The (EU) authorities & their antibiotic development policy: a changing paradigm

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Health Science Sector
Université catholique de Louvain
Brussels, Belgium

Bayer HealthCare
Science For A Better Life

BAYER ANTI-INFECTIVE THERAPIES SYMPOSIUM: ADVANCING TODAY'S PRACTICE & PREPARING THE FUTURE

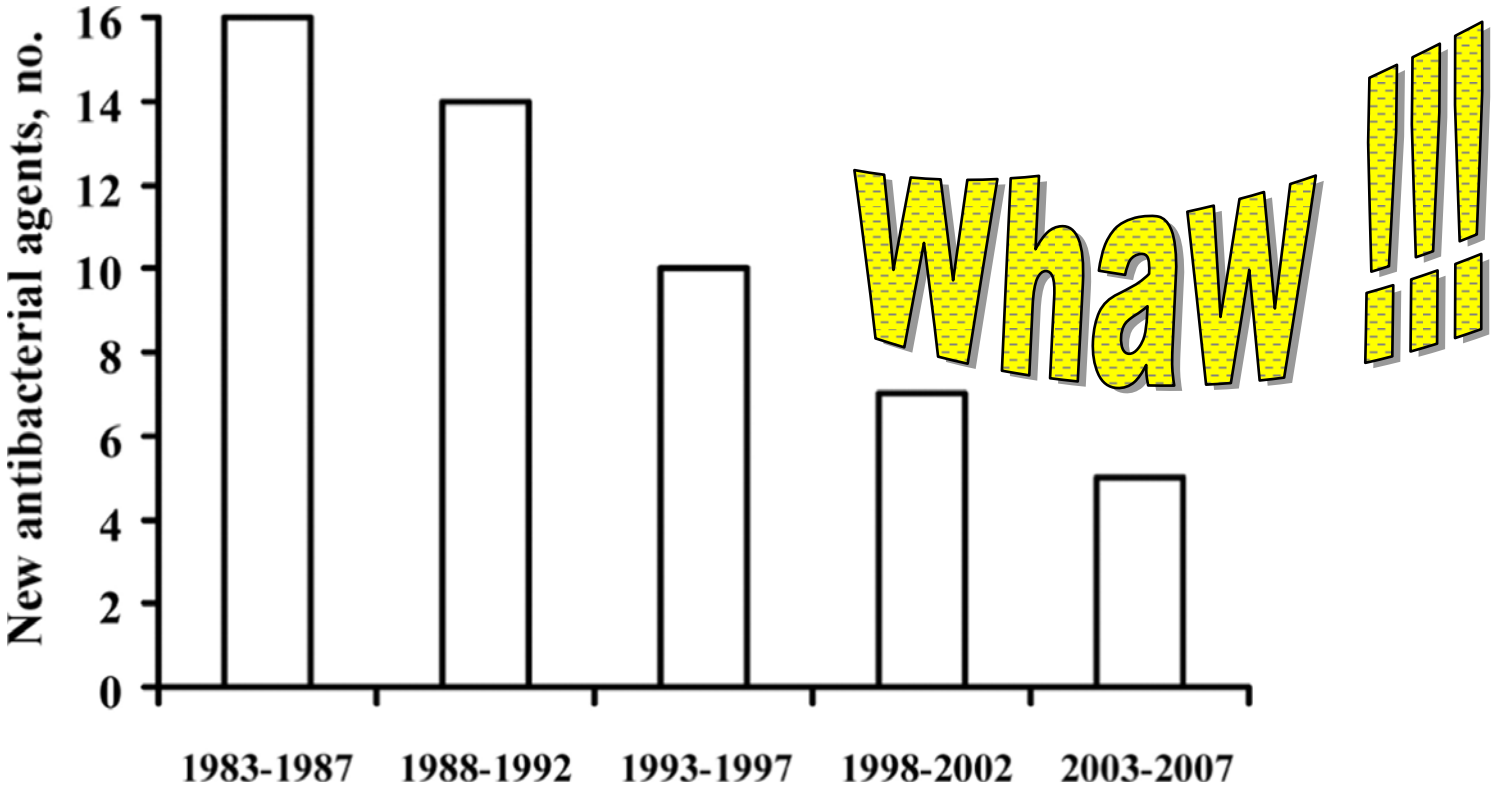
15 May 2014 – Reet, Belgium

Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions
- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, AstraZeneca
- Decision-making and consultation bodies
  - General Assembly (current) and steering committee (part) of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

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

The end of antibiotic research ?



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

No new antibiotics: is it true ?

- A recent article in **Genetic Engineering & Biotechnology News** identified **66 companies involved in antibiotic research**, 86% of which are either small or medium-sized.
- A paper 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 …

- *As of February 2014, there are at least 45 new antibiotics with the potential to treat serious bacterial infections 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)*

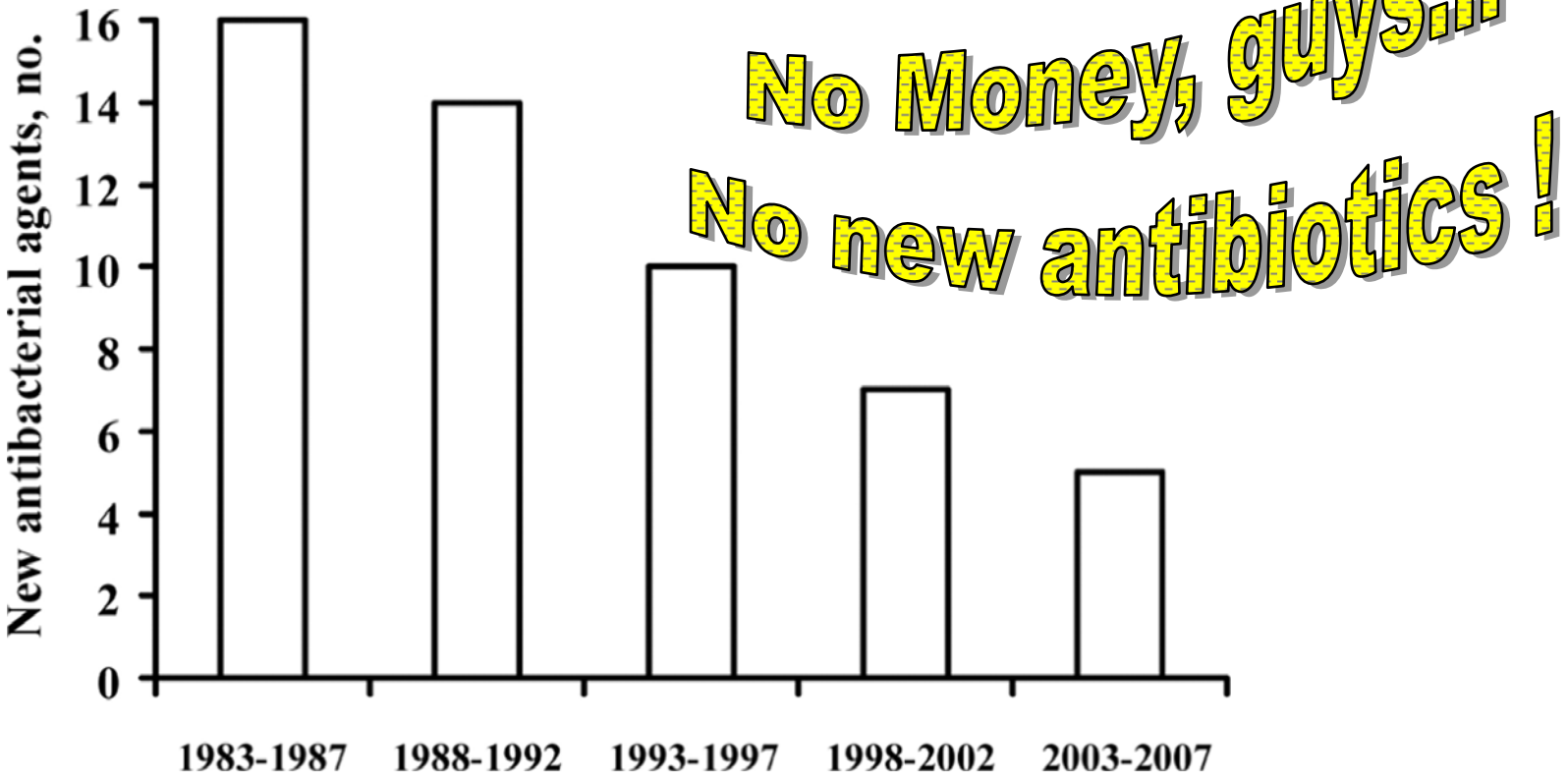
The PEW Charitable Trusts (Health Initiatives)
http://www.pewhealth.org/other-resource/antibiotics-currently-in-clinical-development-85899541594
Last accessed: 8 May 2014

New antibiotics: up to phase I – II and III

- *There are at least 53 systemic antibiotic NCEs in clinical development, of which 13 have reached Phase III testing.*

BioCentury Publications, Inc. , 2012
http://www.biocentury.com/antibioticsncepipeline.htm
Last accessed: 8 May 2014

So what is the real reason ?



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

The "Qualy" of antibiotics (*)

- The **quality-adjusted life year** or **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 **"Qualy" of an antibiotic treatment is 40,000 to 200,000 euros**
- 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 "Qualy" is close to that)
- Find where the problem lies…

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

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 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)
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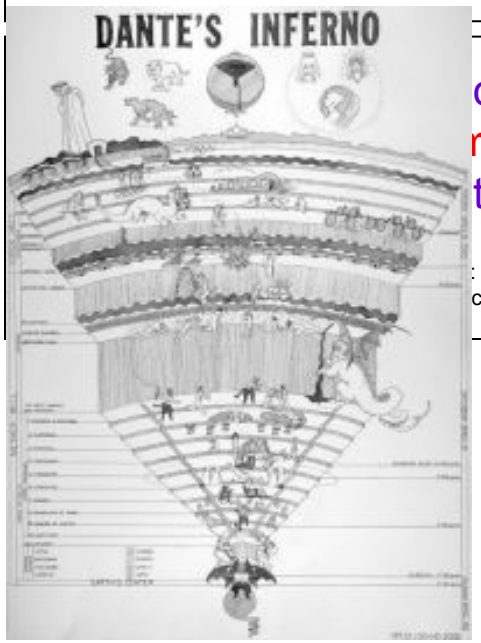

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cessed: 7 November 2013)

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

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

Let us not confuse discovery, development and actual commercialization

Thesis

- There is no real lack of innovation, even if innovation is difficult …
- But there is a real lack of incentive for full clinical development given
  - the time of development that makes the protection period since patent application too short
  - the regulatory hurdles that make development difficult
  - the insistence of authorities to go for low cost that make sales unprofitable

➔ This is where corrective actions need to be taken …

Trans Atlantic Task Force on Antimicrobial Resistance - TATFAR

2009 EU-US Summit Declaration called for the establishment of *"…a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us."*

EU-US Summit – Washington 3 November 2009

This slide from van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

Trans Atlantic Task Force on Antimicrobial Resistance - TATFAR

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Trans Atlantic Task Force on Antimicrobial Resistance - TATFAR

- US and EU membership
- Objective: Promote information exchange, coordination and co-operation between the US and the EU
- 2011 Report: 17 recommended areas for further collaboration

EU-US Summit –November 2009

This slide from van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

TATFAR Recommendations

- **Issue:** Investigators should consider funding sources and research resources on both sides of the Atlantic to support antimicrobial research and antibacterial product development efforts
- **Recommendation 14:** Publicise funding opportunities to the EU and US research communities

This slide from van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

DMID Resources for Researchers

Resources for Researchers

Share this:

Microbiology and Infectious Diseases Resources

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV.

Funding Opportunities

Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.

- NIH-Wide Funding Opportunity Announcements
- NIAID Funding Opportunity Announcements and Requests for Proposals

Product Development Services and Research Tools and Biological Materials

Request development by DMID-funded contractors of critical information needed to move a product through the product development pathway. Note: Services are contingent upon availability of required preliminary data.

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Highlight

Sharing Scientific Success Stories: **DMID WOWS**

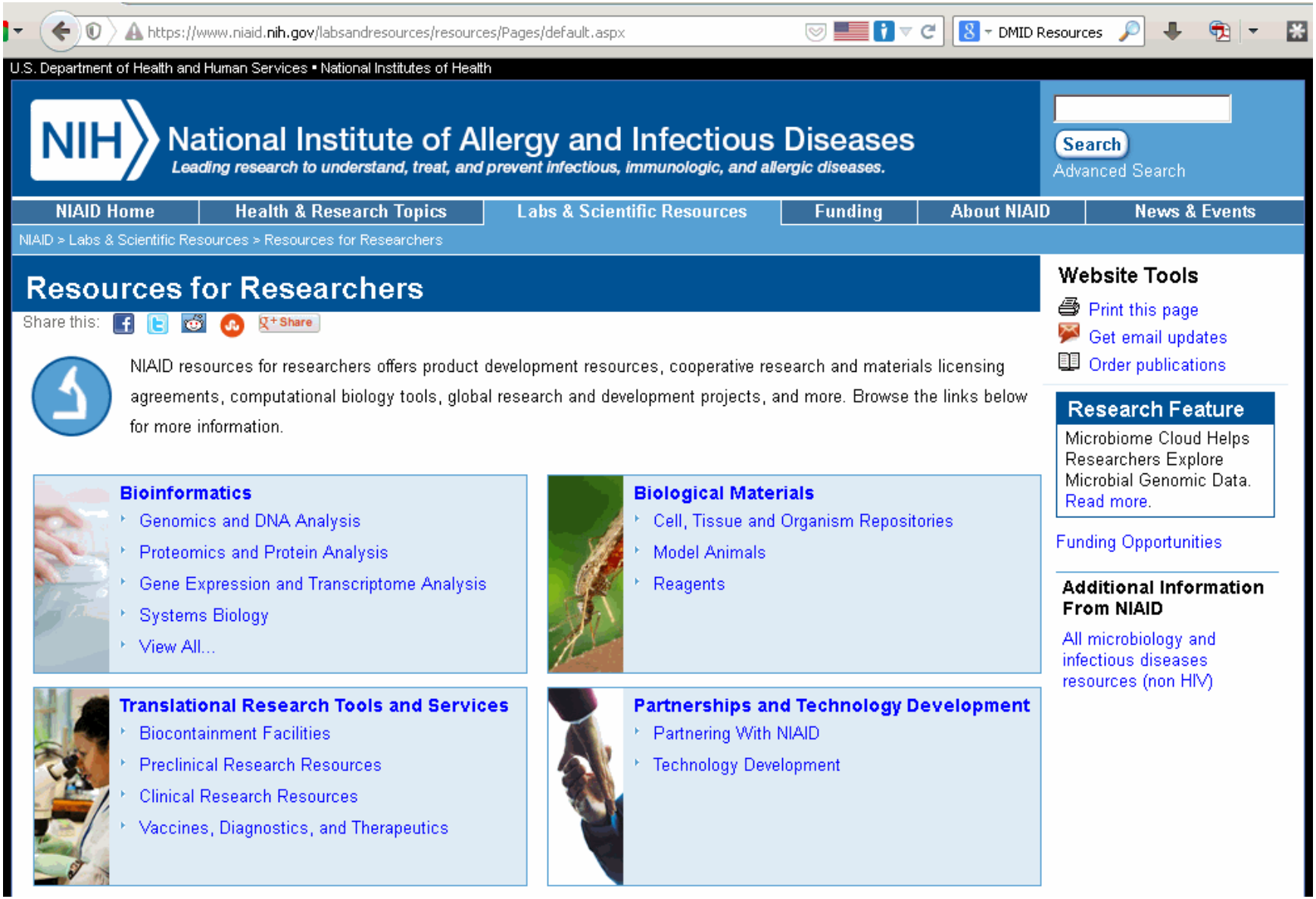
Additional Information From NIAID

All NIAID resources

Web Search Term: **DMID Resources**

This slide from van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

DMID Resources for Researchers



Other key changes in the US …

- **GAIN Act** (Generating Antibiotics Incentives Now) - 2012
  - priority FDA review
  - additional five years of market exclusivity for breakthrough antibiotics that target serious or life-threatening pathogens
  - relaxed its criterion for non-inferiority to within 10%, making it easier to show comparability to drugs already on the market
- **BARDA:** Biomedical Advanced Research and Development Authority
  [within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services]
  - provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies.
- **FDA**:
  - new guidance documents (aBSSSI, cUTIs, cIAIs, …) that are considered being significantly better
- **Department of Health and Human Services** (HHS)
  - awarding funds to allow companies to shift funds around an antibiotic programs (portofolio approach; example: GSK antibiotic programme)

- 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
- Biomedical Advanced Research and Development Authority
  http://www.phe.gov/about/barda/Pages/default.aspx
  Last accessed: 9 May 2014

Monnies from "Big Bother"

U.S. Department of Health & Human Services

Preparedness | Emergency | About ASPR

Office of the Assistant Secretary for Preparedness and Response

Public Health Emergency

Public Health and Medical Emergency Support for a Nation Prepared

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MCM Procurements and Grants

About BARDA

- BARDA Strategic Plan
- Procurement and Grant Awards
- Program Divisions
- Making Progress, End to End, in Medical Countermeasures
- Project BioShield Annual Reports
- Leadership Biographies

Medical Countermeasures Advanced Research, Development and Acquisition Contract and Grant Awards

October 21, 2013: New blood test would provide fast results for medical care after anthrax attack

September 26, 2013: BARDA boosts global ability to respond to pandemics

September 20, 2013: HHS funds development of freeze-dried platelets for disaster response

September 19, 2013: BARDA funds development of device to aid burn patients in disasters

September 19, 2013: HHS replenishes nation's supply of anthrax antitoxin

September 18, 2013: HHS explores new emergency response use for approved steroid

September 17, 2013: BARDA funds study of therapy for thermal burns

September 16, 2013: BARDA evaluates burn dressing for radiation, sulfur mustard burns

August 23, 2013: BARDA Contract Supports Evaluation of Therapy for Severe Thermal Burns

August 22, 2013: BARDA Supports Proof-Of-Concept Studies for Small Molecule Development

July 30, 2013: BARDA contract supports the development of a more effective skin graft to help burn patients after a rad/nuke event

June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis

May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tularemia

May 22, 2013: HHS forms strategic alliance to develop new antibiotics

April 3, 2013: HHS awards contract to create test to identify resistant influenza viruses

This page last reviewed: January 03, 2014

http://www.phe.gov/newsroom/Pages/mcm-procurements.aspx
Last accessed: 8 May 2014

When Big Brother helps Big Pharma…

May 22, 2013: HHS forms strategic alliance to develop new antibiotics

Date: May 22, 2013

Company: GlaxoSmithKline of North Carolina

GlaxoSmithKline US

40 to 200 x 10^6 US$

Contract amount: This agreement is not a contract; other transactional authority was used to create a strategic alliance. BARDA will contribute $40 million over 18-months. The agreement can be extended up to five years and up to a total of $200 million

About the contract: The agreement is the first in which BARDA has taken a portfolio approach with a private sector company instead of contracting to develop a single medical countermeasure. The agreement is flexible, allowing drug candidates to be moved in or out of the portfolio, based on advanced development stage and technical considerations, during joint semi-annual portfolio reviews. Under the agreement, GSK researchers will conduct safety and toxicology testing, clinical pharmacology studies, clinical studies, and non-clinical studies to support approval to treat illnesses caused by bioterrorism agents like anthrax, plague and tularemia, as well as address antibiotic resistance. One of the antibiotics to be further developed under this agreement is GSK'944, the first in class of drugs that targets bacterial DNA replication in a unique fashion. GSK has conducted studies in which GSK'944 protected or successfully treated animals suffering from anthrax, plague, or tularemia.

Additional information: The partnership with GSK is funded by BARDA's Broad Spectrum Antimicrobials Program. BARDA is seeking additional proposals for broad-spectrum antimicrobials that could potentially treat or prevent illness due to biological threat agents. Proposals are accepted through the Broad Agency Announcement BARDA-BAA-12-100-SOL-00011 at www.fbo.gov.

Anthrax, plague, tularemia … and resistance

Press Release: HHS forms strategic alliance to develop new antibiotics

PHE.GOV - Leading a Nation Prepared HHS/ASPR
http://www.piersystem.com/go/doc/3803/1863406/
Last accessed: 8 May 2014

and also helps small pharma for a new ketolide …

May 24, 2013: BARDA supports new broad-spectrum antibiotic to treat anthrax, tulermia

Date: May 24, 2013

Company: Cempra Pharmaceuticals of Chapel Hill, N.C.

Contract amount: $17.7 million for two years

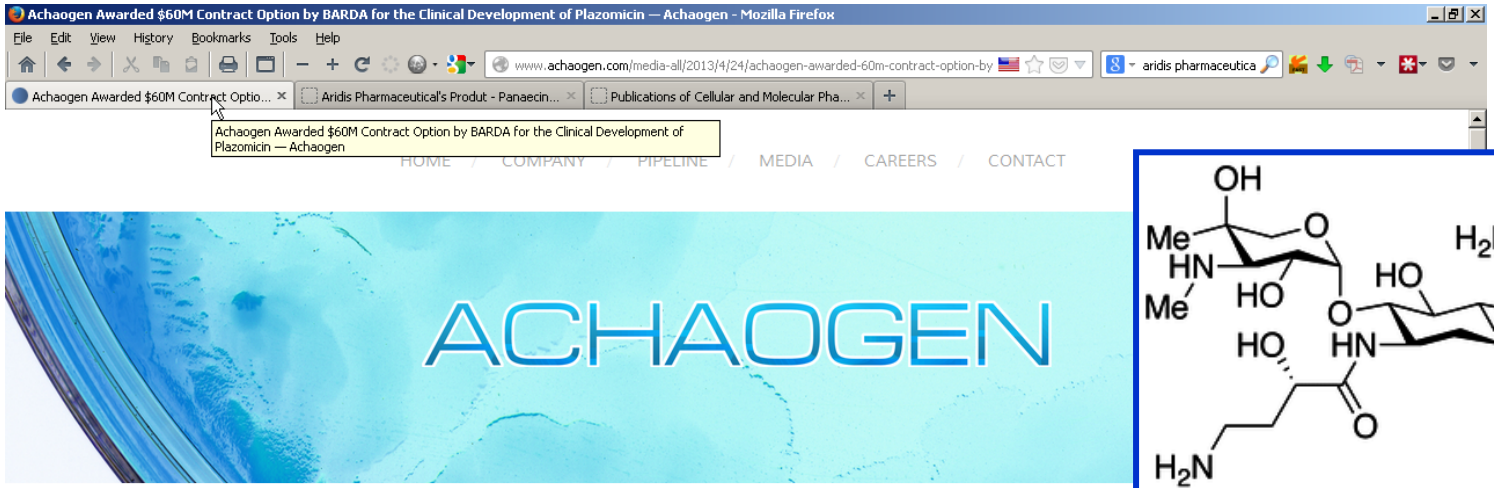
About the contract: The contract supports studies needed to request FDA approval of a drug called solithromycin to treat adults and children infected with anthrax, tularemia or community-acquired bacterial pneumonia. If approved, the drug would be the first orally administrated antibiotic approved in decades to treat children who develop community acquired bacterial pneumonia. Studies of the drug's use in treating anthrax or tularemia will be conducted under the FDA's Animal Efficacy Rule.

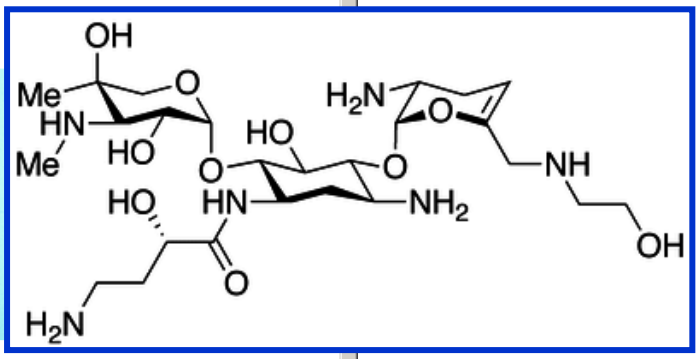
Additional information: BARDA is seeking additional proposals for broad-spectrum antimicrobials that could potentially treat or prevent illness due to biological threat agents. Proposals are accepted through a Broad Agency Announcement BARDA-BAA-12-100-SOL-00011 at www.fbo.gov

Press Release: HHS funds drug development for bioterror infections

PHE.GOV - Leading a Nation Prepared HHS/ASPR
http://www.piersystem.com/go/doc/3803/1863410/
Last accessed: 8 May 2014

And even for an aminoglycoside …





Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin

April 24, 2013

- Contract to fund Phase 3 superiority study of plazomicin in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections -

South San Francisco, CA, April 24, 2013 – Achaogen, Inc. today announced the award of a $60M contract option from the Biomedical Advanced Research and Development Authority (BARDA). The option supports the conduct of a global Phase 3 superiority study that will evaluate the efficacy and safety of plazomicin in treating patients with serious gram-negative bacterial infections due to CRE. This pathogen-specific clinical study represents a new development approach to address unmet medical needs for multi-drug resistant bacterial infections. The study is expected to start in fourth quarter of 2013.

"We are excited and honored to continue the development of plazomicin in partnership with BARDA," said Kenneth J. Hillan, M.B. Ch.B., Chief Executive Officer and Chief Medical Officer of Achaogen. "The growing prevalence of CRE infections poses a substantial public health threat, given the high mortality rates associated with CRE infections. Plazomicin's strong potential to address this public health issue and to contribute to the global effort to guard against bacterial biothreats makes it a critically important agent in the antibacterial pipeline."

Achaogen Inc
http://www.achaogen.com/media-all/2013/4/24/achaogen-awarded-60m-contract-option-by-barda-for-the-clinical-development-of-plazomicin
Last accessed: 8 May 2014

Big Brother in Switzerland…

June 25, 2013: BARDA supports new broad-spectrum antibiotic against glanders, melioidosis

Date: June 25, 2013

Company: Basilea Pharmaceutica International Ltd., Basel, Switzerland

Contract amount: BARDA will provide $16.8 million in the first phase of the contract. The contract can be extended up to a total of six years with BARDA contributing up to a total of $89 million

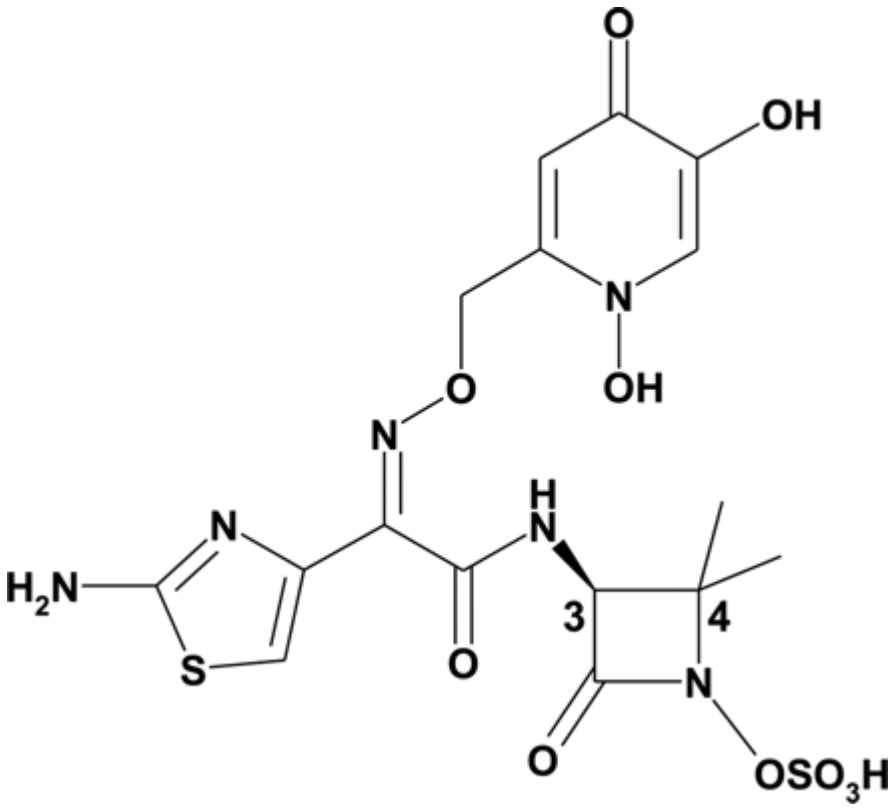
About the contract: This contract is a cost-sharing public-private partnership. The partnership supports Basilea in conducting studies to evaluate the safety and efficacy of the antibiotic BAL30072 to treat Gram-negative infections including melioidosis, glanders, hospital-acquired pneumonia, and complicated urinary tract infections. Results from these studies will support the eventual filing of a new drug application with the FDA. In addition to showing promise in treating melioidosis and glanders, early studies of BAL30072 have demonstrated the drug's potential in treating a broad range of multidrug-resistant Gram-negative bacteria commonly found in hospitals.

Additional information: BARDA is seeking additional proposals for broad-spectrum antimicrobials that potentially could treat or prevent diseases caused by bacterial and viral threat agents, and clinically relevant emerging and drug resistant pathogens that through the Broad Agency Announcement BARDA CBRN BAA-12-100-SOL-00011 at www.fbo.gov.

Press Release: BARDA supports new broad-spectrum antibiotic

PHE.GOV - Leading a Nation Prepared HHS/ASPR
http://www.piersystem.com/go/doc/3803/1863402/
Last accessed: 8 May 2014

Unless Big Brother comes to your help…



Structure of BAL30072

Numerous attempts have been made to introduce iron-binding functional groups into β-lactams since the 1980s, in order to circumvent the limitations imposed by porin mutation or deletion. BAL30072 is a sulfactam, analogous to tigemonam, with a dihydropyridone iron-chelating group.

http://aac.asm.org/content/54/6/2291.full
AAC *June 2010 vol. 54 no. 6 2291-2302*

What in Europe ?

ECDC/EMEA Joint Working Group

- assigned on 28 February 2008.
- technical Report accepted by ECDC/EMEA on 23 July 2009
- circulated for information on 20 August 2009.
- published in September 2009

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf
Last accessed: 9 May 2014

What in Europe ?

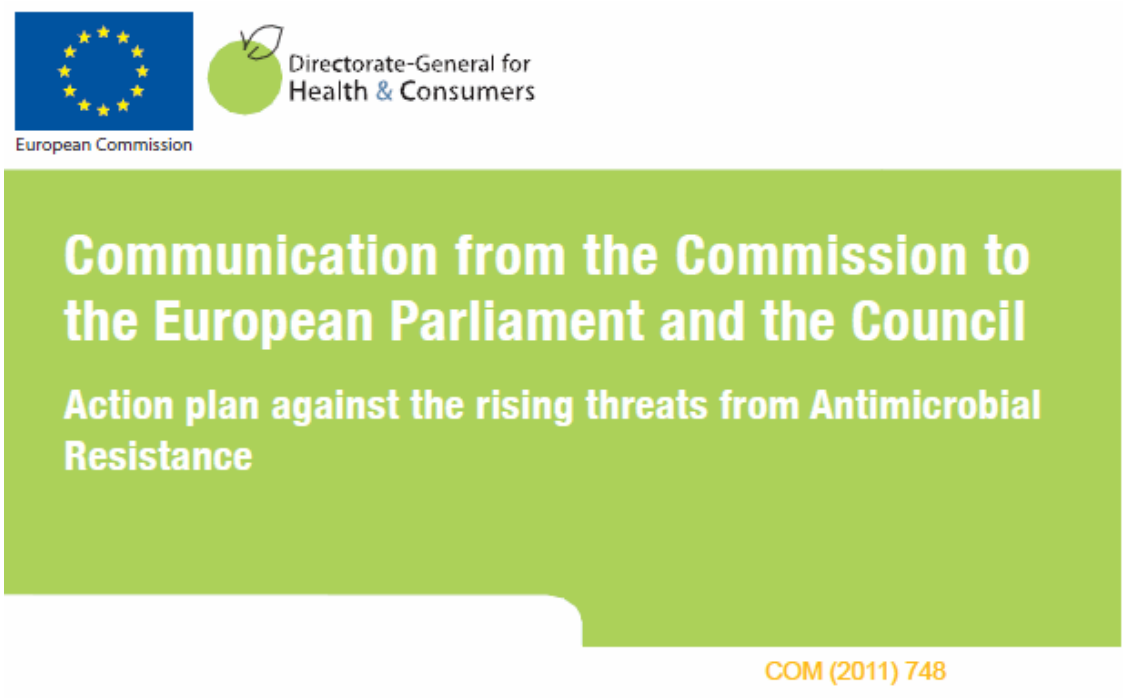
3 Analysis of the research and development pipeline of antibacterial agents

Most relevant findings

- Fifteen systemically administered antibacterial agents with a new mechanism of action or directed against a new bacterial target were identified as being under development with a potential to meet the challenge of multidrug resistance. Most of these were in early phases of development and were primarily developed against bacteria for which treatment options are already available.
- There is a particular lack of new agents with new targets or mechanisms of action against multidrug-resistant Gram-negative bacteria. Two such agents with new or possibly new targets and documented activity were identified, both in early phases of development.

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf
Last accessed: 9 May 2014

The reaction of the EU…



http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf
Last accessed: 8 May 2014

The reaction of the EU…

5-year Action Plan to fight against AMR based on 12 key actions:

….

Action n° 6:
Promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antimicrobials to patients.

Action n° 7:
Promote efforts to analyse the need for new antibiotics into veterinary medicine

….

http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf
Last accessed: 8 May 2014

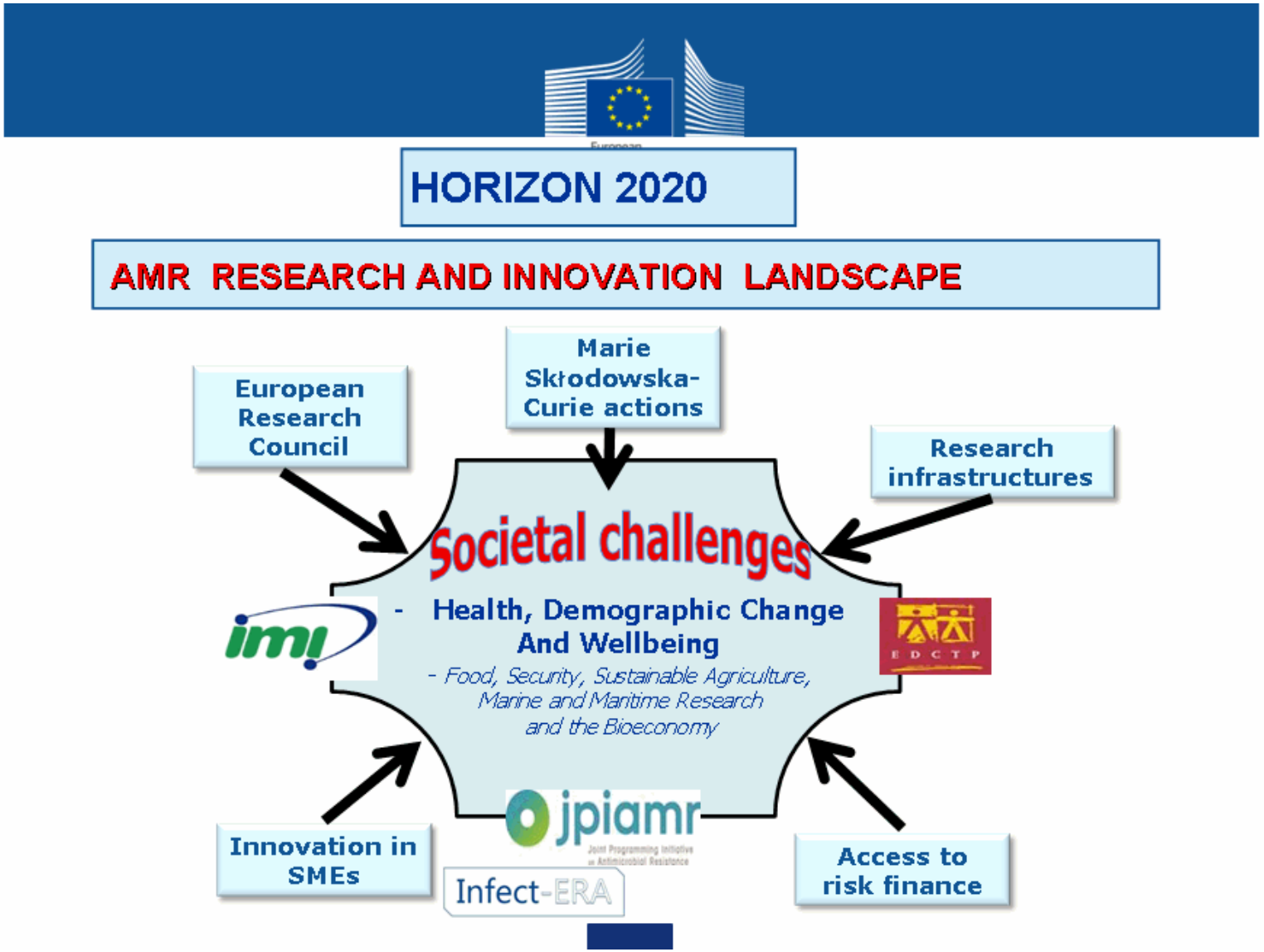
The reaction of the EU…

Action n° 6: To promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antibiotics to patients by:

- *Launching rapidly with EFPIA[12], within the IMI-Joint Undertaking, a programme for research on new antibiotics aimed at improving the efficiency of research and development of new antibiotics through unprecedented open sharing of knowledge.*
- *Establishing an overarching framework agreement with the industry, defining objectives, commitments, priorities, principles and modes of action for public-private collaboration in a longer term perspective. Mobilising adequate resources, within IMI in particular (and its possible successor), FP7 and in the longer term the forthcoming research and innovation programme 2014-2020 (Horizon 2020), in order to support research and development work, based on criteria and modalities adapted to the specific needs and challenges of antibiotic development. Use the flexibility in the current pharmaceutical legislation to give rapid authorisation to new antibiotics and work with stakeholders and the Member States' authorities towards the establishment of adequate market and pricing conditions for new antibiotics.*
- *Ensure conditions for and implement fast track procedures for the marketing authorisation of new antimicrobials.*

http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf
Last accessed: 8 May 2014

Concerted actions…



From van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

Examples of direct ongoing aids to academic/industrial research (FP7)

European Commission

Current activities on Diagnostic test development

COOPERATION

Chips 4 Life

Rapid Microbiologic Diagnostics

C4L aims to develop rapid diagnostic tests to link antibiotic prescription with evidence-based diagnosis. Combining the Multiplex Ligation-dependent Probe Amplification (MLPA) and microfluidic technologies will allow determination of **viral or bacterial origin**, as well as bacterial **resistance** mechanisms.

PARCIVAL

PARCIVAL aims to develop an integrated and automated multi-analyte lab-on-a-disk platform for the fast and reliable sample in -> answer out diagnosis of highly infectious respiratory pathogens, **resistance patterns and biomarkers for individual severity** of the infection.

From van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

Examples of direct ongoing aids to academic/industrial research (FP7)

European Commission

Current activities on Diagnostic test development (INNO-2)

COOPERATION

ROUTINE

ROUTINE aims to develop a test that will integrate sample preparation, DNA amplification and a fluorescent-based read-out on one platform to allow direct detection of **bacteria causing UTI and the associated antibiotic resistances** within 30 min.

Rid RTI

RiD-RTI aims to develop and evaluate three diagnostics products for the rapid (< 2 hrs) diagnosis of CAP, HAP/VAP and ORTIs. The diagnostics products will be 'near patient', reliable, cost-effective and user friendly allowing for **detection, identification, and quantification (for selected targets) and molecular drug susceptibility testing of RTIs**.

From van Hengel and D. Dixon, Meet the Experts: Antimicrobial resistance research, supported by funding from the EU and the US NIH/NIAID, ECCMID 2014, 13 May 2014.

Public/Private shares in Europe

Public-private partnerships

- Pooling expertise, knowledge and resources
- Developing incentives to address major unmet medical needs
- Providing a neutral trusted platform to align public and private interests

An opportunity to combine public and private resources for new antimicrobials

efpia
European Federation of Pharmaceutical Industries and Associations

IMI in action …

- €2 billion 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: 8 May 2014

Some IMI ongoing projects in Infectious Diseases…

- **ADVANCE**
  Accelerated development of vaccine benefit-risk collaboration in Europe
  €10,754,061.-
- **BioVacSafe**
  Biomarkers for Enhanced Vaccine Immunosafety
  € 30,200,000.-
- **COMBACTE ***
  Combatting Bacterial Resistance in Europe
  € 250,484,591.-
- **ENABLE ***
  European Gram-negative Antibacterial Engine
  €100,885,487.-
- **RAPP-ID**
  Development of rapid point-of-care test platforms for infectious diseases
  € 14,448,76.-
- **TRANSLOCATION ***
  Molecular basis of the bacterial cell wall permeability
  € 29,328,006.-

~ 436 x 10^6 € out of which about half is paid by the EU
= 215 x 10^6 €

Grouped under the ND4BD (New Drugs for Bad Bugs) cupola

http://www.imi.europa.eu/
Last accessed: 8 May 2014

What are IMI costs comparing to antibiotic expenses in Belgium

Tableau 3.1.1 Prescriptions des médecins généralistes, spécialistes et dentistes : Répartition entre les groupes anatomiques principaux en 2010

1er niveau ATC	Groupe anatomique principal	Montant brut (milliers EURO)	%	Montant net (milliers EURO)	%	Part personnelle (milliers EURO)	%	DDD/1000 hab/jour	%
J	ANTIINFECTIEUX A USAGE SYSTEMIQUE	318.063	9,8%	263.065	9,7%	54.998	10,4%	31,9	2,7%

http://www.inami.be/drug/fr/statistics-scientific-information/pharmanet/pharmaceutical-tables/pdf/2010/tables2010.pdf
Lats accessed: 8 May 2014

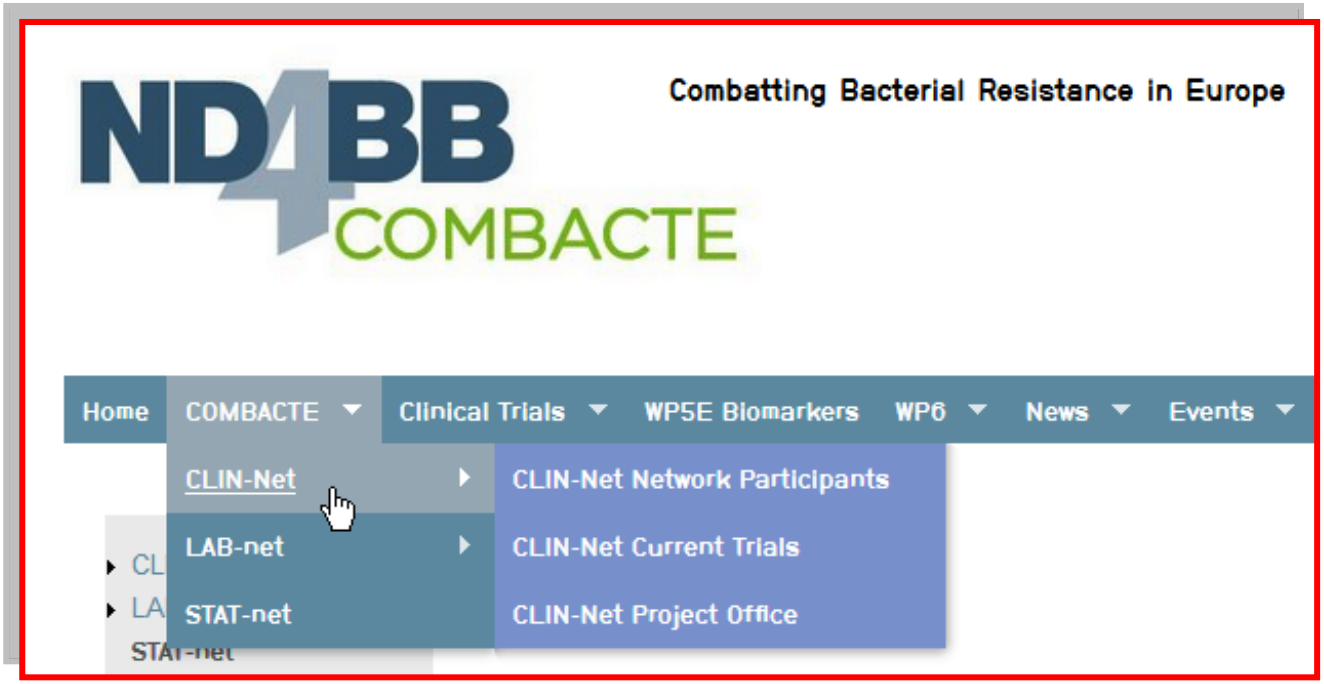
which is about what we paid in Belgium for all antibiotics reimbursed in the community

~ 436 x 10^6 € out of which about half is paid by the EU
= 215 x 10^6 €

Grouped under the ND4BD (New Drugs for Bad Bugs) cupola

http://www.imi.europa.eu/
Last accessed: 8 May 2014

How can you COMBACTE ?



https://www.combacte.com/
Last accessed: 8 May 2014

How can you COMBACTE ?

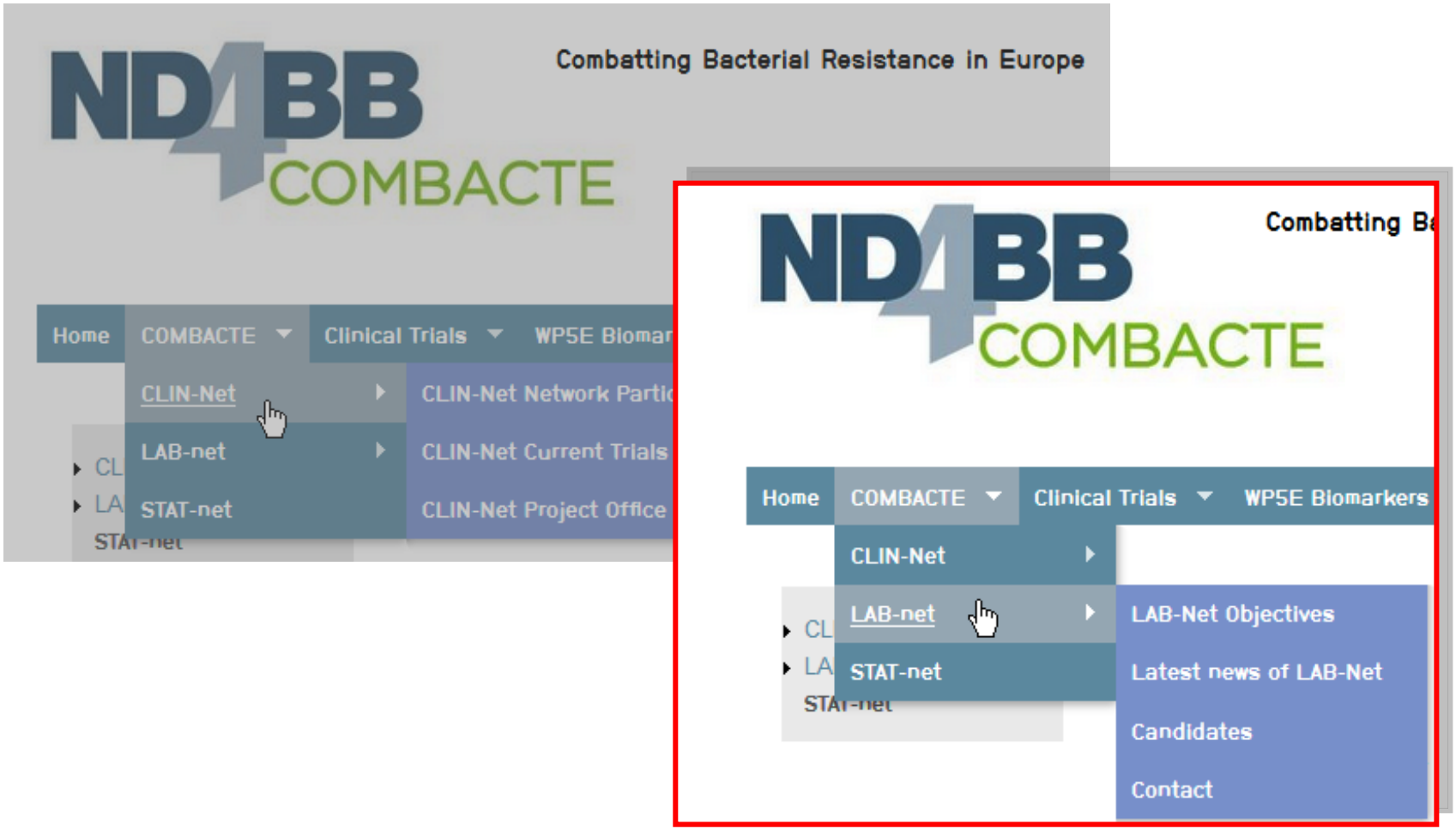
CLIN-Net Network Participants

As of April 2013, 261 clinical sites in 32 countries have expressed an interest in joining CLIN-Net. In the third quarter of 2013, these sites will be approached with an explorative questionnaire to establish their current experience with clinical trials, their facilities to conduct trials and their need for (additional) GCP training.

Further auditing, site visits and certification will start in 2014.

https://www.combacte.com/?q=node/32
Last accessed: 8 May 2014

How can you COMBACTE ?



https://www.combacte.com/
Last accessed: 8 May 2014

Can you ENABLE ?

More specifically, the project is working towards:

- identifying **three antibacterial lead molecules** which, following extensive testing, have been identified as having **promising antimicrobial activity**;
- identifying **two antibacterial clinical candidate molecules**. At this stage, the final structure of the molecule is set. The candidate then undergoes more preclinical testing before being studied in humans;
- progressing **at least one compound into** preclinical and phase 1 clinical studies, i.e. **early clinical safety testing in humans**.

In a nutshell, the unprecedented scientific collaboration carried out within the ENABLE project will **improve early-stage antibacterial drug discovery** and advance the progress of **new medicines** through the scientific pipelines so that they are **ready for testing in patients**.

enableprojectfactsheet.pdf
available from http://www.nd4bb-enable.eu/
Last accessed: 8 May 2014

Will you join ENABLE ?

The new antibiotics programmes run by the ENABLE platform will come from European research institutions and small and medium-sized enterprises (SMEs). There are initially seven programmes in the ENABLE portfolio. In addition, a programme arising from an alliance between GSK and Sanofi will also make use of the platform.

This portfolio of programmes will be expanded through open calls for additional antimicrobial programmes from the academic and SME community, to create **the most promising portfolio of drug candidates to treat Gram-negative infections**. The project has funding to advance a minimum of eight programmes through early testing, with the ultimate goal of obtaining at least one drug molecule for early testing in humans by 2019.

enableprojectfactsheet.pdf
available from http://www.nd4bb-enable.eu/
Last accessed: 8 May 2014

Are you Rapp-ID ?

Development of Rapid Point-of-Care Test Platforms for Infectious Diseases

http://www.ua.ac.be/download.aspx?c=RAPP-ID&n=96887&ct=96873&e=281446
Last accessed: 8 May 2014

Are you Rapp-ID ?

RAPP-ID
Development of Rapid Point-Of-Care Test Platforms for Infectious Diseases

Participant Name	IMI Funding in €
Cardiff University	75 379
Interuniversitair Micro-Electronica Centrum vzw	229 726
Katholieke Universiteit Leuven	366 540
Kungliga Tekniska Hoegskolan	1 236 972
LIONEX GmbH	476 900
Microfluidic ChipShop	467 400
Mobidiag Oy	306 000
Q-linea	430 680
Universite De Geneve	62 100
Universiteit Antwerpen	1 390 684
Universiteit Gent	486 900
University of Cambridge	492 654
University of Twente	364 003
Uppsala University	442 500
TOTAL	6 828 438

http://www.imi.europa.eu/sites/default/files/uploads/documents/2nd%20call/RAPP-IDFundingperParticipant.pdf
Last accessed: 8 May 2014

IMI Call 11 is on its way…

http://www.imi.europa.eu/sites/default/files/uploads/documents/11th_Call/11thCallText_updated20122013.pdf
Last accessed: 9 May 2014

IMI Call 11 is on its way…

TOPICS 6 AND 7:
NEWDRUGS4BADBUGS (

6. ND4BB TOPIC
DEVELOPMENT (
MOLECULES
INFECTIONS DUE
NEGATIVE PATHO(

SUBTOPIC 6A: EPID
DEVELOPMENT O
BIS4αPA, FOR THE
AERUGINOSA DIS(

SUBTOPIC 6B: CLINICA
BREAKING BET
COMBINATION W
AGAINST SEVERE
NEGATIVE PATHO(

INDICATIVE BUDGET

The indicative EFPIA in-kind contribution is up to EUR 19 000 000

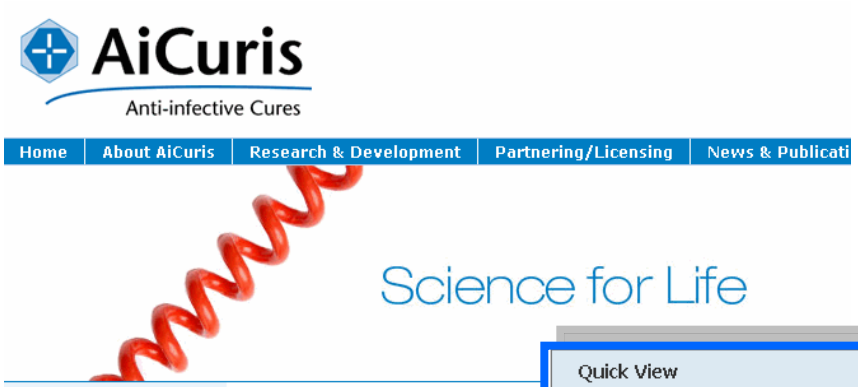
The IMI JU financial contribution will be a maximum of EUR 19 900 000

The total budget is to be divided along the following WPs:

- WP5: Epidemiological study on cUTI
- WP6A: Multiple dose escalation study
- WP6B: Drug-drug interaction study AIC499 with BLI
- WP6C: Mass balance/metabolite identification study
- WP6D: TQT prolongation study
- WP6E: Drug-drug interaction study AIC499/BLI with other drugs
- WP6F: Renal impairment study
- WP6G: Phase 2 PoC trial in cUTI
- WP6H: Phase 2 PoC trial in cIAI
- WP6I: WP6B coordinating centre

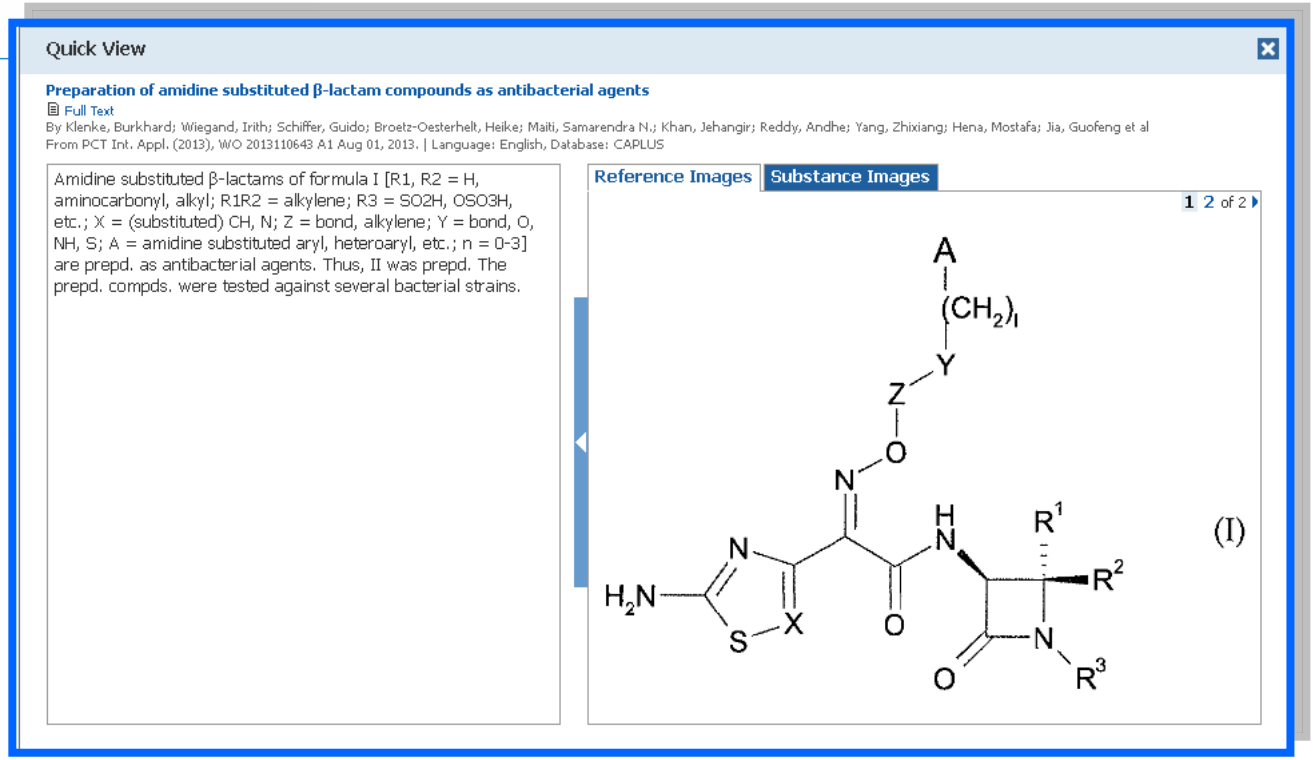
http://www.imi.europa.eu/sites/default/files/uploads/documents/11th_Call/11thCallText_updated20122013.pdf
Last accessed: 9 May 2014

But what is AIC499 ?



http://www.aicuris.com/2/Contact.htm
Last accessed: 9 May 2014

AIC stands for AiCuris



https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
Last accessed: 9 May 2014

But it goes much beyond IMI …

EUROPEAN COMMISSION

MEMO

Brussels, 15 November 2013

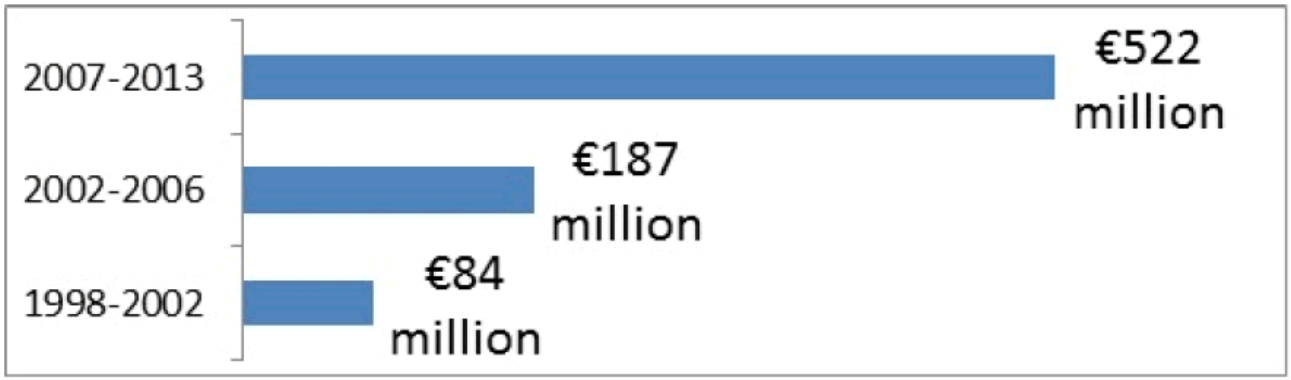
EU launches new research projects to combat anti-microbial resistance

http://europa.eu/rapid/press-release_MEMO-13-996_en.pdf
Last accessed: 8 May 2014

But it goes much beyond IMI …

EU launches nev
microbial resistan

The rising awareness of the AMR threat is reflected in a six fold increase in the amount being invested, from some €84 million during the EU's 1998-2002 research programme to about €522 million for the 2007-13 period.



Most of the EU investment is used to support collaborative projects i.e. international research and innovation teams involving the most capable players from across Europe and abroad.

http://europa.eu/rapid/press-release_MEMO-13-996_en.pdf
Last accessed: 8 May 2014

To be transparent to all of you …

EU la
microb

NOFUN Novel antifungals to treat resistant organisms	UK (coordinator), DE, ES, SE	Michael Bromley, University of Manchester	mike.bromley@manchester.ac.uk	€ 4.550.286
MON4STRAT Therapeutic Beta-Lactam Monitoring for Stratified Treatment of hospital-acquired pneumonia, improved dose-dependent efficacy, decreased treatment duration, and prevention of emergence of resistance	BE (coordinator), FR, ES, US, EE	Bernard Joris, Université de Liege	bjoris@ulg.ac.be	€ 5.988.941
PHAGOBURN Evaluation of phage therapy for the treatment of *Escherichia coli* and *Pseudomonas aeruginosa* burn wound infections (Phase I / II clinical trial)	FR (coordinator), BE, CH	Patrick Jault, Ministère de la Défence	patrick.jault@sante.defense.gouv.fr	€ 3.838.422

http://europa.eu/rapid/press-release_MEMO-13-996_en.pdf
Last accessed: 8 May 2014

To be transparent to all of you …

EU la
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NOFUN
Novel antifungals to tre
resistant organisms

MON4STRAT
Therapeutic Beta-Lacta
Monitoring for Stratifie
Treatment of hospital-
acquired pneumonia,
improved dose-depend
efficacy, decreased
treatment duration, an
prevention of emergen
of resistance

PHAGOBURN
Evaluation of phage
therapy for the treatme
of *Escherichia coli* and
Pseudomonas aerugino
burn wound infections
(Phase I / II clinical trial)

MON4STRAT

Why monitoring β-lactams on line ?

Paul M. Tulkens, MD, PhD
on behalf the
Louvain Drug Research Institute &
the **Louvain Toxicology and Applied Pharmacology**
Université catholique de Louvain,
Brussels, Belgium

MON4STRAT kick-off meeting
Liège, Belgium, 31 March 2014

slides available from http://www.facm.ucl.ac.be/facm-conferences.htm

http://europa.eu/rapid/press-release_MEMO-13-996_en.pdf
Last accessed: 8 May 2014

Summary / Discussion

- 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 aven in infectious diseases (think about anti-HIV and, more, recently about the novel anti-Hepatitis C drugs)
- In face of the vaccuum of new commercializations, 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.
- 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 paid 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)

To conclude…

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

Back-up

Where does the money come from ?

1. Market

Table II. Facts on Small Pharma with Antibiotic Drug Candidates in Phase III

Name (Ticker)	Market Cap 02-May-2014	52-week high	02-May-2014 price	Pull Back	2016 revenue estimates
Actelion (OTCPK:ALIOF)	11.1 B	106.1	99.41	6%	2.2 B
Cubist (CBST)	5.4 B	82.12	71.46	13%	1.7 B
The Medicines Co. (MDCO)	1.69 B	41.28	26.46	36%	950 M
Durata (DRTX)	359 M	16.99	13.49	21%	100M
Cempra (CEMP)	304 M	15.39	9.14	39%	50M
Tetraphase (TTPH)	270 M	17.74	10.50	41 %	0
Achaeogen (AKAO)	230 M	19.69	13.76	30%	0

Seeking-α
http://seekingalpha.com/article/2190903-cempra-dont-throw-the-baby-out-with-the-bathwater?isDirectRoadblock=false&uprof=14
Last accessed: 8 May 2014