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

Paul M. Tulkens, MD, PhD
Françoise Van Bambeke, PharmD, PhD

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute,
Université catholique de Louvain,
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?
  Université de Antioquia (Faculty of Medicine), Medellin, Colombia, 1 December 2015 (this presentation is focused on the US Registration 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 (Symposium: New antibacterial 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?

- dry?
- hopeless?
- messy?
- seamless?
- of global concern?
- under repair?
- in good shape?
New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics

Declining antibacterial approvals (past 25 years)

1983-1987: 16 approvals
1988-1992: 14 approvals
1993-1997: 10 approvals
1998-2002: 7 approvals
2003-2007: 4 approvals
2008-2012: 2 approvals

- telavancin
- ceftaroline
New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics

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

Shall we succeed?

FDA only so far
Our own pipeline (*)…

• in the good old time… (until 2000)

  – aminoglycosides
    • amikacin
    • netilimicin
    • ispepamicin
  – macrolides
    • roxithromycin
    • azithromycin
  – fluoroquinolones
    • moxifloxacin
    • garenoxacin

* 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)
  - aminoglycosides
    - plazomycin
      - papers: 0
  - ketolides
    - solithromycin
      - papers: 4
  - lipoglycopeptides
    - telavancin
      - papers: 3
    - oritavancin
      - papers: 14
  - fluoroquinolones
    - finafloxacin
      - papers: 1
    - delafloxacin
      - papers: 3
  - oxazolidinones
    - tedizolid
      - papers: 3
    - radezolid
      - papers: 2
  - β-lactams
    - ceftobiprole
      - papers: 2
    - ceftaroline
      - papers: 1
    - ceftazidime/avibactam
      - papers: 1
    - doripenem
      - papers: 3

* 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...

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\textsuperscript{a}, Stephan Harbarth\textsuperscript{a, b}

\textsuperscript{a} Infection Control Programme, Geneva University Hospitals and Faculty of Medicine, Switzerland
\textsuperscript{b} Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Switzerland
As a result...

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

<table>
<thead>
<tr>
<th>Drug (brand name) - Company</th>
<th>Antibiotic class</th>
<th>Activity spectrum/resistant pathogens targeted</th>
<th>Phase and indication¹</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone + avibactam [44] (Aryzatom) – AstraZeneca/Astaxis</td>
<td>Cephalosporin + new BLI</td>
<td>Gram–, including MDR P. aeruginosa, ESBL-producing strains and KPC</td>
<td>Approved February 2015 for cIAI in combination with netomizaldis and for cUTI in patients who have limited or no alternative treatment options, in phase III for HAP/VAP and cIAI</td>
<td>Approved February 2015 Not submitted yet Not submitted yet</td>
</tr>
<tr>
<td>Cefozaxone + tazobactam [41] (ZerbaaM1) – Cubist Pharmaceuticals / Merck Sharp &amp; Dohme</td>
<td>Cephalosporin + BLI</td>
<td>Gram–, including carbapenemase, piperacillin-tazobactam and ceftdoxime-resistant Pseudomonas aeruginosa, ESBL-producing strains</td>
<td>Approved for cUTI and cIAI, in phase II for VAP and phase I for paediatric use</td>
<td>Approved December 2014 Under review since August 2014 Under review since September 2014²</td>
</tr>
<tr>
<td>Cefotriglavin medecin [42] (Zavntu/Mabola) – Basilea Pharmaceuticals/Quinilnes</td>
<td>Cephalosporin</td>
<td>Gram– and –, including MRSA, VRSA, piperacillin- and ceftriaxone-resistant Stenotrophomonas maltophilia, Enterobacteriaceae, P. aeruginosa</td>
<td>Approved for CABP and HAP, excluding VAP</td>
<td>Not submitted additional phase III data required Approved October 2013 Approved December 2014</td>
</tr>
<tr>
<td>Oritavancin [42] (OrxactTM) – The Medicines Company</td>
<td>Glycopeptide</td>
<td>Gram–, including MRSA</td>
<td>Approved for ABSSI, in phase I for paediatric use</td>
<td>Approved May 2015 Approved May 2014 Under review²</td>
</tr>
<tr>
<td>Teixobactin phosphate [43] (GivectroTM) – Cubist Pharmaceuticals / Merck Sharp &amp; Dohme</td>
<td>Oracinolidine</td>
<td>Gram–, including MRSA and linezolid-resistant MRSA</td>
<td>Approved for ABSSI, in phase III for HAP/VAP and for ABSSI in adolescents</td>
<td>Approved June 2014 Approved June 2014 Approved March 2015 Under review since second quarter 2014²</td>
</tr>
<tr>
<td>Dalbavancin [42] (DalvanorTM/ XydalbaTM) – Actavis / Durata Therapeutics</td>
<td>Glycopeptide</td>
<td>Gram–, including MRSA</td>
<td>Approved for ABSSI, in phase III for CABP and phase I and II for paediatric use</td>
<td>Approved May 2014 Approved May 2014 Unknown</td>
</tr>
<tr>
<td>Mepemehex–RPMX7000 [54, 55] (CarbavanceTM) – The Medicines Company</td>
<td>Carbapenem + new class of BLI</td>
<td>Gram–, including CRE and particularity KPC</td>
<td>Phase III for cUTI and infections caused by CRE¹</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Erapacoline [56] – Tetraphase Pharmaceuticals</td>
<td>Tetracycline</td>
<td>Gram– and –, including CRE, ESBL-producing strains, MDR Acinetobacter baumannii, VRE, MRSA</td>
<td>Phase III for cUTI and cIAI¹</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Plazomicin [57] – Anaerogen</td>
<td>Aminoglycoside</td>
<td>Gram–, including CRE</td>
<td>Phase III for bloodstream infection and nosocomial pneumonia caused by CRE⁵</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Delafloxacin [51] – Melinta Therapeutics</td>
<td>Fluoroquinolone</td>
<td>Gram– and –, including MRSA</td>
<td>Phase III for ABSSI</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Solithromycin [52] – Celphost Pharmaceuticals</td>
<td>Macrolide</td>
<td>Gram–, including macrolide-resistant strains</td>
<td>Phase III for CABP and uncomlicated gonorrhoea in phase I for paediatric use</td>
<td>NA NA NA</td>
</tr>
</tbody>
</table>

¹ Information retrieved from clinicaltrials.gov as of March 2015.
² Personal communication.
² Completion of trial expected in 2016; clinicaltrials.gov identifiers: NCT02106945 and NCT02106496.
³ Completion of trial expected in 2015; clinicaltrials.gov identifiers: NCT01976939 and NCT01844989.
⁴ Completion of trial expected in 2017; clinicaltrials.gov identifiers: NCT01978371. ABSSI = acute bacterial skin and skin structure infections; BLI = ß-lactamase inhibitor; CABP = community-acquired bacterial pneumonia; cIAI = complicated intra-abdominal infections; CRE = carbapenem-resistant Enterobacteriaceae; cUTI = complicated urinary tract infections; ESBL = extended spectrum ß-lactamase; Grams = 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...

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

1953

Vancomycin
(Edmund Kornfeld at Eli Lilly)

1996

oritavancin (LY333328)
(R. Cooper et al. at Eli Lilly)

1999

dalbavancin (BI397-B0)
(A. Malabarba et al. at Gruppo Lepetit S.P.A and Biosearch)

2000

telavancin (TD-6424)
(M. Leadbetter at Theravance)

3 Malabarba et al. Drugs of the Future (1999), 24(8), 839-846
Lipoglycopeptides: towards registration

Vancomycin
(Edmund Kornfeld at Eli Lilly)\(^1\)

oritavancin (LY333328)
(R. Cooper et al. at Eli Lilly)

dalbavancin (BI397-B\(_0\))
(A. Malabarba et al. at Gruppo Lepetit S.P.A and Biosearch)

telavancin (TD-6424)
(M. Leadbetter at Theravance)

Oxazolidinones: a successor for linezolid?

1987
Dup721
(Slee et al. at du Pont)¹

1995
linezolid (U100766)
(Barbachyn et al. at Upjohn)²

2005

2014

tedizolid (DA-7157)
(Rhee et al. at Dong Pharmaceuticals)³

Trius Pharmaceuticals → Cubist → Merck (USA, EU) → Bayer (LA, Asia)

---

³ Rhee et al. PCT Int. Appl. (2005), WO 2005058886 A1 Jun 30, 2005
Zhanel et al. Drugs. 2015;75:253-70.
Ceftolozane (+tazobactam) – Avibactam (+ ceftazidime): the new Graal?

2004 2004

Ceftolozane (FR264205) (Ohki et al. at Fujisawa) ¹

Avibactam (AVE1330A / NXL104) (Bonnefoy et al. at Aventis) ²

Antipseudomonal cephalosporin

Inhibitor of β-lactamases (class A, C and some D)

tazobactam

Cubist

Novexel / Forrest / AstraZeneca

Ceftazidime

FDA

2014 2015

Cubist → Merck

Actavis


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 both hospital and community

* 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>
<thead>
<tr>
<th>GIDP qualifying pathogen names [20]</th>
<th>Gram</th>
<th>Opportunistic</th>
<th>Hospital acquired</th>
<th>Community acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td>Gram-</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Burkholderia cepacia complex</td>
<td>Gram-</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Campylobacter species</td>
<td>Gram-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Gram+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae (especially Citrobacter, Enterobacter cloaceae, Klebsiella pneumoniae, Escherichia coli, Proteus vulgaris, Salmonella, Serratia marcescens, Shigella)</td>
<td>Gram-</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>Gram+</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gram-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis complex</td>
<td>NA</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Gram-</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Gram-</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Nontuberculous mycobacteria species</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Gram+</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Streptococcus agalactiae (group B)</td>
<td>Gram+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Gram+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes (group A)</td>
<td>Gram+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>Gram-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coccioidoides species</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcus species</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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].
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? 🇺🇸

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 both hospital and community

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

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 both hospital and community

2. The GAIN act … (“Generating Antibiotic Incentives 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,” including that which may be applied 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.

---

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 both hospital and community

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

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](http://www.phe.gov/about/barda/Pages/default.aspx)
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 both hospital and community

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

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/bar/](http://www.phe.gov/about/bar/)
A view from Europe

THE INNOVATIVE MEDICINES INITIATIVE

The Innovative Medicines Initiative (IMI) is Europe’s largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA.

• €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

IMI NEWSFLASH

26/05/2015: Less than 3 weeks to go to the IMI Stakeholder Forum 2015
http://t.co/8H20u6QtUs
Register at http://t.co/g6Vsujm6ly #IMISF2015

22/05/2015: RT
@IMI_LifeTrain: New
@IMI_LifeTrain case study online: @OrionPharma’s

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

![Diagram showing phases of clinical trials with numbers of patients: preclinical n ~ 50, phase I, phase II n ~ 300, phase III N ~ 6000]
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 –

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

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**.

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?

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 %)

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)

LIMITED TRIALS
- Rare MDR organisms
- Few patients
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)
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) 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.

1. Genetic Engineering and Biotechnology News 14 Aug 2013
   Last accessed: 8 May 2014

New antibiotics: up to phase I – II ...

As of December 2014, an estimated 37 new antibiotics 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.
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 development¹ and even more at preclinical level.


• The real question is how we should approve and use them so as to protect them...
So what is the real reason?

With the current system, antibiotics are not profitable

The "QALY" of antibiotics

- The **quality-adjusted life year (QALY)** 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 …

---

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 \(\rightarrow\) **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** ».

  (last accessed: 7 November 2013)

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

  (last accessed: 7 November 2013)

---

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


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


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?

- Fixed revenue
- Ceiling model
- Classical model
The avibactam UK model?

- Company wins
- NHS wins
- Fixed revenue
- Ceiling model

Revenue vs. Sales diagram.
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 an 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) 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;


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)

we must change !
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 public 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?

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?