Driving Innovation by Delinking Investment in Antibiotic R&D from Sales Revenues

Kevin Outterson

Boston

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DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

BOSTON UNIVERSITY

CHATHAM HOUSE The Royal Institute of International Affairs

CARB-X

Acknowledgements

- Chatham House Working Group on

New Business Models for Abx (2013-present)

- DRIVE-AB (IMI/ND4BB) (2014-present)
- Longitude Prize (rapid POC abx dx) (2014-present)
- Consultancies with companies (Roche/Genentech/PureTech) but all fees donated to Habitat for Humanity or MSF
- CDC Working Group on AMR (2012-2014)
- Eastern Research Group Report for US DHHS (2011-2014)
- CARB-X (2016-2021)

All comments today are my own opinions and

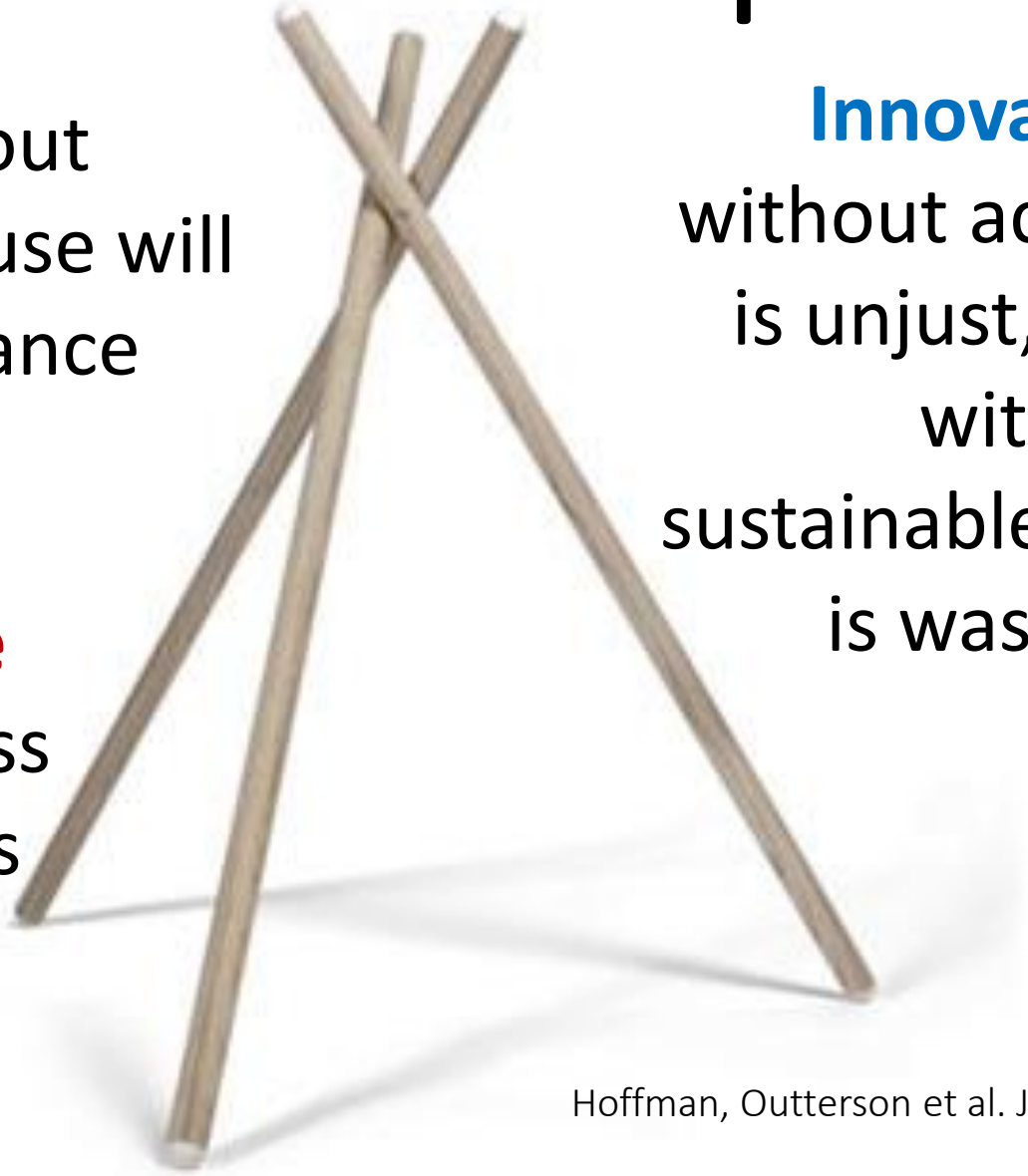
do not necessarily reflect the positions held by my colleagues

The Antibiotic Tripod

Access without sustainable use will speed resistance

Innovation without access is unjust, and without sustainable use is wasteful

Sustainable use constrains access and undermines innovation



Hoffman, Outterson et al. JLME 2015

The players

	Pre-Clin	P1/2	P2/3	Market
US BARDA	+++	+++	+++	
US NIAID	+++	+++	++	
EC (JPIAMR, IMI, FP6, FP7, H2020)	+++	+++	+++	
Wellcome Trust (UK)	+++	++		
Other Governments (e.g., UK AMRC, UK-China Fund)	+	+		
FDA		+++	+++	
EMA		+++	+++	
PMDA		+	+	
SE (2H09 EU Presidency)				+++
Chatham House (2014-15)				+++
WHO Global Action Plan (2014+)				+
US PCAST, CARB, & PACCARB (2014+)				++
DRIVE-AB (IMI, 2014-17)				+++
UK (O'Neill AMR Review, 2014-16)				+++
Duke-Margolis (2016+)				+++
NE (1H16 EU Presidency)				+++
DE (2017 G20 run-up)				++

Funding & resources

Updated Guidance

Major reports

UNGA 2016

+++: Strongly engaged; ++: Visibly engaged; + Early engagement &/or limited details`

Convergence of principles

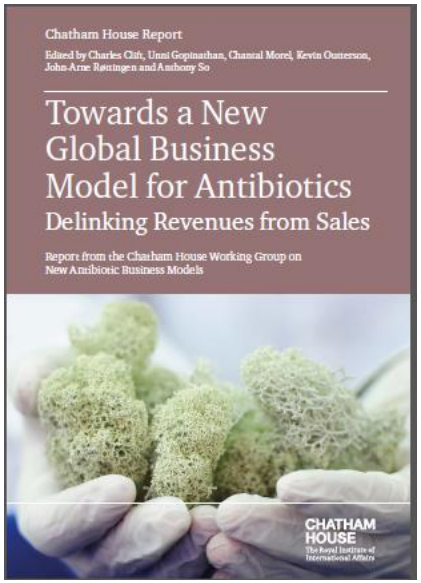
G7 GERMANY 2015

WORLD ECONOMIC FORUM

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

- Need for both "push" and "pull" mechanisms
- Delinkage (i.e., revenues delinked from volumes sold)
- Access and sustainable use are integral
- Global collaboration and financing necessary



OECD
BETTER POLICIES FOR BETTER LIVES

World Health Organization

DNDi
Drugs for Neglected Diseases *initiative*

DRIVE AB
RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

EUROPEAN COUNCIL

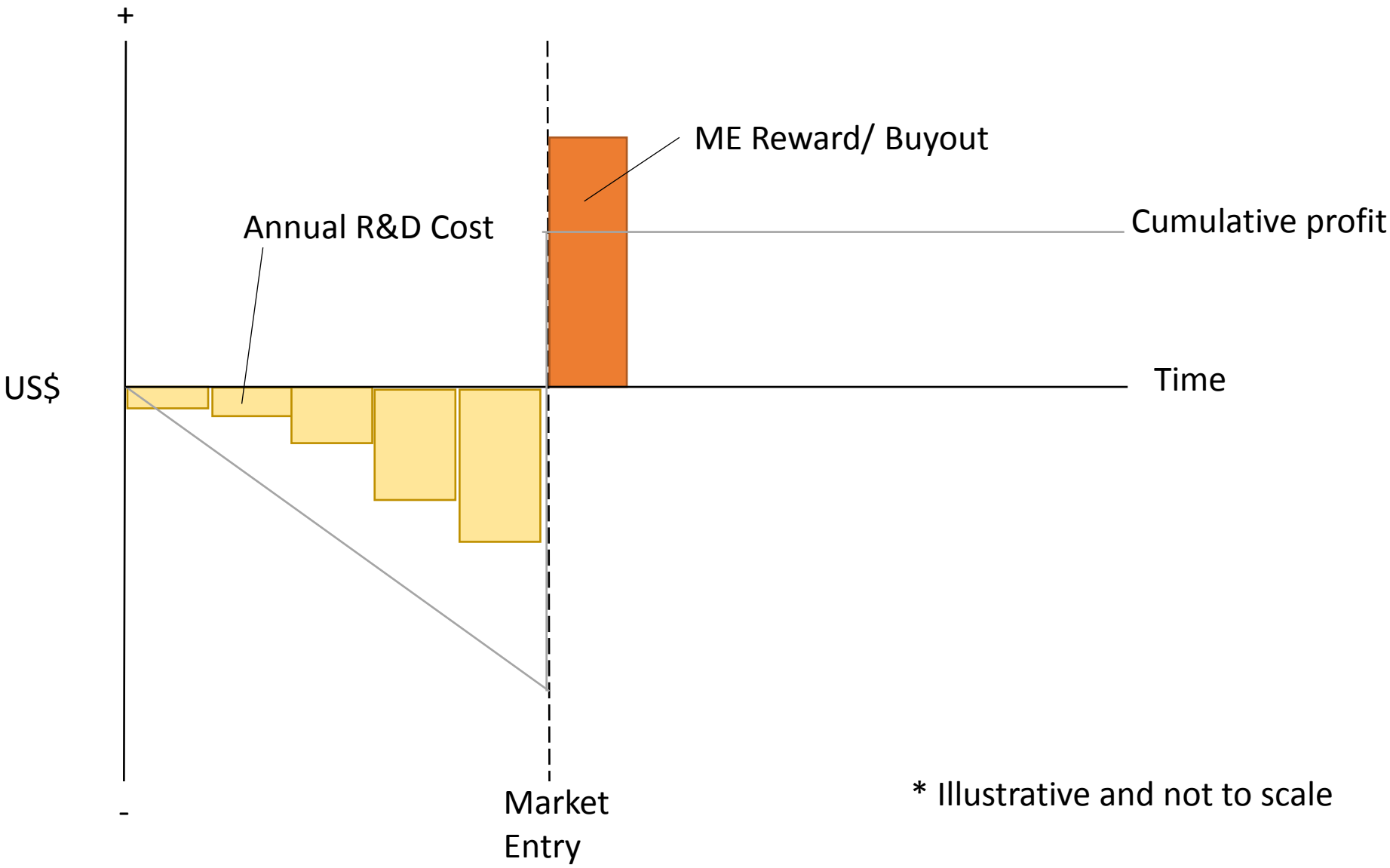
June 17, 2016: "Actively engage in initiatives and proposals to implement a new business model to bring new antibiotics to the market, including models in which investment costs or revenues are de-linked from sales volumes."

Definitions

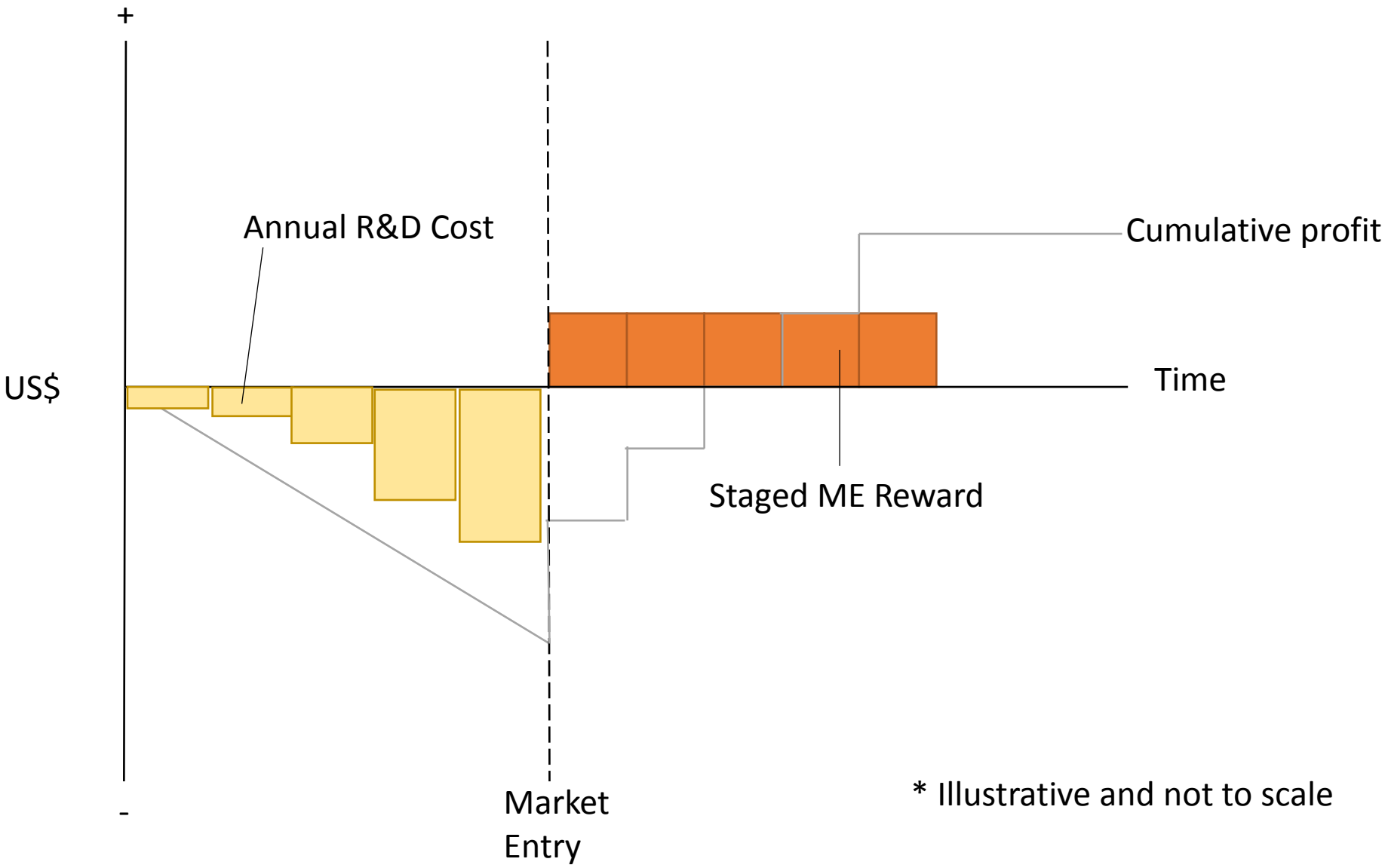
Market Entry Reward: A payment to developers of new antimicrobials for prospectively defined unmet needs

- Conditions of acceptance (promotion, global access, regulatory, etc)
- Full IP buyout and Fully De-linked MER (single payment) considered and not developed further
- Fully de-linked (staged) = Shared Risk Model
- Partially de-linked (single or staged payment) considered

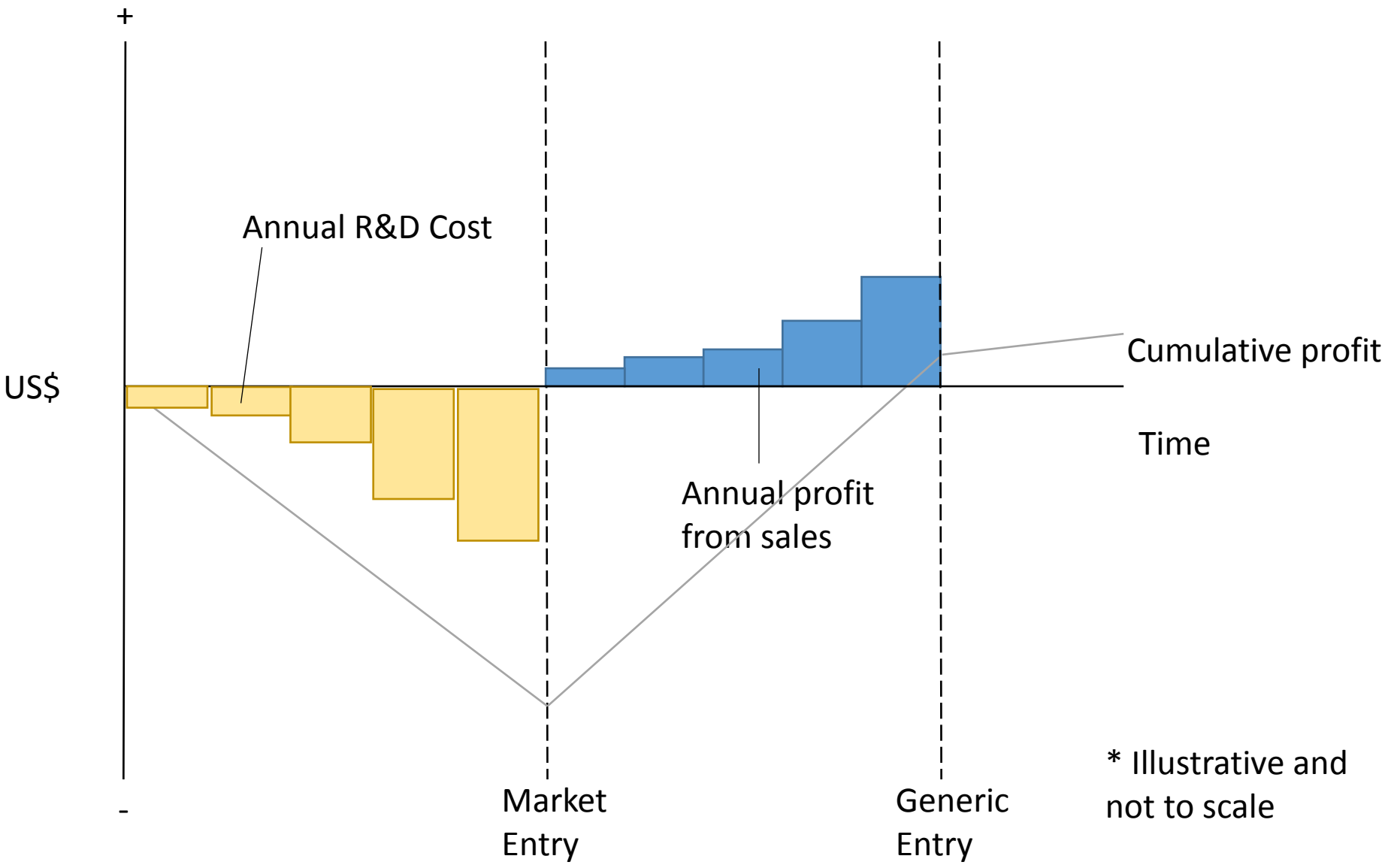
Market Entry Reward Models: Fully De-linked (Single Payment)



Market Entry Reward Models: Fully De-linked (Staged)



Status quo


+
US$
Annual R&D Cost
Cumulative profit
Time
Annual profit
from sales
-
Market
Entry
Generic
Entry
* Illustrative and
not to scale

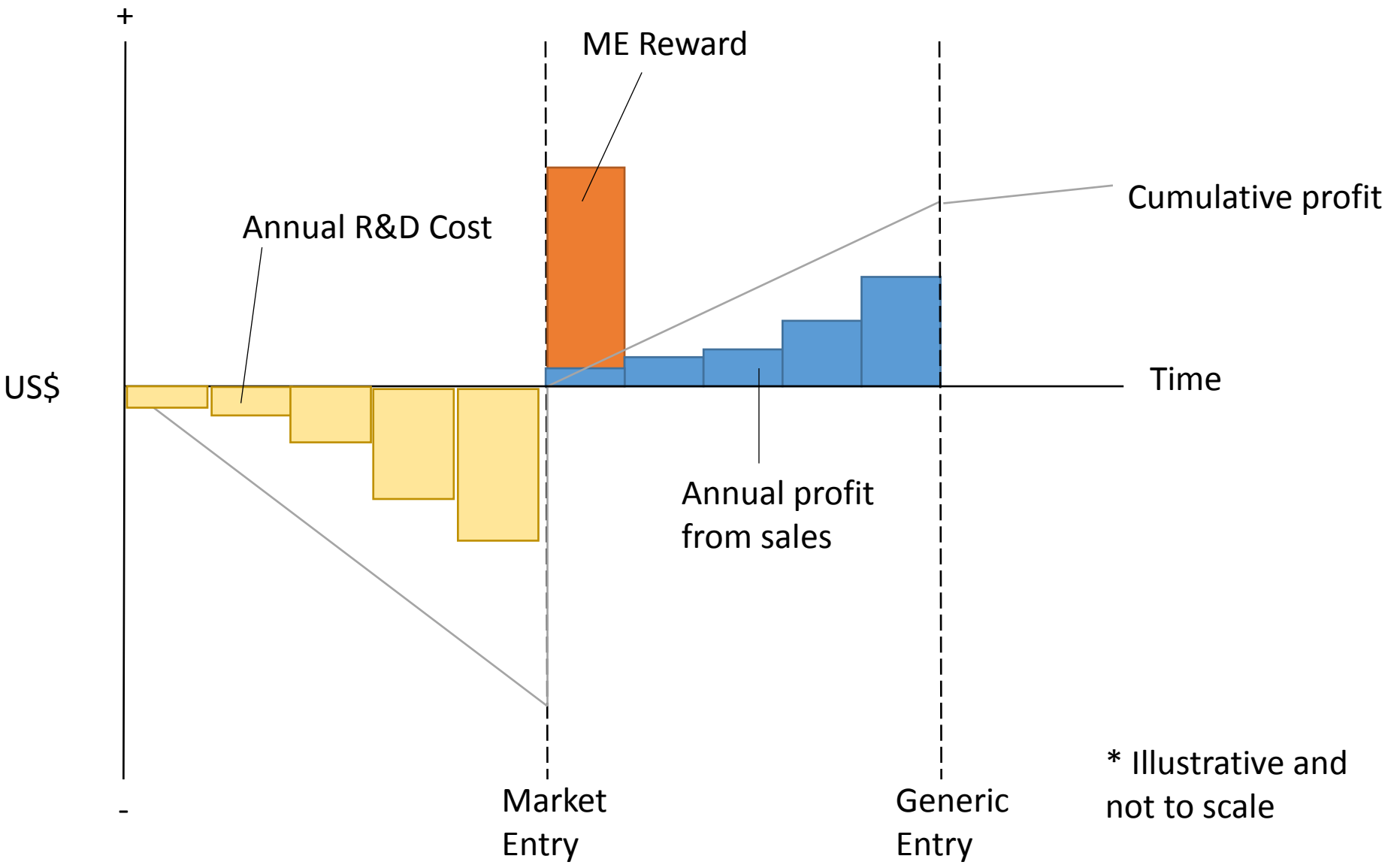
Market Entry Rewards: Fully De-linked

- No developer revenue derived from sales
- Significant funding required (AMR Review: US$4B/antibiotic; Sharma/Towse: US$3B/antibiotic)
- Staggered payment MER = Shared Risk model
- Complex post buyout pricing to promote appropriate use and stewardship

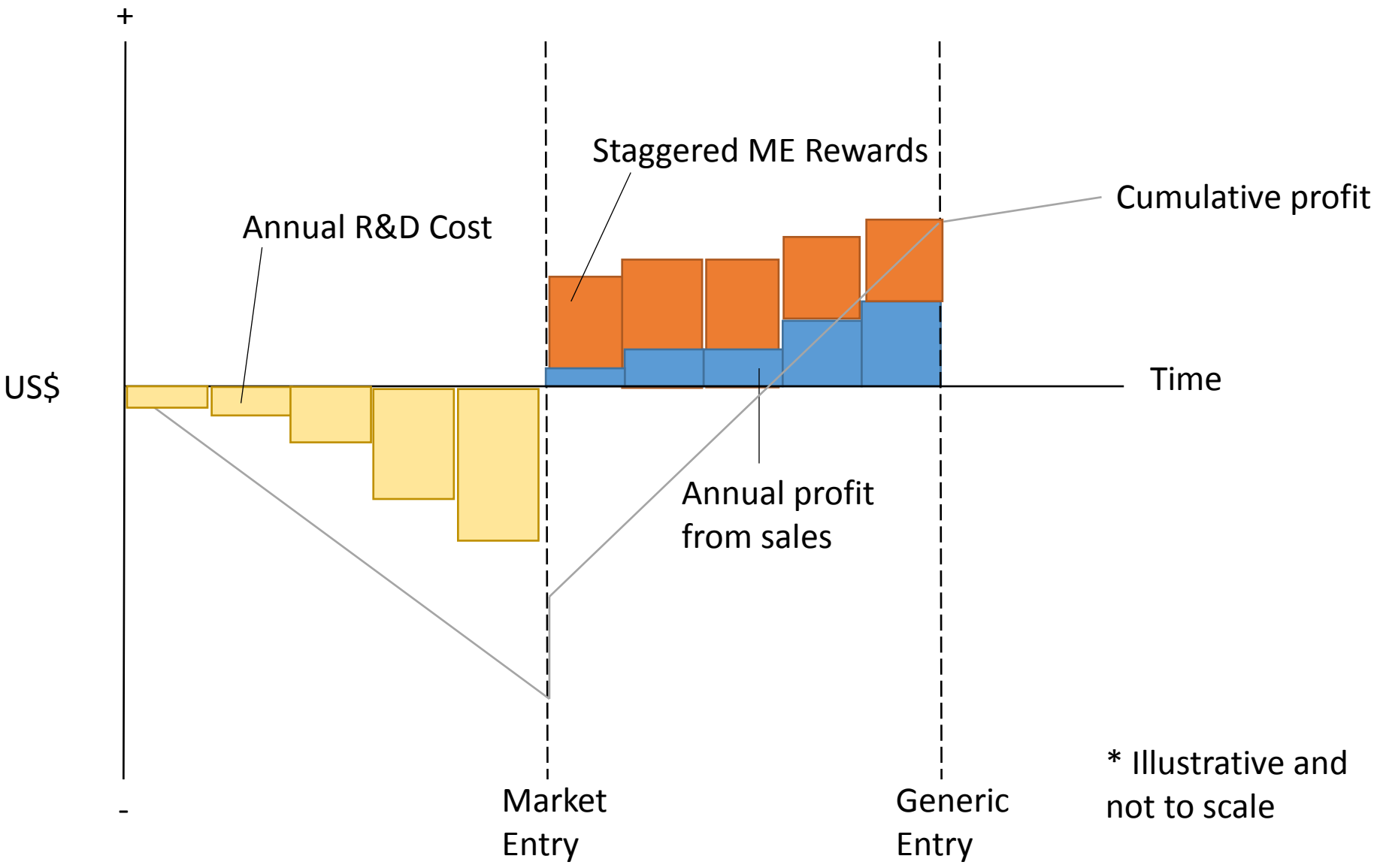
One-time payment:

- Little incentive for further development
  - Outterson Rex – benchmark payments
- Potential supply risk

Market Entry Reward Models: Partially De-linked (Single Payment)



Market Entry Reward Models: Partially De-linked (Staged)



Market Entry Rewards: Partially De-linked

- Partially de-linked model: some developer revenue derived from sales
  - Stewardship and access conditions
- Relatively less funding required (AMR Review: US$1-1.6B/antibiotic) but still attractive since revenue brought forward and some sales profit
- Developer retains some risk and “skin in the game” for further innovation + sustained supply
- Market rewards better, later-approved products
- Based on current pricing/reimbursement systems

Partially De-linked MERs vs Shared Risk Models

Partially de-linked MERs

- Partially de-linked
- Conditions of acceptance (stewardship, access)
- Simple to administer (award MER -> existing pricing and reimbursement system)

Shared Risk

- Fully de-linked (potentially)
- Conditions of participation (stewardship, access)
- “Cap and Collar” model with revenue claw back (potentially)
- New system to administer

Market Entry Rewards

1. Structure
2. Magnitude
3. Adjustments
4. Other rules
5. Funding

Market Entry Rewards

Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach

John H Rex, Kevin Outterson

Lancet Infect Dis 2016; 16: 500–05

AstraZeneca Pharmaceuticals, Waltham, MA, USA, F2G Pharmaceuticals, Eccles, Cheshire, UK, and University of Texas Medical School-Houston, Houston, TX, USA (Prof J H Rex MD); and Boston University School of Law, Boston, MA, USA, and Chatham House, London, UK (Prof K Outterson JD)

Despite the life-saving ability of antibiotics and their importance as a key enabler of all of modern health care, their effectiveness is now threatened by a rising tide of resistance. Unfortunately, the antibiotic pipeline does not match health needs because of challenges in discovery and development, as well as the poor economics of antibiotics. Discovery and development are being addressed by a range of public–private partnerships; however, correcting the poor economics of antibiotics will need an overhaul of the present business model on a worldwide scale. Discussions are now converging on delinking reward from antibiotic sales through prizes, milestone payments, or insurance-like models in which innovation is rewarded with a fixed series of payments of a predictable size. Rewarding all drugs with the same payments could create perverse incentives to produce drugs that provide the least possible innovation. Thus, we propose a payment model using a graded array of benchmarked rewards designed to encourage the development of antibiotics with the greatest societal value, together with appropriate worldwide access to antibiotics to maximise human health.

Structure

- Guaranteed, unambiguous payment upon FDA registration
- Size of payment varies with TPP
- Payment spread over 5 years
- No profits from sales volume
- Conditions for stewardship & global access

Market Entry Rewards

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Magnitude

	Payments from governments	Expected NPV benchmark at commencement of R&D
Sertkaya et al[11]	$919 million (spread over entire R&D process and at registration; USA only)	$100 million
Sharma and Towse[18]	$2·5 billion ($500 per year for 5 years)	$300 million
Review on Antimicrobial Resistance[19]	$2–4 billion (paid 3 years after registration)	Not stated

All values are in US$. R&D=research and development.

Table 1: **Nominal and expected net present value (NPV) estimates of the needed size of antibiotic delinkage payments**

Taking the smallest estimate, roughly adjusted to 2017 dollars = $1b total or a base payment of $200m a year paid for five consecutive years after FDA/EMA registration.

Market Entry Rewards

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Model to provoke debate

- Define one base payment as $200m/yr x 5yr
  - This is the global PROFIT to the developer
  - No other profit permitted; actual sales effectively at cost
- Then this scheme on a global basis…

Requirement	Step earned
FDA & EMA approval, treats a CDC 2013 threat pathogen	1x Base
Treats CDC Urgent pathogen	1x Base
Treats CDC Serious pathogen	0.5x Base
First of a novel class	1x Base
2nd, 3rd, or 4th of a novel class	0.75x, 0.5x, or 0.25x Base

Requirement	Step earned
5th or later of novel class, but offering safety, efficacy or dosing improvement	0.1x Base
Delivery of pediatric commitment	Cost recovery payment
2nd, 3rd, or 4th defined indication for a given agent	0.25x Base for each
Oral dosage form	0.25x Base

[1]Rex & Outterson. LID 2016. It is possible to earn multiple payments, but CDC pathogen category payments can only earned once. Payments need not be concurrent. Defined Indications Novel Class are broadly lumped, not finely divided – a consensus rule may be needed. Slide from Rex.

Model to provoke debate

- Define one base payment as $200m/yr x 5yr
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A spectacular new oral Gram-negative agent would be well rewarded: 3.75 x base in this case

global basis…

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Adjustments

	Annual payment*
Drug approved at US FDA and European Medicines Agency to treat at least one defined infection‡ caused by at least one or more pathogens listed on the CDC 2013 threat assessment as either urgent, serious, or of concern to public health[2]	Base payment†
Has a clinical spectrum of activity on the label that includes one or more urgent pathogens on the CDC 2013 threat assessment§	Bonus equal to one base payment
Has a clinical spectrum of activity on the label that includes one or more serious pathogens on the CDC 2013 threat assessment§	Bonus equal to 50% of a base payment
Is the first approved drug to act via a given mechanism of action¶	Bonus equal to a base payment
Is the second, third, or fourth agent approved to act via a given mechanism of action	Bonus equal to 75% of a base payment for a second agent, 50% for a third agent, or 25% for a fourth agent
Is the fifth or subsequent agent to act via a specific mechanism of action but offers a medically relevant improvement in safety, efficacy, or ease of dosing	Bonus equal to 10% of a base payment
Delivery of agreed paediatric commitment studies‖	Payments based on model or separate contract open to tender
Is approved for a second, third, or fourth defined infection‡ for a specific agent‖	Bonus equal to 25% of a base payment
Approved in oral dosage form‖	Bonus equal to 25% of a base payment

Also consider a much smaller but long-term “market access” payment to support warm mfg base

Adjustments

- Target Product Profile (previous slides)
- Clawback for federal grants & tax credits (assumed in ERG)
- Global coordination

Market Entry Rewards

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Other Rules

- Payment rules must be guaranteed when R&D decisions are made (i.e., grandfathered for > decade)
- Payments cease if drug withdrawn from market or key conditions violated
- Generics may need special rules

Market Entry Rewards

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Funding

1. General taxation
2. Pay or play
3. User fees
4. Transferable exclusivity vouchers (In US only, with guardrails)

2 – AMR Review; 3- Hollis & Ahmed NEJM 2013; 4- Outterson & McDonnell, Health Affairs May 2016

Bottom Line

- Globally coordinated
- Tripod
- Both push & pull
- Billions, not millions
- Sustainable, not short-term

Tweeting antibiotics R&D @koutterson

Research papers at Google Scholar & SSRN

Kevin Outterson
Boston University

DRIVE AB WP2 – Full vs. hybrid models of market entry rewards

Literature on market entry prizes (cont.):

- Wiki article on prizes as an alternative to patents: https://en.wikipedia.org/wiki/Prizes_as_an_alternative_to_patents
- Davis L. (2004). How effective are prizes as incentives to innovation? Evidence from three 20th century contests. DRUID Summer Conference 2004: Elsinore, Denmark. http://www.druid.dk/conferences/summer2004/papers/ds2004-114
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DRIVE AB WP2 – Full vs. hybrid models of market entry rewards

Literature on market entry prizes (cont.):

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- Outterson K. (2014). New business models for sustainable antibiotics. *Chatham House*: London. https://www.chathamhouse.org/sites/files/chathamhouse/public/Research/Global%20Health/0214SustainableAntibiotics.pdf
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- Renwick MJ, Brogan D, Mossialos E. (2016). A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *J Antibio. 69: 73-88.* http://www.nature.com/ja/journal/v69/n2/pdf/ja201598a.pdf
- Rex JH, Outterson K. (2016). Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. *Lancet Infect Dis.* 16(4):500-5. http://www.ncbi.nlm.nih.gov/pubmed/27036356