EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA activities in the fight against AMR
Human medicines aspects

Joint PCWP/HCPWP meeting on AMR, 19 September 2017

Presented by Dr. Marco Cavaleri

Head of Office, Anti-infectives and Vaccines, European Medicines Agency

On-going harmonization efforts

- TATFAR (Trans-Atlantic Task Force on Antimicrobial Resistance);
  - provides an excellent tool to foster discussion between EMA and FDA in the area of antibacterial drugs development. Now expanded to Canada.
- interaction on development plans for antibiotics:
  - new development plans (scientific advice stage) are mutually discussed between FDA and EMA on a monthly basis.
  - EMA-FDA Consultative Advice procedure allows sponsors to request scientific advice from one regulatory agency and concurrently notify the other regulatory agency of the request
  - Initiatives for setting up clinical trials networks that that could run pivotal studies according to standardized protocols agreed by EMA&FDA

On-going harmonization efforts

7 September 2016
European Medicines Agency

Meeting Summary

Tripartite meeting held between the EMA, FDA and PMDA at the EMA, London, on 1-2 September 2016 to discuss regulatory approaches for the evaluation of antibacterial agents

On-going harmonisation efforts
FDA-EMA-PMDA meeting in Vienna April 2017

- Areas were identified where a move to convergence was agreed.
- Some aspects of clinical development programs for drugs intended to treat patients infected with multi-drug resistant bacteria were agreed.
- Areas were identified where currently differences remain, e.g. primary endpoint for CAP. Further scientific discussion and sharing of information may help to achieve convergence in those areas.

CURRENT DIFFERENCES DO NOT PREVENT AN EMA-FDA AGREED SINGLE DEVELOPMENT PLAN

On-going harmonisation efforts
FDA-EMA-PMDA meeting in Vienna April 2017

EMA, PMDA, and FDA will be working to update guidance documents to reflect the agreed areas of convergence.

In the meantime, EMA, PMDA, and FDA will provide advice to drug developers that is consistent with the agreements reached. Prior advice on drug development is not impacted.

NEXT MEETING PLANNED FOR OCTOBER 2017 in JAPAN

Examples of agreement - cUTI Primary Endpoint

	FDA	EMA
Primary endpoint	**Combined clinical and microbiologic response (<1x10^{4}CFU/mL)** at TOC at least 5 days post completion of therapy; OR co-primary 5 days post-randomisation before PO switch and 7 days post-completion of therapy	**Microbiological response (<1x10^3 CFU/mL)** at TOC 7 days post-completion of therapy, regardless of whether there was an IV/PO switch (based on requirement for **≥10^5 CFU/mL** at baseline)

Agreed proposal for convergence: Clinical response and Microbiological response with a microbiological reduction cut-off at 1x10^3 CFU/mL

Examples of agreement – cUTI study population

	FDA	EMA
Population	At least 30% patients with pyelonephritis (for an indication including pyelonephritis)	Separate trials in cUTI and pyelonephritis OR limit % with pyelonephritis and stratify

Agreed proposal for convergence: instead of conducting separate trials in cUTI and pyelonephritis, include both with at least 30% cUTI patients and at least 30% pyelonephritis patients

Alternative therapies/ approaches

Bacteriophages

- Regulatory issues related to the need of changing the composition of the medicinal product over time. Lack of solid clinical data. *EMA Workshop held on 8 June 2015*

Monoclonal antibodies

- Variety of targets. Important to have proof of concept for specific activities. Few products in advanced stage.

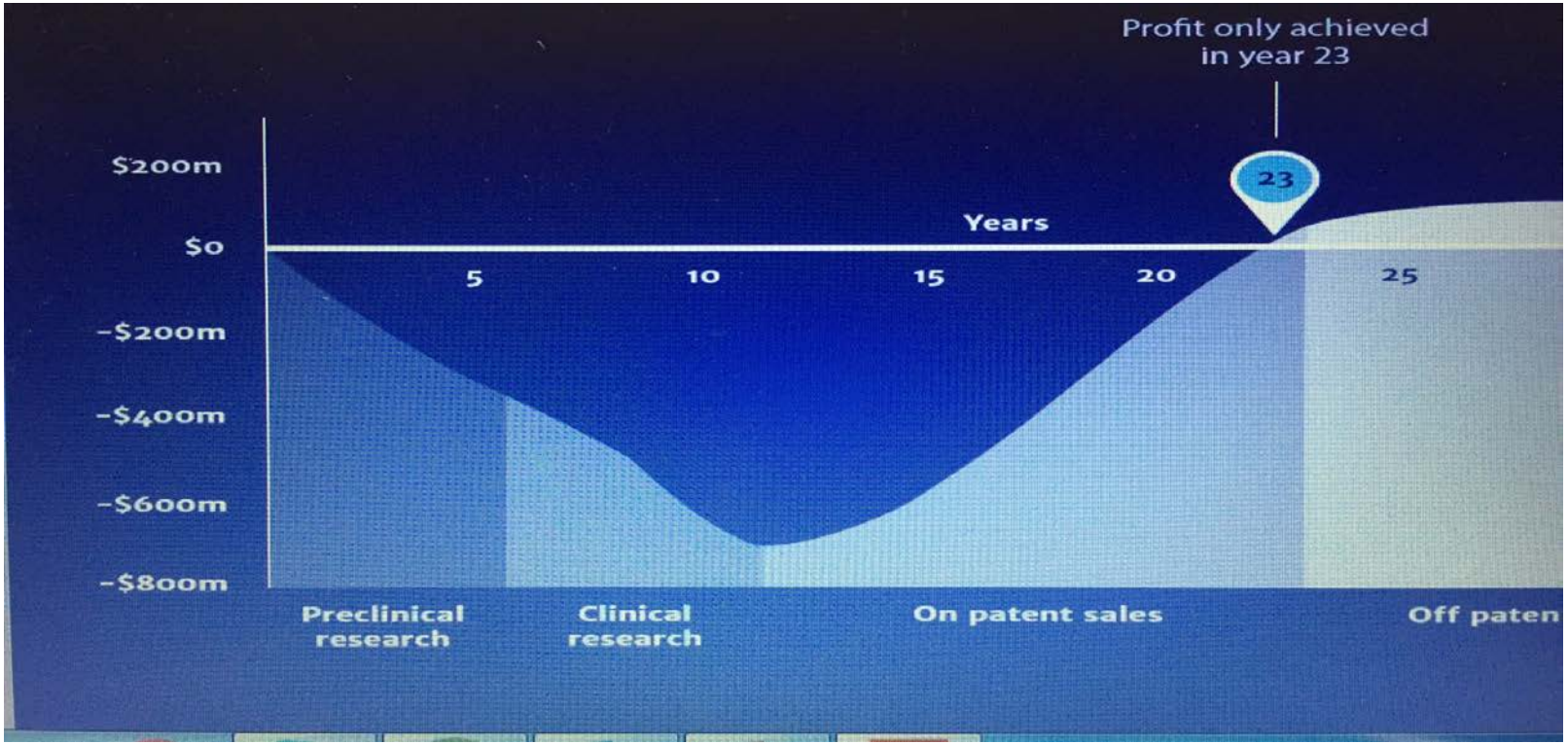
Vaccines for healthcare associated infections

- Scientific difficulties acknowledged. Target of future interactions with FDA. High potential impact in case of success.

Combination therapy for prevention of resistance

- Important to explore the regulatory options to make such approaches viable

Challenge of Antibiotic Reimbursement



O'Neill Report 2016

WE NEED NEW BUSINESS MODELS

Push and pull incentives:

- **“Push”** incentives that support discovery and early phases of development, e.g. JPIAMR, EC grants, CARB-X
- “**Pull**” incentives that **delink** payment from prescribing volume i.e. encourage **stewardship, e.g.:**
  - A fully delinked market entry reward (no sales-based income)
  - A market-priced market entry reward (some sales-based income)
- Several initiatives in the EU and US to discuss approaches, e.g. TATFAR, Duke-Margolis PAVE, DRIVE-AB
- Long-term supply issues, e.g. forgotten antibiotics

HTA challenges for antibiotics

- Concerns that current HTA/payer methods may not capture the full range of benefits of antibiotics, including value of tackling AMR
- 2 key challenges:
  1. Clinical trials typically designed to demonstrate non-inferiority, whereas HTA bodies generally require demonstration of clinical superiority
  2. HTA bodies/payers generally do not offer opportunity to demonstrate public heath benefits of antibiotics, including tackling rise in AMR

EMA role on prudent use for human medicines

- Old and new antibacterial agents need to be preserved and used rationally, but regulators should not dictate criteria for clinical practice, e.g. by defining line of use for reasons other than B/R
- A pragmatic approach towards rapid diagnostics in the context of product information needs to be retained at this stage
- Difficult to take clear-cut regulatory position on off-label use which in many cases can be justified
- Modernisation of SmPCs of “old antibiotics” is the most valuable contribution to rational use, i.e. ensuring that updated Product information on indications of use, posology, is provided in a harmonised way for all EU healthcare professionals

Completed referrals for antibacterials

Approved name	INN	Associated names	Opinion date	EC decision date
Ciproxin	ciprofloxacin		24.07.2008	07.10.2008
Augmentin	amoxicillin+clavulanic acid		19.01.2009	19.10.2009
Meronem	meropenem		23.07.2009	15.10.2009
Tazocin	piperacillin/tazobactam	Tazobac, Tazocel, Tazonac	21.10.2010	21.02.2011
Fortum	ceftazidime	Cefortam,. Glazidin, Panzim, Solvetan	21.10.2010	13.01.2011
Tienam	imipenem/cilastatin	Conet, Imipem, Primaxin, Tenacid, Zienam	06.12.2010	10.03.2011
Tavanic	levofloxacin	Tavanic and associated names	24.05.2012	31.07.2012
Zinnat	cefuroxime axetil	Cefuroxima Solasma, Cefuroxima Allen, Cefuroxima Duncan, Elobact, Nivador, Oraxim, Selan, Tilexim, Zinadol, Zipos, Zoref	24.05.2012	23.08.2012
Zinacef	cefuroxime sodium	Curocef, Curoxim, Curoxim Monovial, Curoxima, Curoxime, Zinnat, Zinocep, Zinocep Vena	24.05.2012	10.09.2012
Targocid	teicoplanin	Targocid, Teicomid	30.05.2013	12.09.2013
Rocephin	ceftriaxone		23.01.2014	21.03.2014
Colistin	Polymyxin-containing		23.10.2014	16.12.2014
Vancocin	vancomycin		18.05.2017	

Post-authorisation activities: other considerations

- The value of the inclusion of clinical breakpoints in the SmPC of antibacterial agents is currently under discussion considering the difficulties in keeping product information updated and aligned across EU for both originators and generics

- Surveillance studies to monitor emergence of resistance are included in the RMP, but they don't refer to safety issues and not obvious to take action on B/R based on emergence of resistance

One health topics:

- The impact of veterinary use of medicines on human health in terms of AMR will remain a relevant area for interaction and discussion
- Participation of IDWP/EMA in the AMEG group activities, e.g. scientific advice on restriction of use of antibiotics in veterinary medicine
- Advice from IDWP on human aspects to CVMP AWP on specific topics, e.g. reflection paper on ‘the use of Aminopenicillins (+inhibitor combinations) in animals in the EU: development of resistance and impact on animal and human health’
- Common issues related to innovative medicines such as phages

Key areas for future focus

- Continuous evolution of regulatory guidance based on experience gained and need to cover also for alternative approaches
- Strengthened international interactions
- Need of new business models that could contemplate pull incentives beyond the “funding research” strategy so far adopted in the EU
- Support to initiative such as the clinical trials network in order to make clinical development easier and faster
- Discussion with HTAs about evidence from limited clinical development to address public health value of new antibacterials

Any questions?

Further information

Dr Marco Cavaleri
Head of Anti-infectives and Vaccines, Human Medicines Evaluation Division

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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