approved March 2015	Under review since second quarter 2014[2]
Dalbavancin [42] (DalvanceTM/ XydalbaTM) – Actavis / Durata Therapeutics	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase III for CABP and phase I and III for paediatric use	Approved May 2014	Approved March 2015	Unknown
Meropenem+RPX7009 [54, 55] (CarbavanceTM) – The Medicines Company	Carbapenem + new class of BLI	Gram–, including CRE and particularly KPC	Phase III for cUTI and infections caused by CRE[3]	NA	NA	NA
Eravacycline [56] – Tetraphase Pharmaceuticals	Tetracycline	Gram+ and –, including CRE, ESBL-producing strains, MDR *Acinetobacter baumanii*, VRE, MRSA	Phase III for cUTI and cIAI[4]	NA	NA	NA
Plazomicin [57] – Achaogen	Aminoglycoside	Gram–, including CRE	Phase III for bloodstream infection and nosocomial pneumonia caused by CRE[5]	NA	NA	NA
Delafloxacin [51] – Melinta Therapeutics	Fluoroquinolone	Gram+ and –, including MRSA	Phase III for ABSSSI	NA	NA	NA
Solithromycin [52] – Cempra Pharmaceuticals	Macrolide	Gram+, including macrolide-resistant strains	Phase III for CABP and uncomplicated gonorrhoea, in phase I for paediatric use	NA	NA	NA

[1] Information retrieved from clinicaltrials.gov as of March 2015.
[2] Personal communication.
[3] Completion of trial expected in 2016; clinicaltrial.gov identifiers: NCT02168946 and NCT02166476.
[4] Completion of trial expected in 2015; clinicaltrial.gov identifiers: NCT01978938 and NCT0184485.
[5] Completion of trial expected in 2017; clinicaltrial.gov identifiers: NCT01970371.
ABSSSI = acute bacterial skin and skin structure infections; BLI =: β-lactamase inhibitor; CABP = community-acquired bacterial pneumonia; cIAI = complicated intra-abdominal infections; CRE = carbapenem-resistant *Enterobacteriaceae*; cUTI = complicated urinary tract infections; ESBL = extended spectrum β-lactamase; Gram+ = Gram-positive; Gram– = Gram-negative; HAP = hospital-acquired pneumonia; KPC = *Klebsiella pneumoniae* carbapenemase; MRSA = meticillin-resistant *Staphylococcus aureus*; VAP = ventilator-acquired pneumonia; VRSA = vancomycin-resistant *Staphylococcus aureus*

As a result…

Established in 1871

Swiss Medica

Formerly: Schweizerische Medizinische Wochensch

1. ceftazidime-avibactam
2. ceftozolane-tazobactam
3. ceftobiprole
4. oritavancin
5. tedizolid
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7. meropenem-RPX7009
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9. plazomycin
10. delafoxacin
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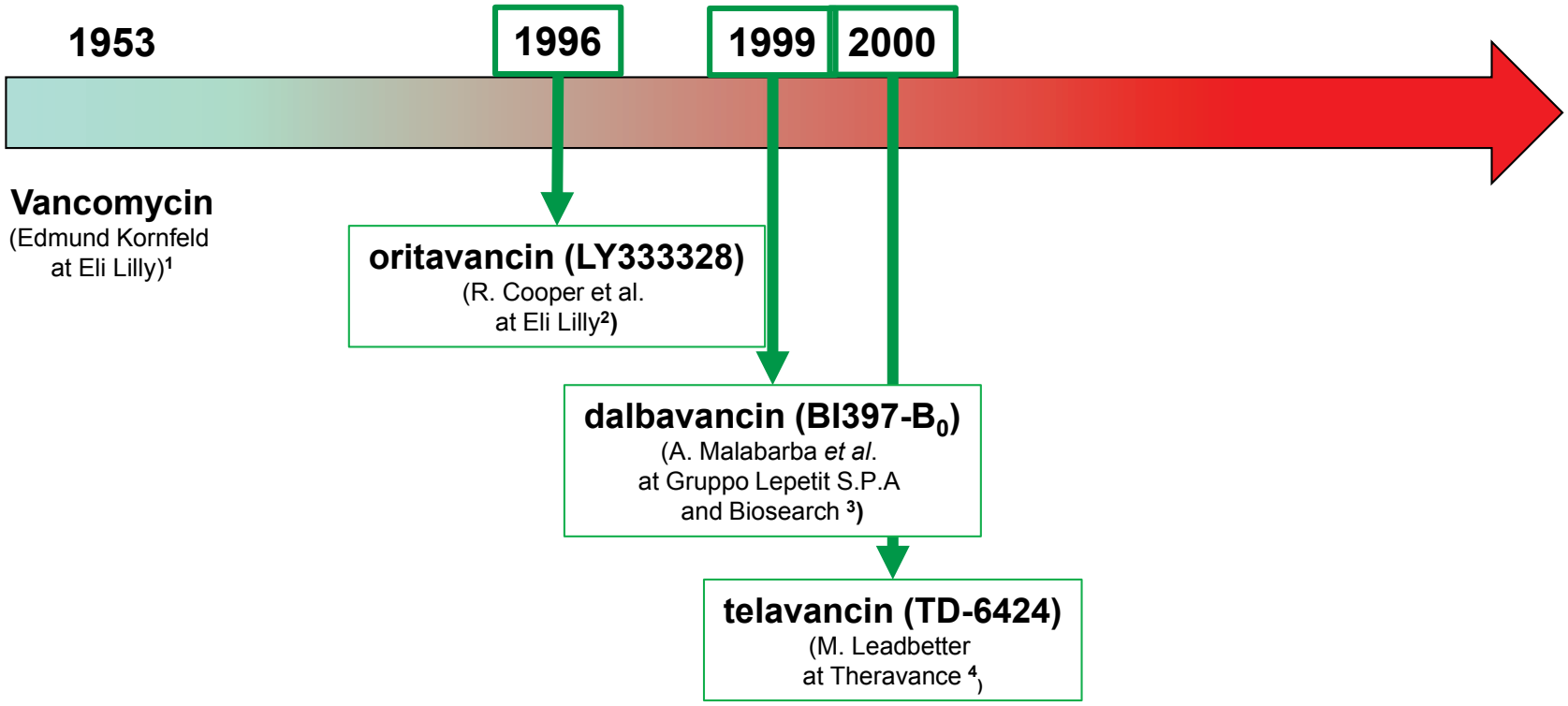
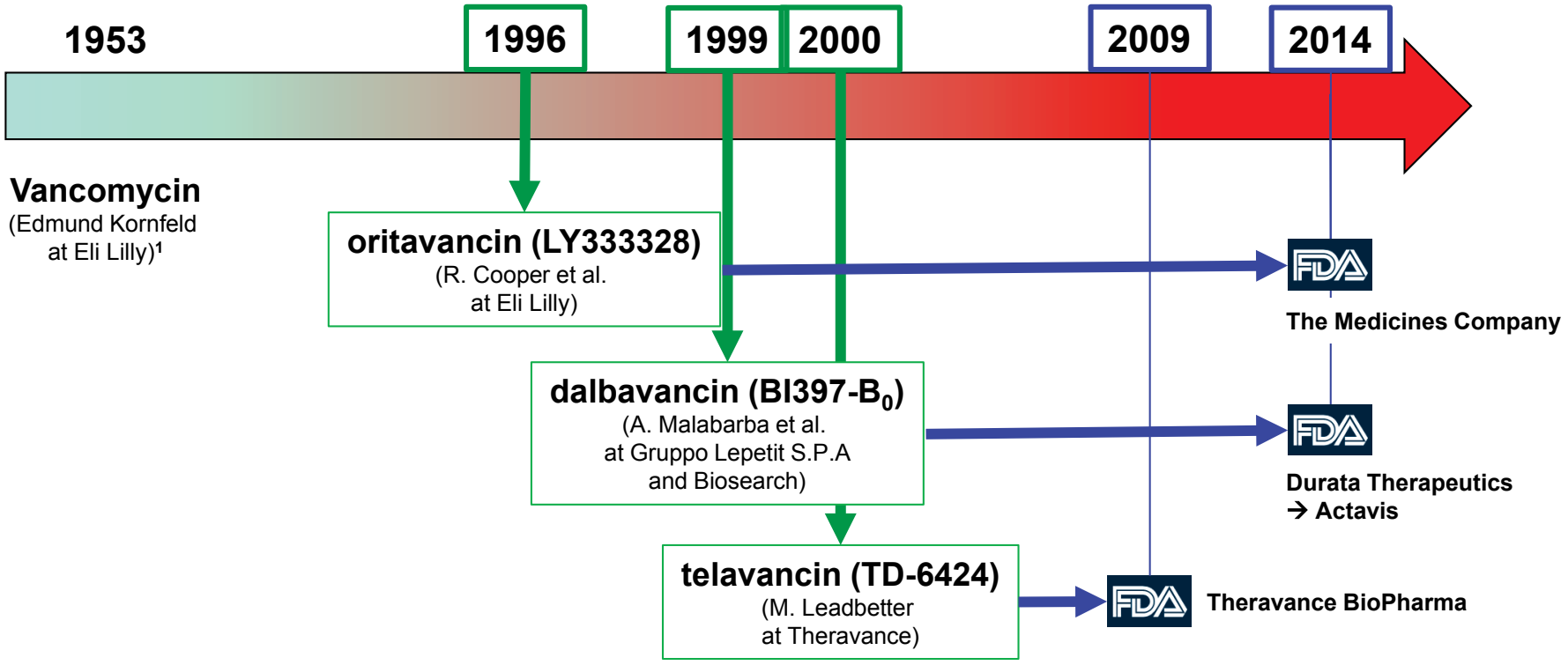
Lipoglycopeptides history: the discovery



1 McCormick *et al.* Vancomycin, a new antibiotic. I. Chemical and biologic properties. Antibiot Annu. 1955-1956;3:606-11
2 Cooper *et al.* Journal of Antibiotics (1996), 49(6), 575-581.
3 Malabarba *et al.* Drugs of the Future (1999), 24(8), 839-846
4 Leadbetter et al. PCT Int. Appl. (2001), WO 2001098328 A2 20011227.
See also: Van Bambeke Drugs, in press
(unedited typescript available at http://www.facm.ucl.ac.be/Full-texts-FACM/in-press/vanbambeke-Lipoglycopeptides-drugs-accepted.pdf)

Lipoglycopeptides: towards registration



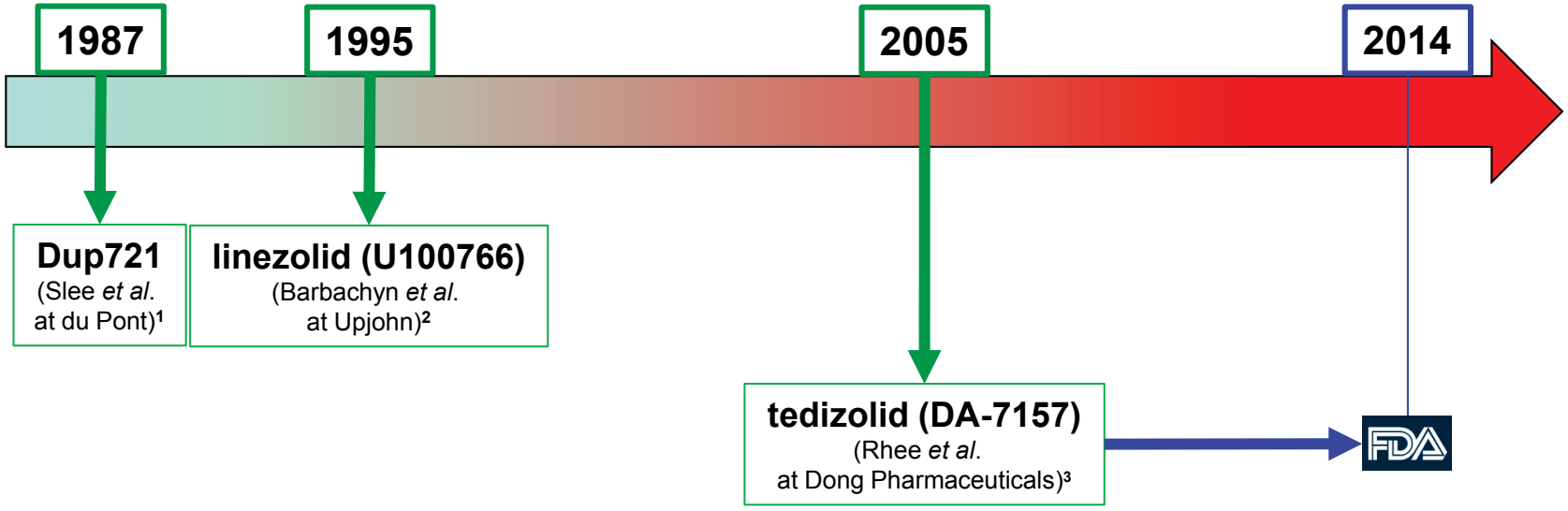
[1] Wenzler E, Rodvold KA. Telavancin: The Long and Winding Road From Discovery to Food and Drug Administration Approvals and Future Directions. Clin Infect Dis 2015;61 Suppl 2:S38-S47.

[2] Butler MS, Hansford KA, Blaskovich MAT et al. Glycopeptide antibiotics: back to the future. J Antibiot (Tokyo) 2014;67(9):631-44.

[3] Van Bambeke *et al.* Glycopeptides (Dalbavancin, Oritavancin, Teicoplanin, Telavancin, Vancomycin) - Update 2009. Antimicrobial Therapy and Vaccines. Vol. II: Antimicrobial Agents (2009) 42pp; available at http://www.antimicrobe.org

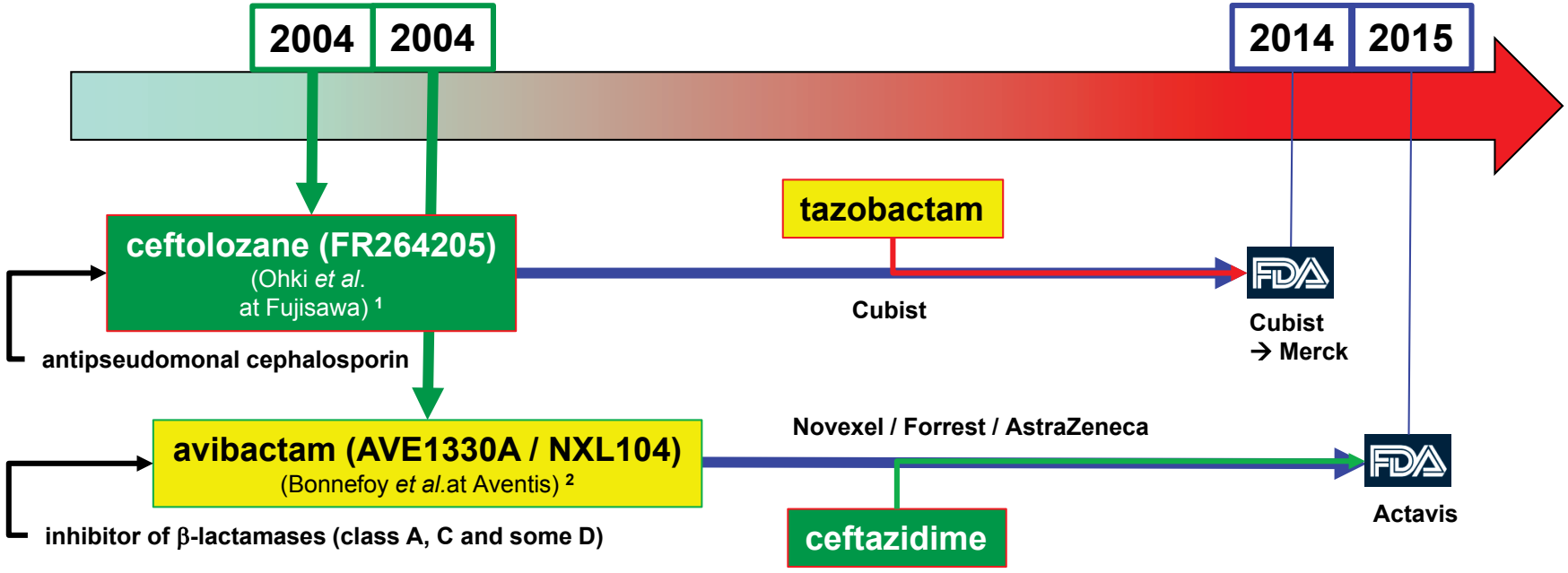
[4] Van Bambeke Lipoglycopeptide antibacterial agents in Gram-positive infections: A comparative review. Drugs, *in press* (unedited typescript available at http://www.facm.ucl.ac.be/Full-texts-FACM/in-press/vanbambeke-Lipoglycopeptides-drugs-accepted.pdf)

Oxazolidinones: a successor for linezolid ?



1 Slee et *al.* Antimicrob Agents Chemother. 1987;31:1791-97
2 Barbachyn et al. PCT Int. Appl., WO 9507271 A1 Mar 16, 1995
3 Rhee *et al*. PCT Int. Appl. (2005), WO 2005058886 A1 Jun 30, 2005
See also: Ford et al. Curr Drug Targets Infect Disord. 2001;1:181-99
Zhanel *et al.* Drugs. 2015;75:253-70.

Ceftolozane (+tazobactam) **– Avibactam** (+ ceftazidime)**: the new Graal ?**



[1] Ohki *et al*. PCT Int. Appl. (2004), WO 2004039814 A1 2 Liang et al. PCT Int. Appl. (2004), WO 2004080391 A2 20040923
[2] Bonnefoy *et al.* J. Antimicrob. Chemother. (2004) 54 (2): 410-417

Why do see that in the US ?

1. Definition of the "**Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need**" by the FDA *

   → list of 21 microorganisms from <u>both hospital and community</u>

* US eCFR Title 21, Chapter I, Subchapter D, §317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health. 2014 [12.01.2015].
Available from: http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=8508abd4d5a913bee24de949bb1920d2&ty=HTML&h=L&r=PART&n=pt21.5.317

Why do see that in the US ?

Table 1: Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need.

QIDP qualifying pathogen names [20]		**Type of infection**		
Bacteria	**Gram**	**Opportunistic**	**Hospital acquired**	**Community acquired**
Acinetobacter species[1]	Gram–	X	X	
Burkholderia cepacia complex	Gram–	X	X	
Campylobacter species	Gram-		X	X
Clostridium difficile[1]	Gram+		X	X
Enterobacteriaceae[1] (especially *Citrobacter, Enterobacter cloacae, Klebsiella pneumoniae, Escherichia coli, Proteus vulgaris, Salmonella, Serratia marcescens, Shigella*)	Gram–	X	X	X
Enterococcus species	Gram+		X	X
Helicobacter pylori	Gram–			X
Mycobacterium tuberculosis complex[1]	NA	X		X
Neisseria gonorrhoeae[1]	Gram–			X
Neisseria meningitidis	Gram–			X
Nontuberculous mycobacteria species	NA	X		X
Pseudomonas species[1]	Gram–	X	X	
Staphylococcus aureus[1, 2]	Gram+	X	X	X
Streptococcus agalactiae (group B)	Gram+			X
Streptococcus pneumoniae	Gram+	X		X
Streptococcus pyogenes (group A)	Gram+			X
Vibrio cholerae	Gram–			X
Fungi				
Aspergillus species	NA	X		
Candida species	NA	X		X
Coccidioides species	NA			X
Cryptococcus species	NA	X		

[1] Key unmet need due to high and increasing prevalence of XDR or PDR strains [21]
[2] Unmet need primarily for blood, bone and prosthesis infections and not for skin infection.
NA = Not applicable.

* US eCFR Title 21, Chapter I, Subchapter D, §317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health. 2014 [12.01.2015].
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2. The GAIN act … ("*Generating Antibiotic Incentive Now*") at the US House of Representatives *

   – **additional five years of exclusivity** for those new antibiotics designated under the law as a "qualified infectious disease product," … in addition to any existing exclusivity, including that which may be applicable under Hatch-Waxman (five years or three years), orphan drug (seven years), or pediatric exclusivity (six months).

   – **Fast track and priority review status** and **expedited regulatory approval process** with FDA.

   – **FDA-issued new guidance** on the development of pathogen-focused antibiotics

*Available from: http://www.gpo.gov/fdsys/pkg/BILLS-112hr2182ih/pdf/BILLS-112hr2182ih.pdf
See also: http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics

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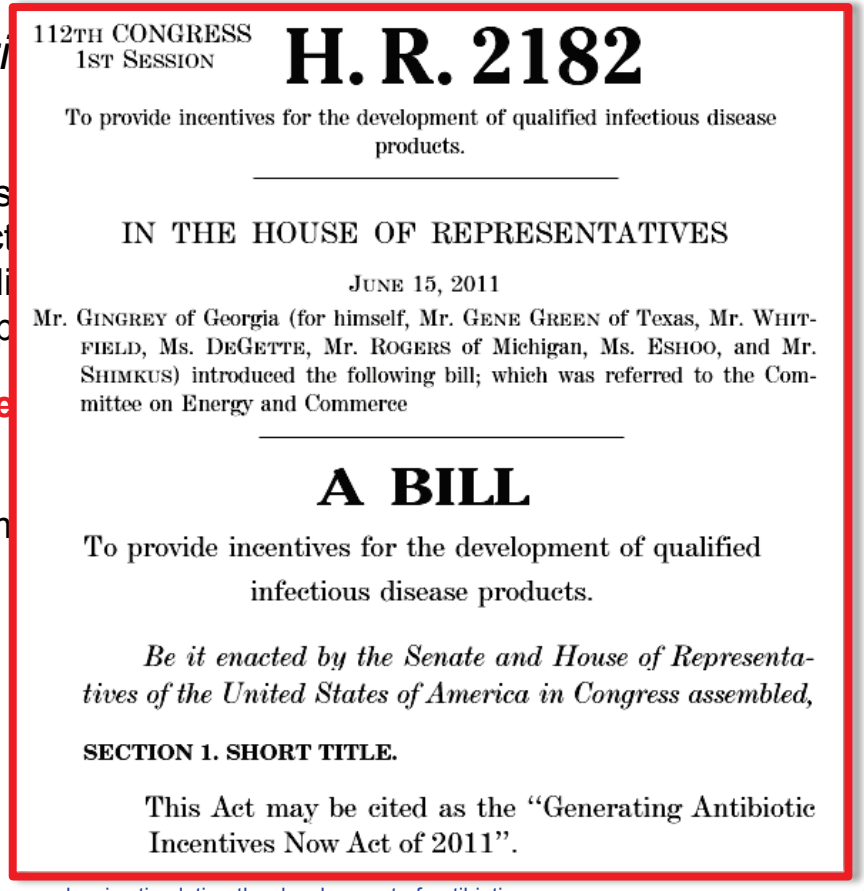

112TH CONGRESS
1ST SESSION

H. R. 2182

To provide incentives for the development of qualified infectious disease products.

IN THE HOUSE OF REPRESENTATIVES

JUNE 15, 2011

Mr. GINGREY of Georgia (for himself, Mr. GENE GREEN of Texas, Mr. WHITFIELD, Ms. DEGETTE, Mr. ROGERS of Michigan, Ms. ESHOO, and Mr. SHIMKUS) introduced the following bill; which was referred to the Committee on Energy and Commerce

A BILL

To provide incentives for the development of qualified infectious disease products.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Generating Antibiotic Incentives Now Act of 2011".

*Available from: http://www.gpo.gov/fdsys/pkg/BILLS-112hr2182ih/pdf/BILLS-112hr2182ih.pdf
See also: http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics

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   - **FDA-issued new guidance** on the development of pathogen-focused antibiotics

3. The **Biomedical Advanced Research and Development Authority** (BARDA) activities *

   - integrated, systematic approach to the **development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies**

* http://www.phe.gov/about/barda/Pages/default.aspx

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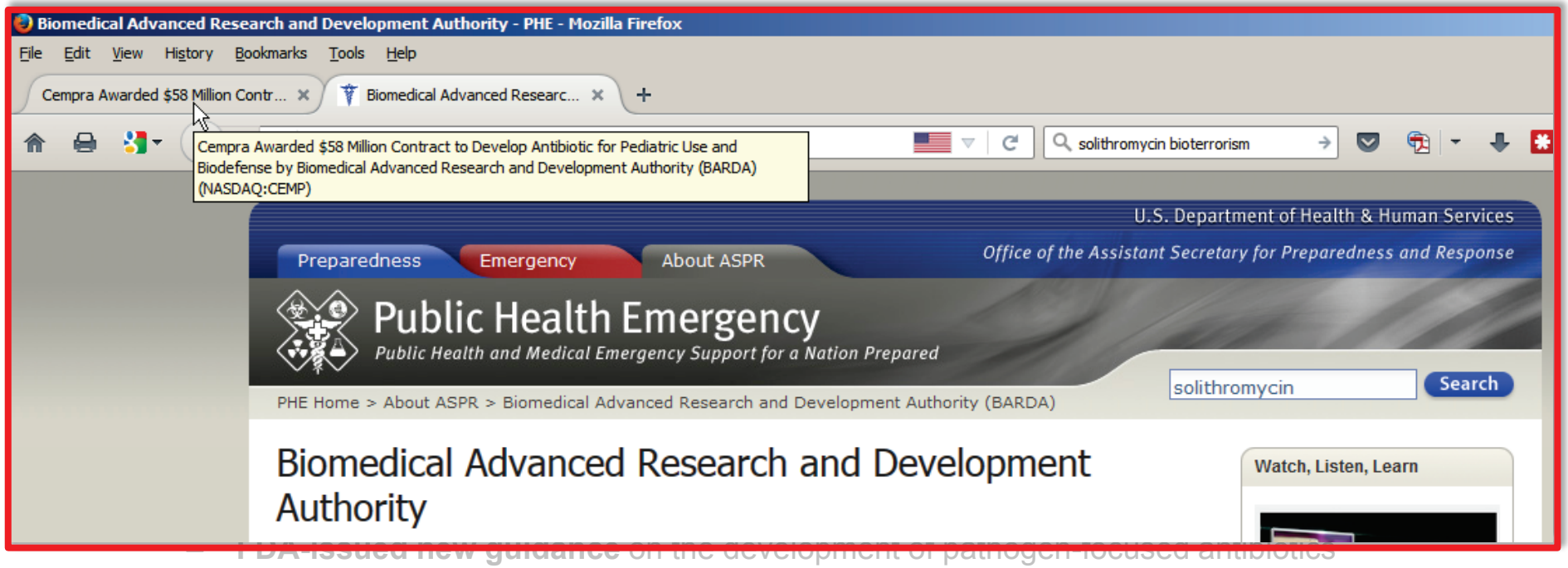

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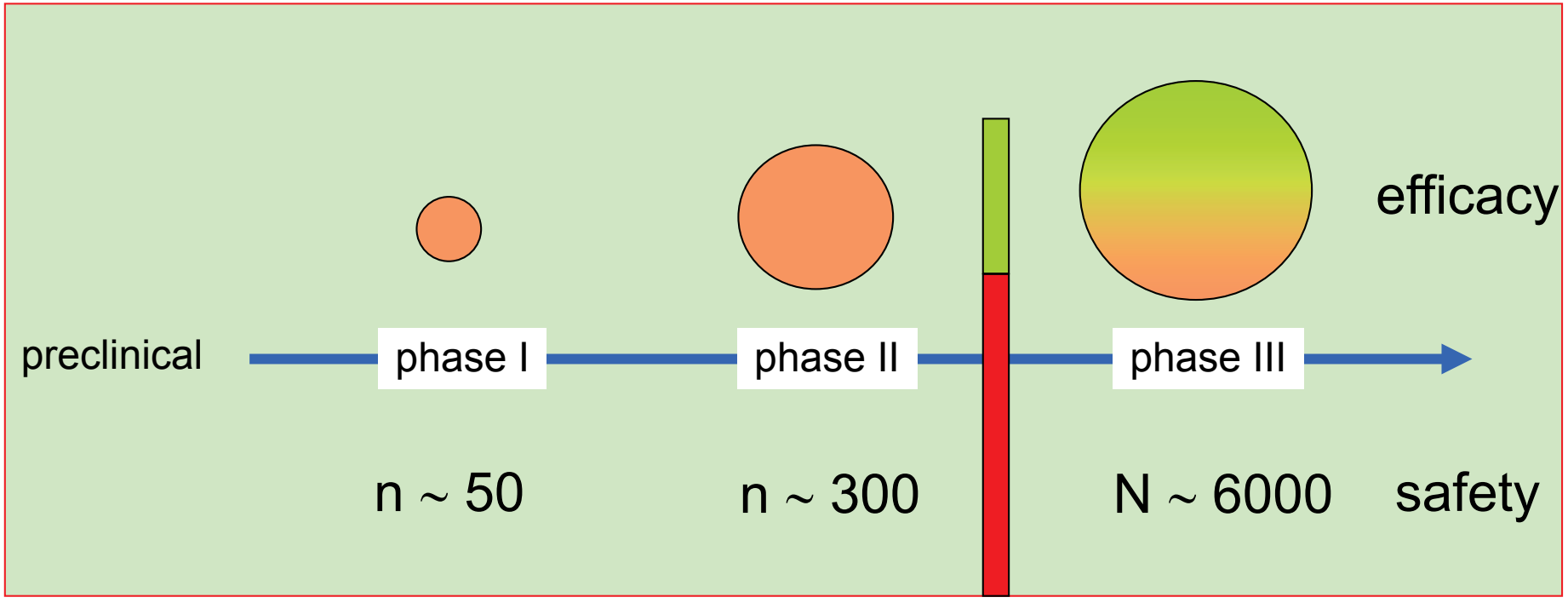
A view from Europe

- €2 billions euro budget…
- collaborative research projects and networks of industrial and academic experts…
- collaborative ecosystem for pharmaceutical research and development (R&D)…
- increase Europe's competitiveness globally…
- establish Europe as **the most attractive place for pharmaceutical R&D**

http://www.imi.europa.eu/
Last accessed: 26 May 2015

Early registering at FDA and EMA for efficacy …

- 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



More about EMA ?

Circumstances in which only limited clinical data can be generated

- organisms with specific types and/or patterns of multi-resistance currently uncommon or rare
- few patients that can be enrolled in commonly sought indications.

Addendum to the note for guidance on evaluation of medicinal products indicated for the treatment of bacterial infections (CPMP/EWP/558/95 Rev 2) to address indication-specific clinical data – http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129443

More about EMA ?

Circumstances in which only limited clinical data can be generated

- organisms with specific types and/or patterns of multi-resistance currently uncommon or rare
- few patients that can be enrolled in commonly sought indications.

Acceptable approaches

- strong prediction of efficacy in the intended use(s) from PK/PD analyses
- limit to one randomized and active controlled study in a specific type of infection where resistant organisms are frequent
- evidence of efficacy through non-controlled studies in situations where resistance is very problematic *(retrospective comparison)*
- use of flexible (adaptive) study design

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What EMA has in store for drug developers…

- **A test agent** expected or shown to be **clinically active against multi-resistant Gram-negative pathogens** could be indicated for studied infections **without qualification by pathogen**.
- Details of the actual organisms treated would be reflected in the "Pharmacodynamic" section of the SmPC along with mention of the evidence supporting activity (specific multi-resistant organisms).
- **A pathogen-specific indication is a possibility**.
- The label could include **a restriction to use when other commonly used agents are not suitable for the individual patient.**

Addendum to the note for guidance on evaluation of medicinal products indicated for the treatment of bacterial infections (CPMP/EWP/558/95 Rev 2) to address indication-specific clinical data – http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129443

Antibiotic pipeline: can we do better ?

- Equivalence to current options in comparative clinical trials

  ⇨ This will raise issues for reimbursement,
  especially against the generics of the comparators
  used in these studies

  ⇨ Need to design superiority trials and
  to focus pricing and reimbursement
  for documented cases of infection by resistant organisms

Non-inferiority vs superiority trials ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NON-INFERIORITY if NO evidence of spontaneous resolution rate (more effective than placebo)

Indications (and delta):

- Community-acquired pneumonia (-10%; more in PORT scores of IV-V)
- Hospital-acquired pneumonia and ventilator-associated pneumonia (less than ≤ -12.5%)
- Skin and soft tissue infections (-10%)
- Intra-abdominal infections (-12.5%)
- Urinary tract infections (-10 %)

→ DRUG/comparator trial

SUPERIORITY if spontaneous resolution (placebo effective)

- Acute bacterial maxillary sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Acute otitis media
- Superficial skin infections (such as impetigo and minor wounds)
- Inhaled antibacterial agents (excl. CF)

→ Placebo/ DRUG/comparator trial

LIMITED TRIALS

- Rare MDR organisms
- Few patients

→ DRUG non comparative trial

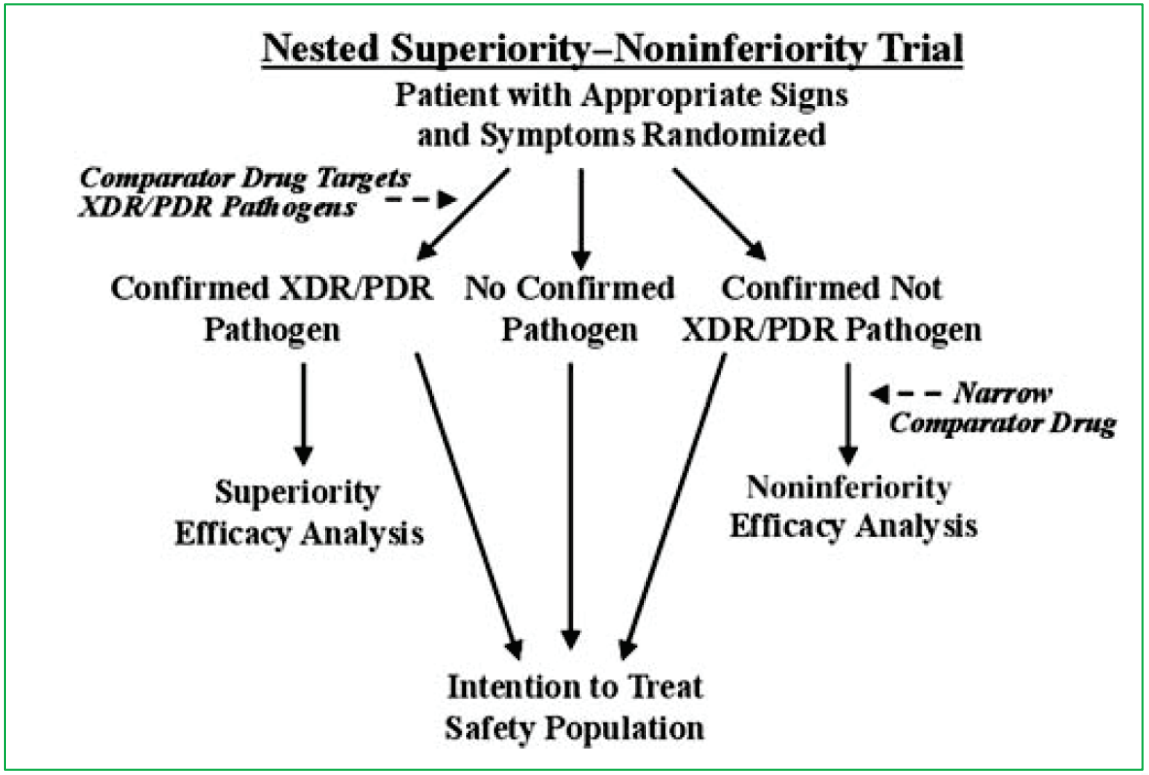
Non-inferiority vs superiority trials ?

White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens

Clinical Infectious Diseases 2012;55(8):1031–46

Infectious Diseases Society of America (IDSA)[a]

IDSA PUBLIC POLICY



No new antibiotics: is it true ?

- In 2013, an article in **Genetic Engineering & Biotechnology News** identified **66 companies involved in antibiotic research**, 86% of which are either small or medium-sized.
- A paper published in 2013 in **Journal of Antibiotics** (Tokyo)[2] lists **22 new antibiotics launched since 2000** and discusses the development status, mode of action, spectra of activity, historical discovery and origin of the drug pharmacophore (natural product, natural product derived, synthetic or protein/mammalian peptide) of **49 compounds** and **6 β-lactamase/β-lactam combinations** in active clinical development are discussed.

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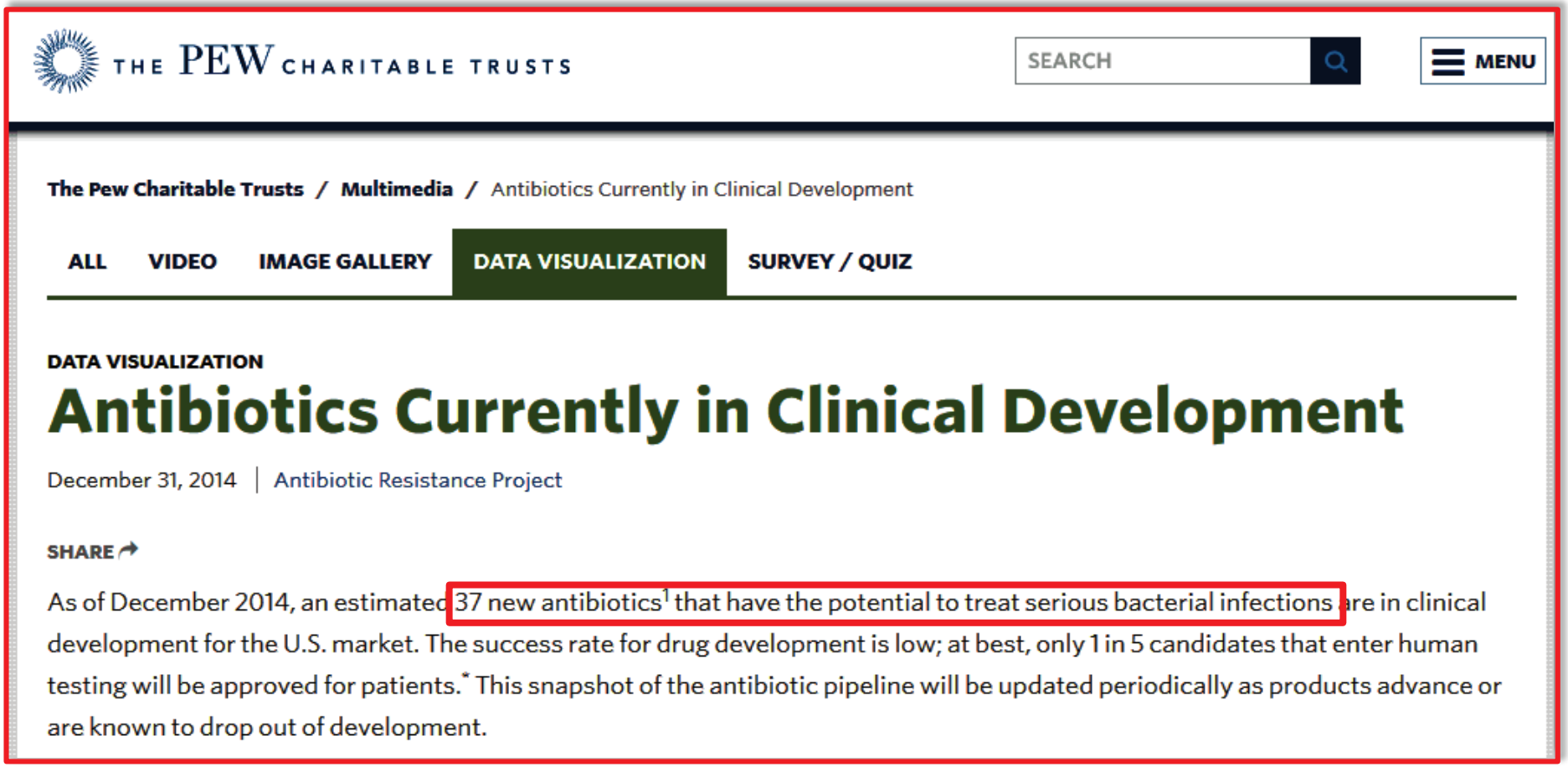
1. Genetic Engineering and Biotechnology News 14 Aug 2013
   http://www.genengnews.com/insight-and-intelligenceand153/biopharmas-drive-antibiotic-development/77899874/
   Last accessed: 8 May 2014
2. Butler *et al* Journal of Antibiotics (Tokyo) 2013;66:571–591

New antibiotics: up to phase I – II …



THE PEW CHARITABLE TRUSTS

SEARCH

MENU

The Pew Charitable Trusts / Multimedia / Antibiotics Currently in Clinical Development

ALL VIDEO IMAGE GALLERY DATA VISUALIZATION SURVEY / QUIZ

DATA VISUALIZATION

Antibiotics Currently in Clinical Development

December 31, 2014 | Antibiotic Resistance Project

SHARE

As of December 2014, an estimated 37 new antibiotics[1] that have the potential to treat serious bacterial infections are in clinical development for the U.S. market. The success rate for drug development is low; at best, only 1 in 5 candidates that enter human testing will be approved for patients.* This snapshot of the antibiotic pipeline will be updated periodically as products advance or are known to drop out of development.

The PEW Charitable Trusts (Health Initiatives)
http://www.pewhealth.org/other-resource/antibiotics-currently-in-clinical-development-85899541594
Last accessed: 26 May 2015

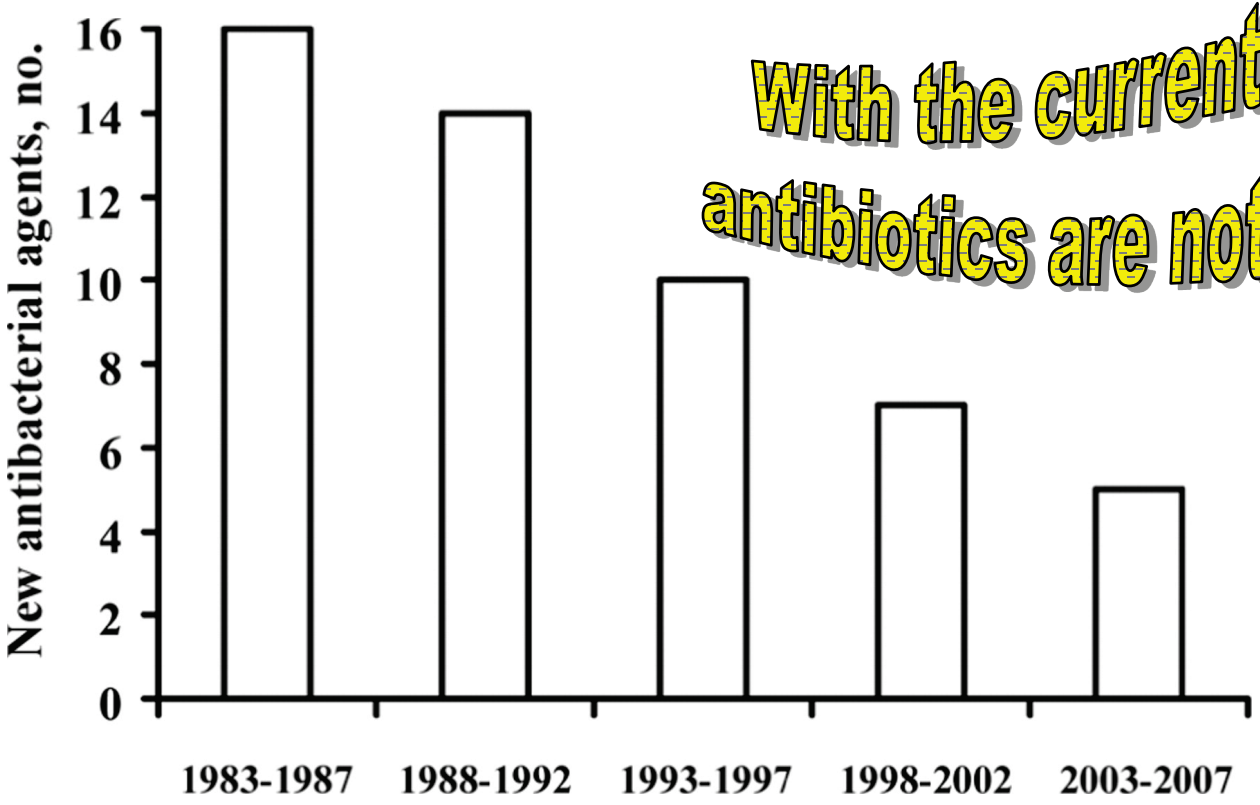
Antibiotic pipeline: did you change your mind ?

- We now have at least 6-7 new **approved** molecules that partially meet our needs for fighting resistant bacteria !
- These molecules have existed for at least 10 years (and may not be totally new…) but their development and registration has been unlocked thanks to the financial stimulations and easier filing processes.
- There is actually **a much large number of molecules in clinical development** [1] and **even more at preclinical level**.

- The real question is how we should approve and use them so as to protect them…

[1] http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development

So what is the real reason ?



With the current system, antibiotics are not profitable

Boucher H W et al. Clin Infect Dis. 2009;48:1-12

The "QALY" of antibiotics [1]

- The **quality-adjusted life year** (**QALY**) [2] is a measure of **disease burden**, including both the quality and the quantity of life lived. It is used in assessing the **value for money of a medical intervention**.
- If antibiotics **prolong your life of 2 to 10 years**, and the cost of one year of **your life is 20,000 euros**, then the value of the **"QALY" of an antibiotic treatment should be 40,000 to 200,000 euros for those successfully treated (or 10,000 to 50,000 if taking into account those who survive without antibiotic)**
- But the real cost and reimbursement of an antibiotic treatment is **MUCH less**
- For comparison, the cost of an anticancer treatment for 1 year survival is…. **up to 20,000 to 70,000 euros…** (and the accepted "QALY" is close to that)
- Find where the problem is …

[1] inspired by Hollis & Ahmed, Preserving Antibiotics Rationally, New Engl. J. Med. 2013; 369,26:2474-2476

[2] Sassi F. (2006). Calculating QALYs, comparing QALY and DALY calculations. Health Policy Plan 21(5):402-408. (see also http://www.eufic.org/article/en/artid/Measuring-burden-disease-concept-QALY-DALY/ - last accessed: 23 May 2015)

A too simple example from Belgium ?

- For **antibiotics** and **antifungals**, if a medical doctor or a dentist prescribes for an **acute treatment**:
  - under the name of the active compound: the rules of prescription under INN (*) are of application → **delivery of the cheapest preparation available**
  - under a trade name: as from **1st Mai 2012**, the pharmacist must deliver the product available in the group of « **the cheapest drugs** ».

Official text in French available at: http://www.inami.fgov.be/drug/fr/drugs/general-information/antibiotic/index.htm (last accessed: 7 November 2013)

- The drug acquisition cost for the treatment of a **community acquired pneumonia** following the **recommandations of BAPCOC** (**) (amoxicillin [3 g per day in 3 administrations for 5 to7 days] is only **13-14 €** … (ex-factory price: ~7 €)

Source: Belgian "Répertoire commenté des médicaments" available at http://www.cbip.be/GGR/Index.cfm?ggrWelk=/nIndex/GGR/Stof/IN_A.cfm (last accessed: 7 November 2013)

* INN: International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee

A spiral to death (in Belgium) ?

- For **antibiotics** and **antifungals**, if a medical doctor or a dentist prescribes for an **acute treatment**:
  - under the name of the active compound: the rules of prescription under INN (*) are of application (delivery of the cheapest preparation available)
  - under a trade name: as from **1st Mai 2012**, the pharmacist must deliver the product available in the group of « **the cheapest drugs** ».

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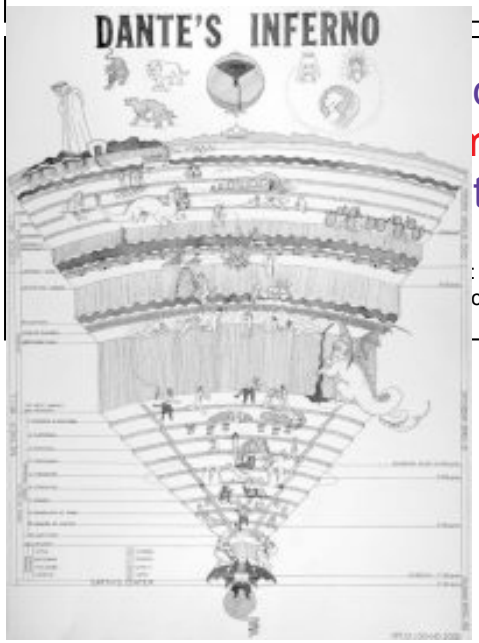

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This infernal spiral (to low prices) make innovators to leave the field

* INN: International International Nonproprietary Name
** BAPCOC: Belgian Antibiotic Policy Coordination Committee

Is the market broken ?

- The final price of antibiotics is driven to VERY low prices, which makes new antibiotics unprofitable … unless sold widely… **which is NOT what we would like to see (but is what generic producers do) !**

- In parallel, the EU and the USA have taken useful initiatives to foster the **discovery of new antibiotics,** which is now **gaining momentum**

- But the process of **development** and **effective and safe availability for the public** still need to be addressed … with **a view on low scale sales**

Towards proposals ?

1. Dissociate the discovery/development process from the commercialization

- Private/public partnership (PPP) on a competitive basis ("grant application" type)
- After approval (EMA), select only the best and most needed candidates for actual commercialization
- Keep the other ones on the shelf but rewards the discoverers/developers

PPP empowers the public authority

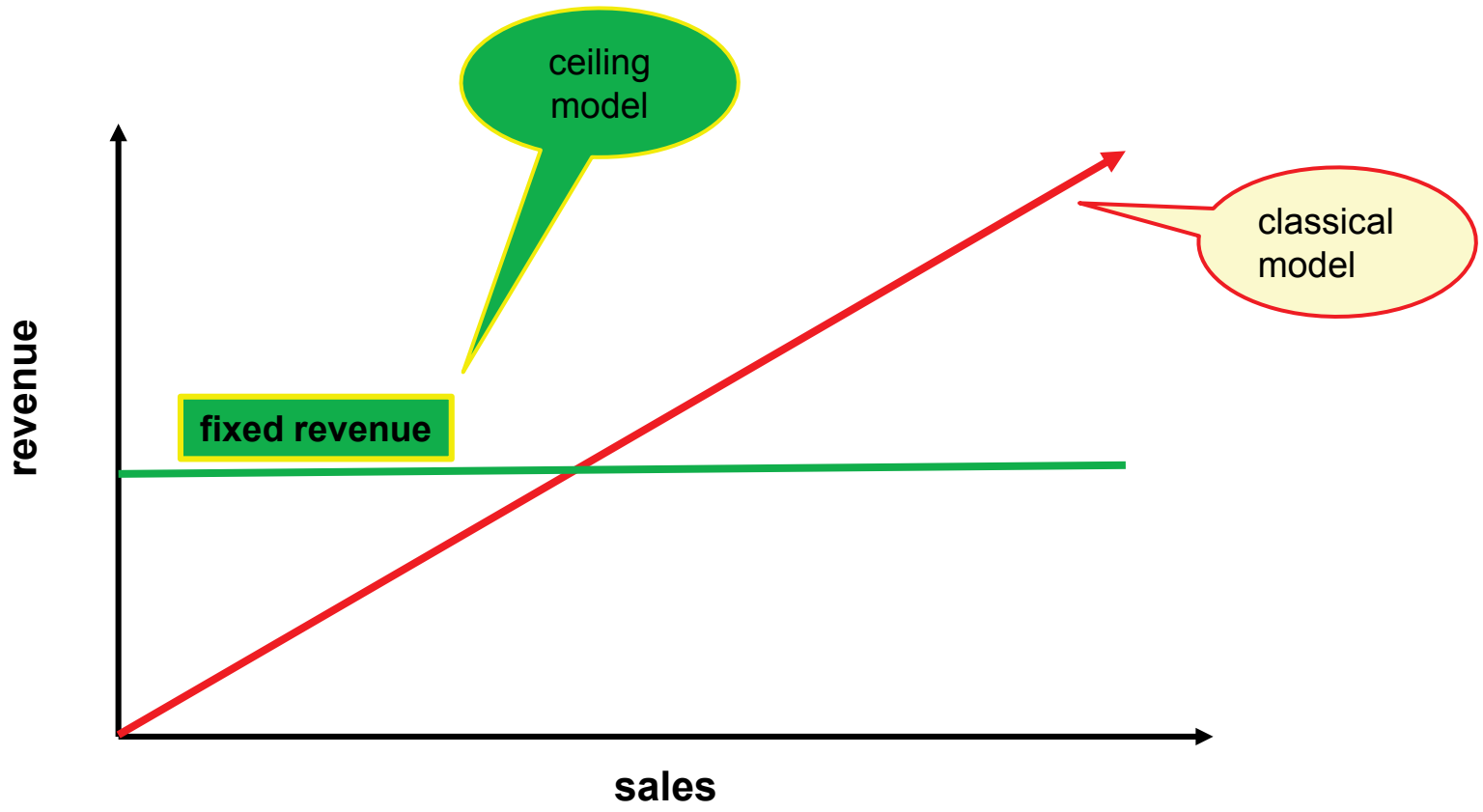
Towards proposals ?

2. **For new antibiotics** allowed for commercialization, define selected and limited indications and allow for **"life-saving" drugs prices** with

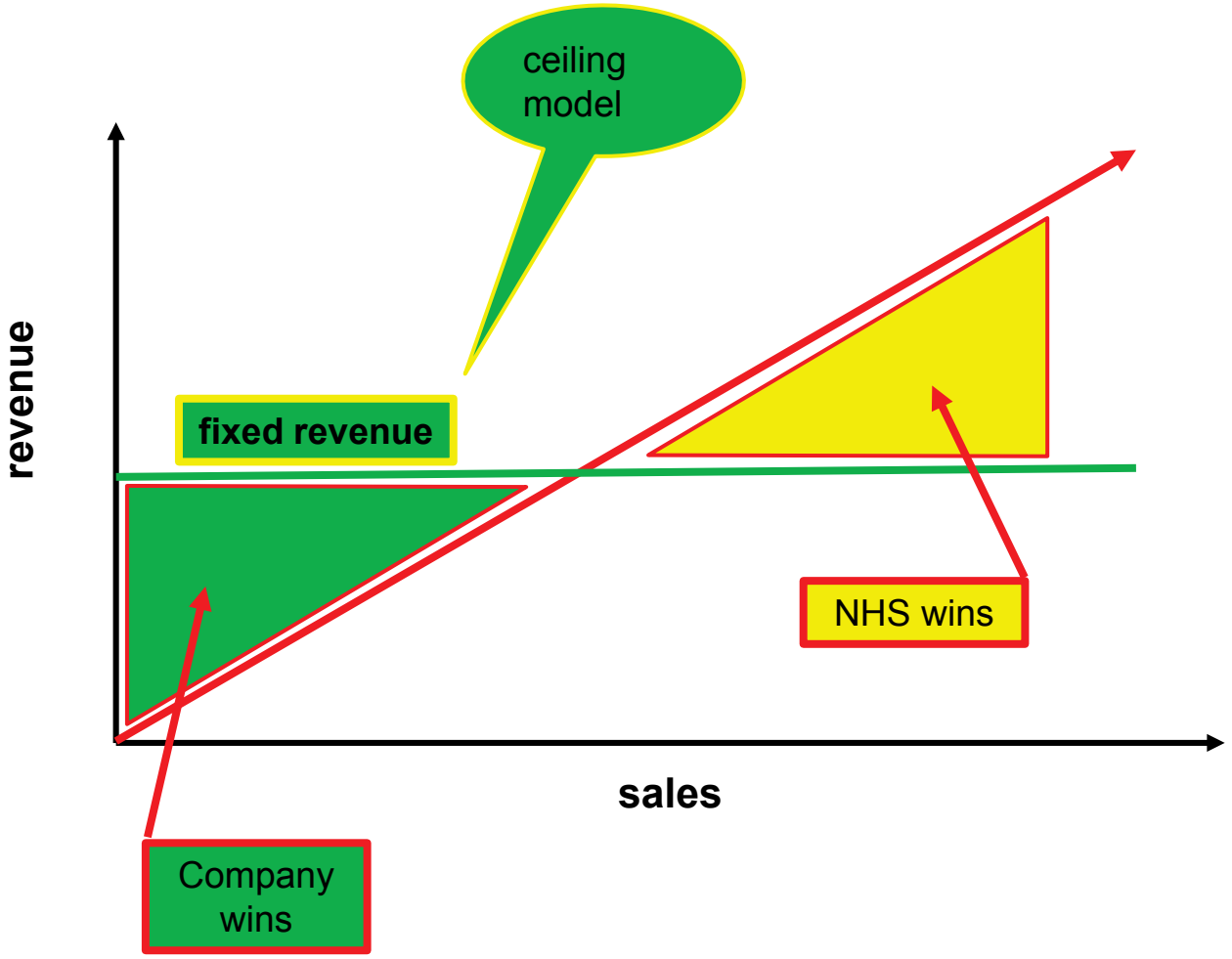
   – reversion of part of the profits to the discovery process, and

   – control by the Public Services in an ethical way

The avibactam UK model ?



The avibactam UK model ?



Towards proposals ?

3. **For "older" antibiotics**, propose a **tender to best offering** for **linked**

   – **responsible and prudent use** (accepted limits in volume and active participation to public initiatives limiting the inappropriate use)

   – **price** (but this will not be the only consideration) and respect of antibiotic "value" as a important public health commodity

Towards proposals ?

None of these proposals are for all situations !

This is not true !

Each proposal must be tested in its appropriate environment ...

But others may have similar ideas…

The European Parliament Resolution of May 19, 2015, on Safer Healthcare in Europe (Improving Patient Safety and Fighting Antimicrobial Resistance) [1] provides some hints:

"62. Calls on the Member States and the Commission to start a reflection process to develop **a new economic model**, that ***de-links the volume of sales from the reward paid for a new antibiotic***, which would reflect the societal value of a new antibiotic and allow for sufficient return on investment for the company, while the purchaser would gain the right to use the product and have full control over volumes;"

"63e: encourage the development of new revenue models whereby ***economic returns for companies are de-linked from prescribed volumes of antibiotics***, while encouraging pharmaceutical innovation and balancing it with the sustainability of health systems;

[1] http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P8-TA-2015-0197+0+DOC+XML+V0//EN&language=EN (last accessed: 26-05-2015)

The real question is to know who will pay for the de-linking ….

- The **Public Authorities** (**by purchasing the compounds**)
- The **Industry** by obtaining **a reasonable price** for the efforts made and the low-scale sales

Summary / Discussion / Food for thought

- Antibiotics have been a "gold treasure" for Industry for many years until the late 90's

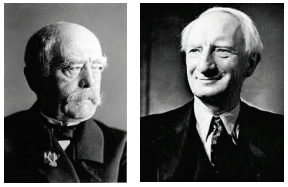
- The decision to "**go for generics**" made by many countries, the **restrictive policies** of health authorities, the **regulatory hurdles**, the **rapid attrition of molecules** due to emergence of resistance and the **short courses** of antibiotics have, altogether, **discouraged Big Pharma** with reorientation towards more profitable businesses, even in infectious diseases (think about anti-HIV and, more, recently about the novel anti-Hepatitis C drugs)

Summary / Discussion / Food for thought

- In face of the vacuum of renewed commercialization, public authorities have decided (i) to **ease the registration process**; (ii) to **give incentives** to companies for discovery; (iii) **invest large amounts of money into development** programmes

- But we also **DO need** to secure a **limited use of antibiotics** while **rewarding** those who find and develop them (empowering the pubic service)

- This will lead us to a **new paradigm** that has never been observed so far in which public and private companies cooperate, but where also **a large part of the expenses are covered by the tax-payers, supplying what social security does not want to pay** (thus, moving from a Bismark to a Beveridge model for health support)



So, it a nutshell…

While strolling through Rotterdam
and seeing the building of a Dutch High School …

Or getting really novel solutions ?

Public transport in Medellin

This was presented as a
"major improvement (and brilliant idea) for urban transport"
at the Belgian Prime Time News
on November 27, 2015

What about the future ?