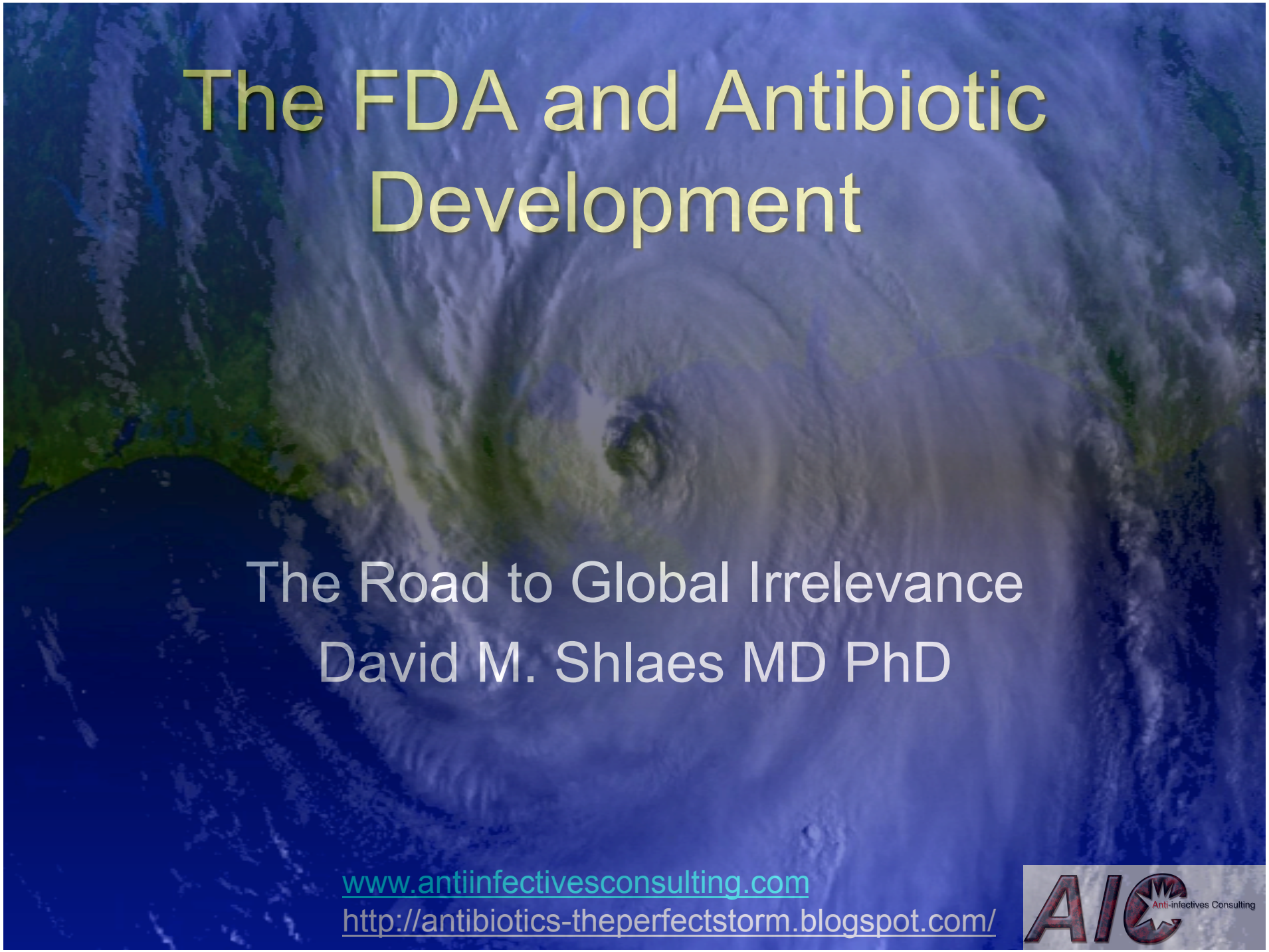
The FDA and Antibiotic Development
The Road to Global Irrelevance
David M. Shlaes MD PhD
www.antiinfectivesconsulting.com
http://antibiotics-theperfectstorm.blogspot.com/
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Disclaimers

- I make my living by consulting
  - Large PhRMA
  - Biotech
  - Academics
- “Active” member of IDSA.
- I am NOT a statistician!
- Mostly working on antibiotics, occasionally antiviral drugs.
- A recent client list can be found on my website.
- The views I present today are my own.

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Outline

- Think of this talk as tough love.
- Resistance is global.
  - We need a pipeline of new antibiotics active against resistant pathogens.
- FDA is releasing guidance requiring infeasible trial designs.
- The US antibiotic market share is decreasing.
  - It will soon make sense to ignore the US.
- Companies continue to abandon the field.
- The FDA must provide feasible guidance.

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Antibiotic-Resistance is a Global Problem

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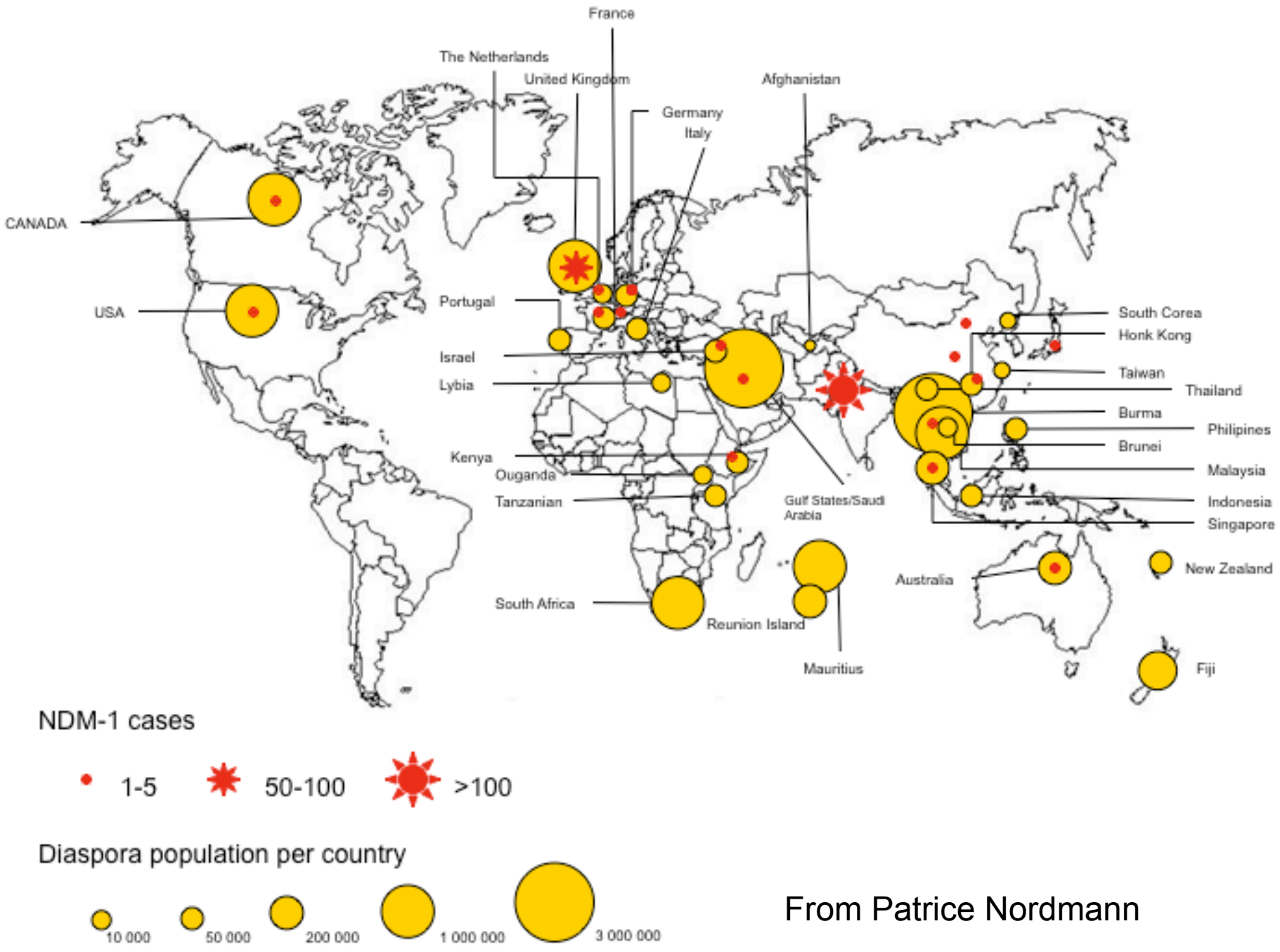

From Patrice Nordmann

KPC Carbapenemase

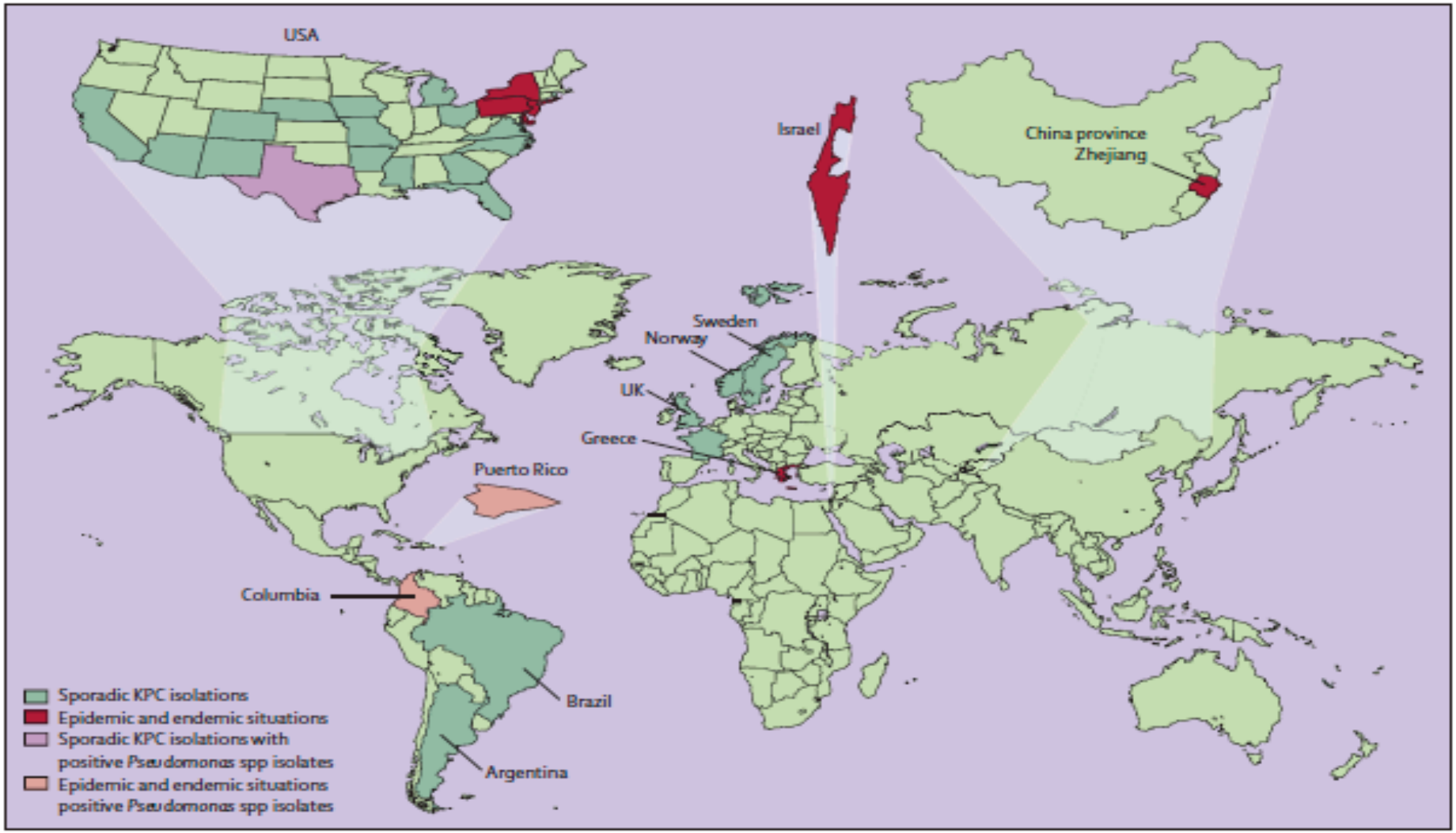

Figure 2: Geographic distribution of KPC worldwide

The Low Point

- At the last ICAAC, Mark Goldberger, former Director ODE IV at FDA, stated that our letter, Shlaes and Moellering, entitled, The FDA and the End of Antibiotics, 2002, was the low point in FDA-industry relations on antibiotics.
- Little did he know . . .

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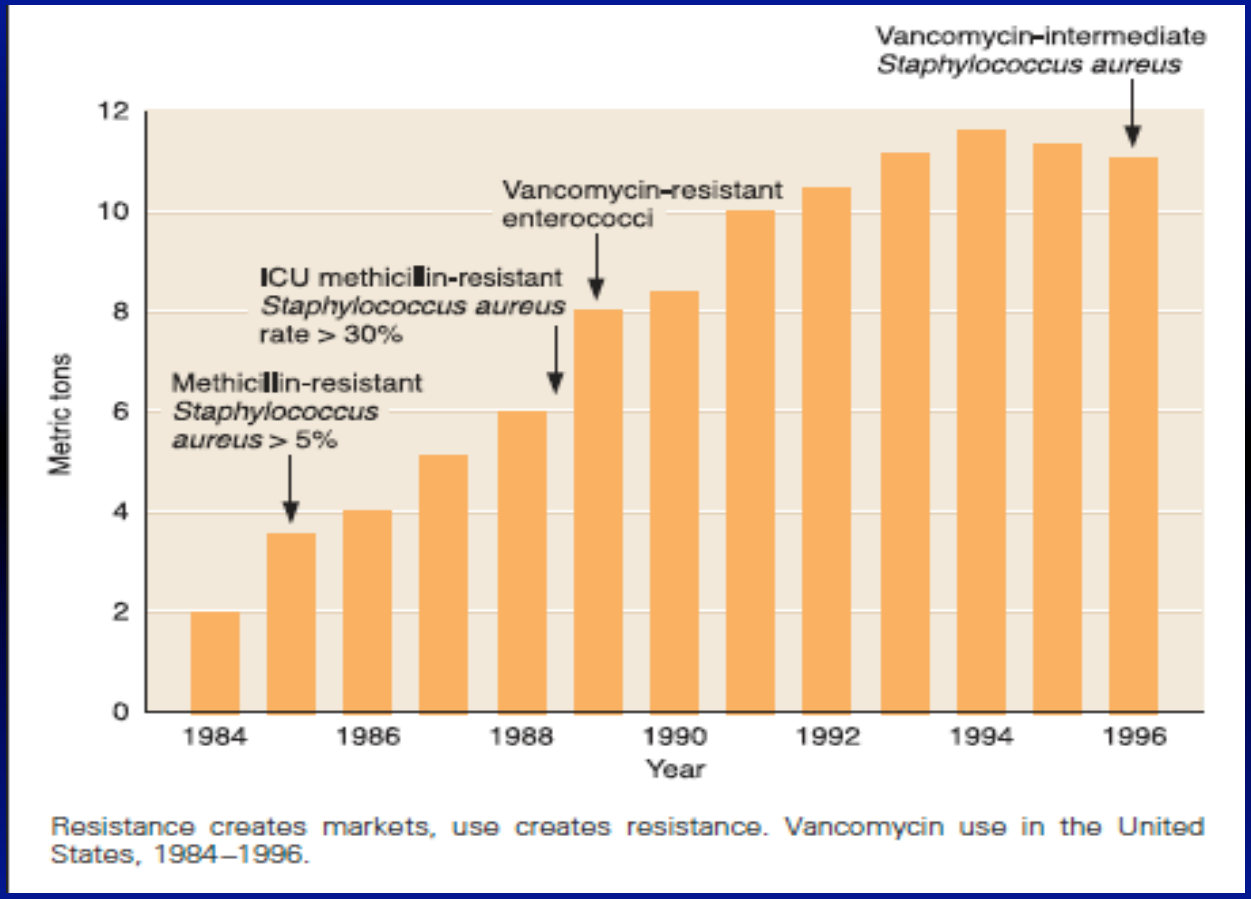

Resistance creates markets, use creates resistance. Vancomycin use in the United States, 1984–1996.

Synercid - 1999

Linezolid – 1999

Daptomycin – 2003

10-14 years will seem short if things don't change.

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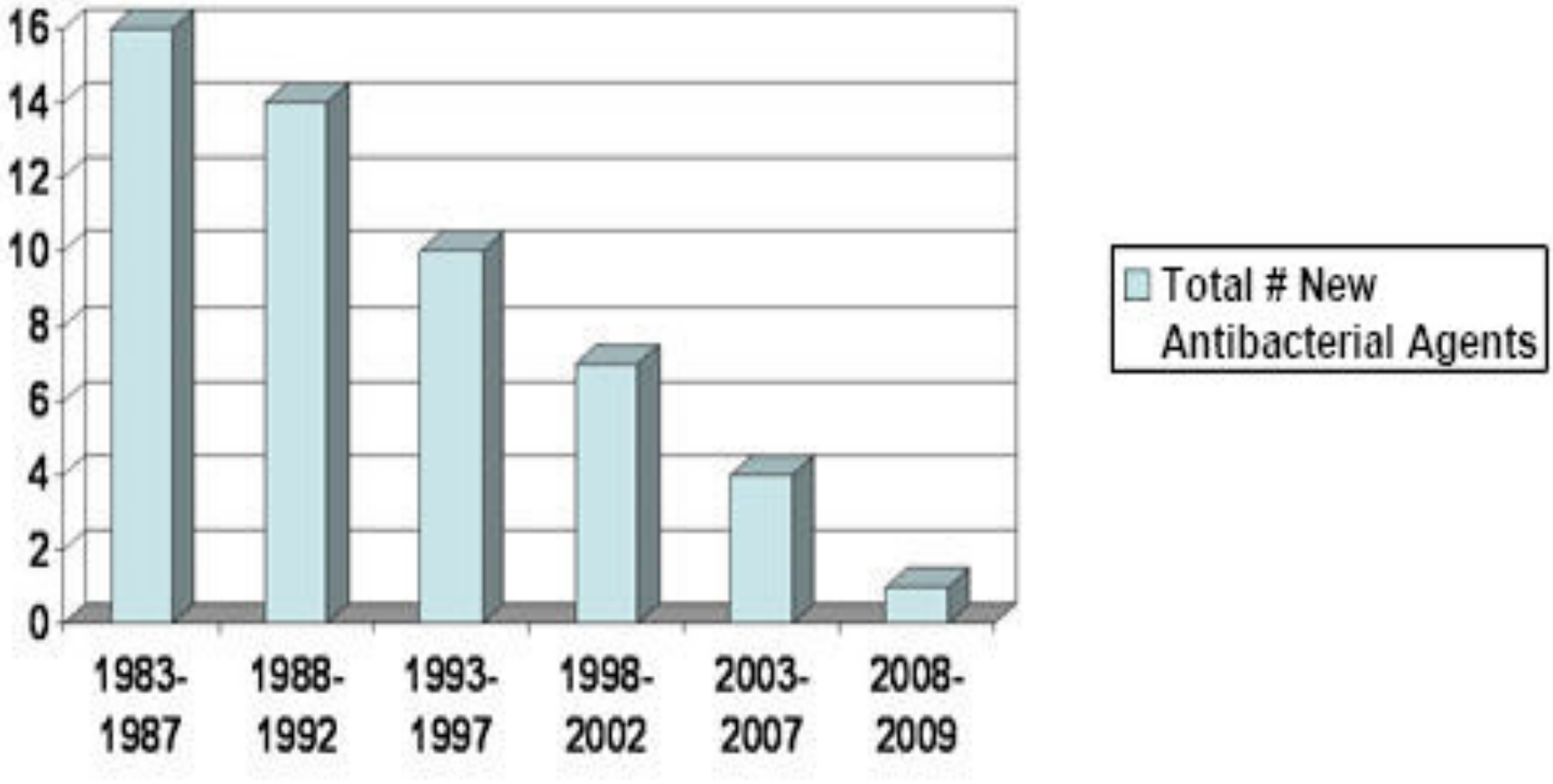
DECLINING ANTIBACTERIAL APPROVALS (PAST 25 YEARS)



Spellberg, *CID* 2004, Modified

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Tigecycline example

Indication	Cure Rate	90% Power 10% delta	90% Power 15% delta
CAP (Total Number for 2 Studies) 70% evaluability	**85%**	1532	688
Skin (Total Number for 2 Studies) 60% evaluability	**80%**	2248	1000
IAI (Total Number for 2 Studies) 60% evaluability	**70%**	2948	1316
HAP (Total Number for 1 Study) 60% evaluability	**65%**	1598	710
TOTAL		**8326**	**3714**
		80% Power 10% delta	**80% Power 15% delta**
TOTAL		**6226**	**2770**

Decreasing from 90% to 80% power doubles the risk of a false negative result when the agent is actually not inferior (thanks to M. Wible)

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FDA Accomplishments (per Dr. Woodcock to Congress)

- While invalidating previous guidance for antibiotics, the FDA has released the following new guidance documents in recent years.
  - NI Trial Design
  - Development of drugs for otitis, sinusitis and acute bacterial exacerbations of COPD (3 documents)
  - Community acquired bacterial pneumonia
  - ABSSSI
  - *HAP/VAP*

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FDA Accomplishments

- Mild infections guidance – infeasible – calls for placebo controlled trials
  - Otitis requirement recently made irrelevant by data.
  - Highly controversial in mod-severe ABECOPD.
- ABSSSI – Trial design is feasible, but according to IDSA, endpoint is clinically irrelevant.

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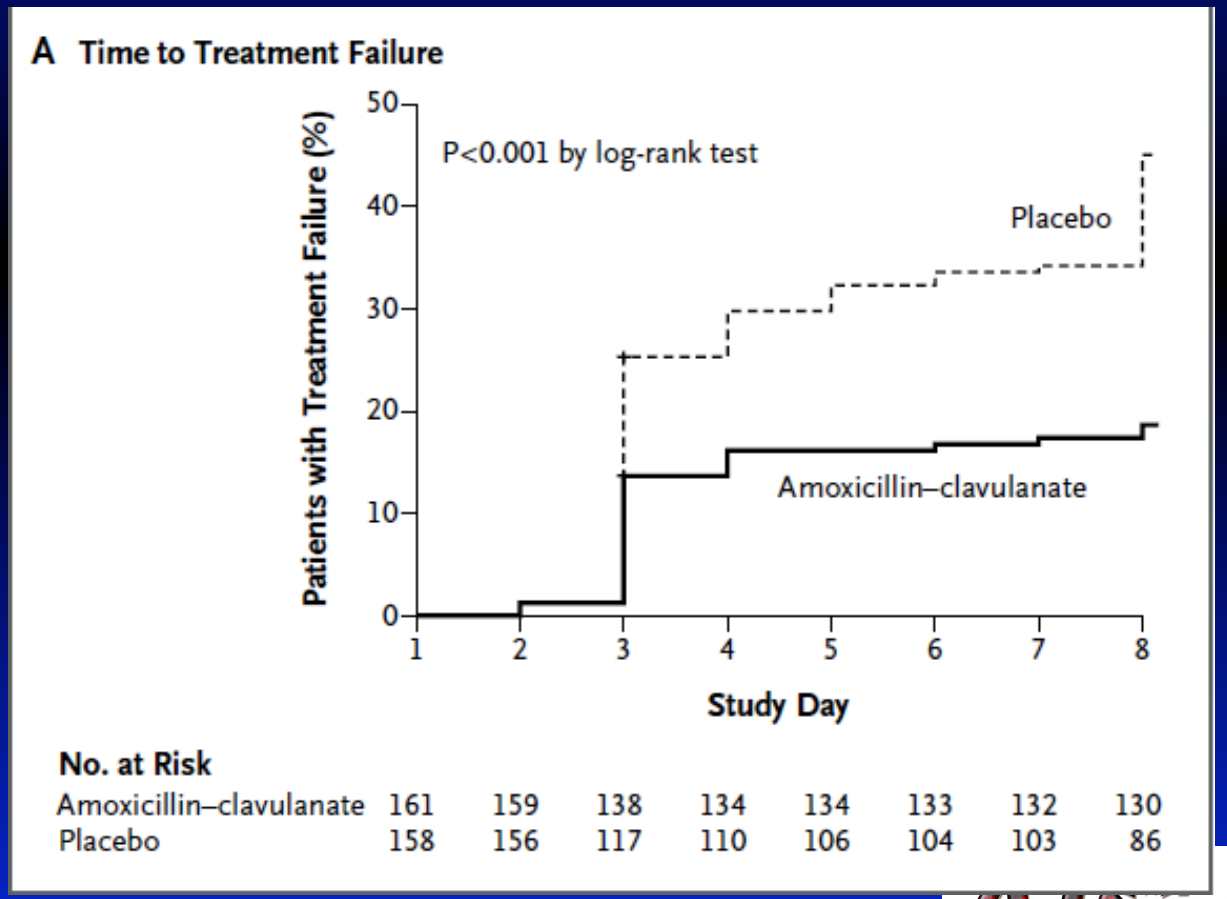
Otitis Media – middle ear infection of childhood

- 2 very recent studies – 3-5 years to complete.



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CABP Guidance

- Community acquired bacterial pneumonia – under revision in response to an uproar from stakeholders over trial feasibility and relevance of endpoints.

DRAFT Guidance CABP 2009

- Efficacy population – microbiologically documented.
- NI margin – oral drugs – 10%.
- Assume – 90% power, 85% cure, 85% clinical evaluability, 25% microbiologically documented.

		Total enrolled
CE	0.85	
ME	0.25	2524
Total of 2 trials		5048

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HAP/VAP Guidance

- HAP/VAP – just released. Trial design is infeasible based on disease epidemiology and enrollment numbers required.

HAP/VAP Guidance

- Endpoint is 28 day all cause mortality.
- Assure overall mortality rate of 20% (APACHE II >15).
- NI margin 10%.
- Analysis pop = microbiologically documented (usually about 50% of enrolled).
- For a 80% powered study – you need 2012 patients enrolled.
- Enrollment rates are about 0.1 per center per month.
- Such a trial that used 300 centers (!!!) would require 5 years to complete and would be financially prohibitive ($300-600MM). A 90% powered study would require 8 years to complete.
- The numbers are even worse if you have to use the 1.67 OR method for calculating an NI margin.

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FDA and Generic Antibiotics

- In 2006, US marketing approval for telithromycin for otitis, sinusitis and ABECOPD was withdrawn.
  - Rare but serious liver tox.
  - They had not proven efficacy via placebo-controlled trials as is now required but was not required when S-A developed the drug.
- But approvals for generic antibiotics for the same indications were never based on placebo-controlled trials.
- Some generics have a tox profile similar to telithromycin.
- The generics have neither been reviewed nor withdrawn.
- Are our generic antibiotics safe and effective???

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FDA Accomplishments

- The FDA allows themselves the prerogative of changing their trial design requirements after trials have been initiated or even completed based on agreements between the sponsor and the FDA on the original trial design.
  - They have exercised this prerogative on several occasions.
  - Companies have gone belly up as a result.

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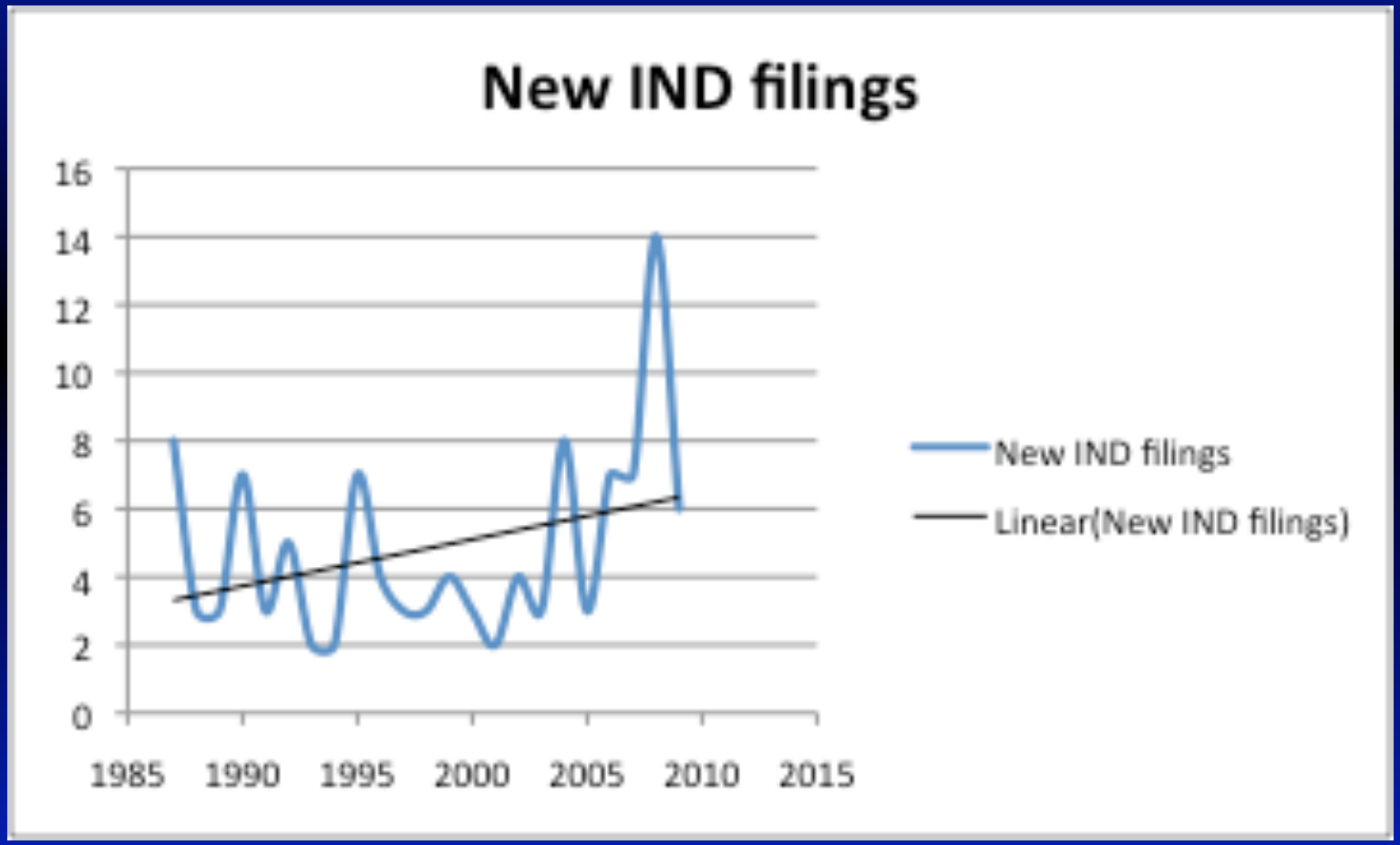
FDA Accomplishments



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Indications for Anti-infectives

Clinical Trial Feasibility, Market Attractiveness, and Medical Need for New Antibiotics			
Indication	**Are Trials Feasible**	**Market attractive**	**Medical Need for New Antibiotics**
Skin infections	**Yes**	**Yes**	**For oral drugs**
Community-acquired pneumonia	**No**	**Yes**	Not at this time
Hospital acquired pneumonia	**No**	**Yes**	**YES**
Ventilator associated pneumonia	**No**	**Yes**	**YES**
Intra-abdominal infections	Yes	Moderate	Moderate - for resistant pathogens
Urinary tract infections	Yes	No	**YES - for resistant pathogens**
Bone and Joint infections	No	Maybe	**For oral drugs**
Heart valve infections	No	No	Not at this time
Fever in neutropenic patients	No	Yes	For resistant pathogens
Otitis media	No	Yes	Not at this time
Acute bacterial exacerbations of chronic bronchitis	No	Yes	Not at this time
Acute Bacterial Sinusitis	No	Yes	Not at this time
Pharyngitis	?	No	No

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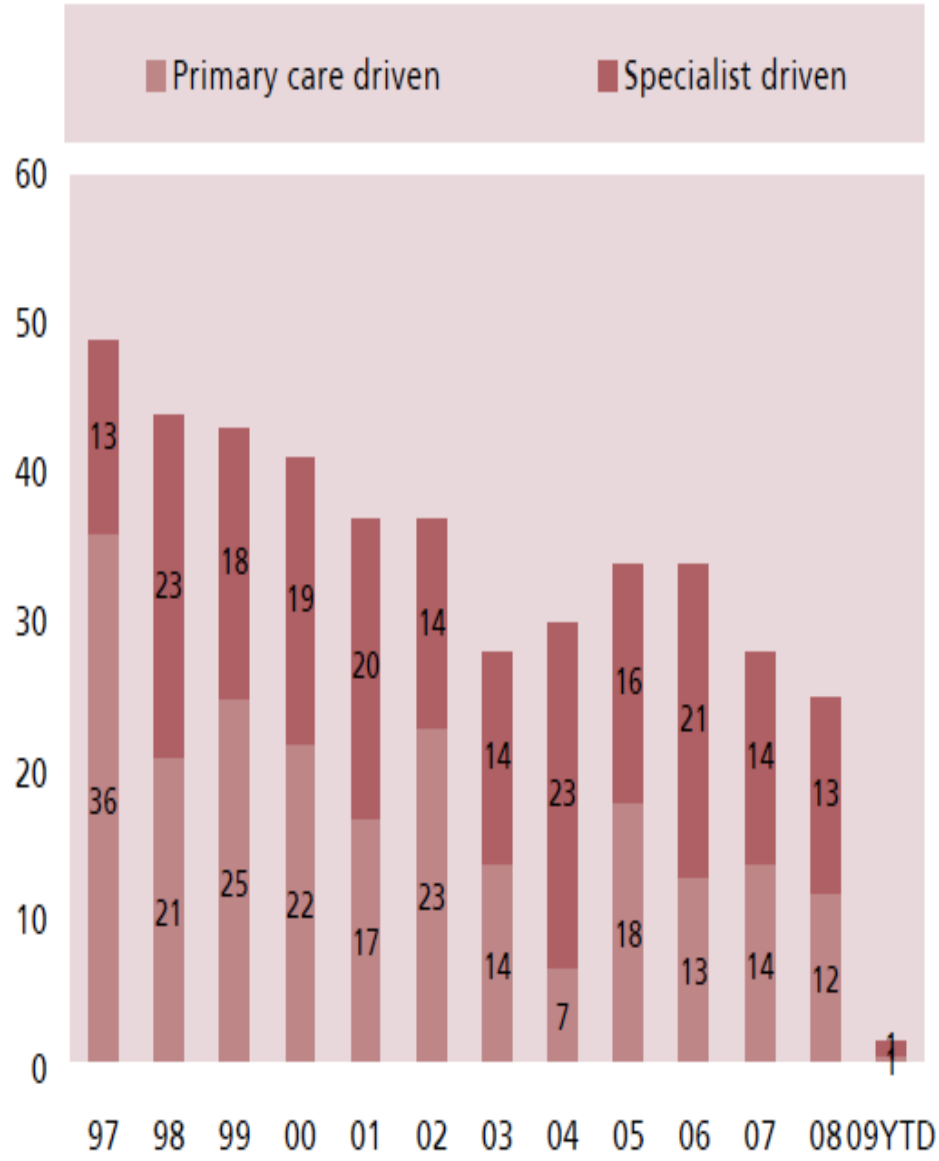
Global NCE ("new chemical entity") launches (Source: IMS)



R&D spending as % of pharmaceutical company revenues (Source: Company data & LSR estimates)

PhRMA – why do this?

Table 6-3. Net present value (lifetime earnings minus lifetime costs) of drugs.

Net Present Value (NPV) of Drugs 1990-94

	Mean NPV
All Drugs	$0.8B
Antibiotics	$1.1B
Statins	$15B
SSRI anti-depressants	$11B

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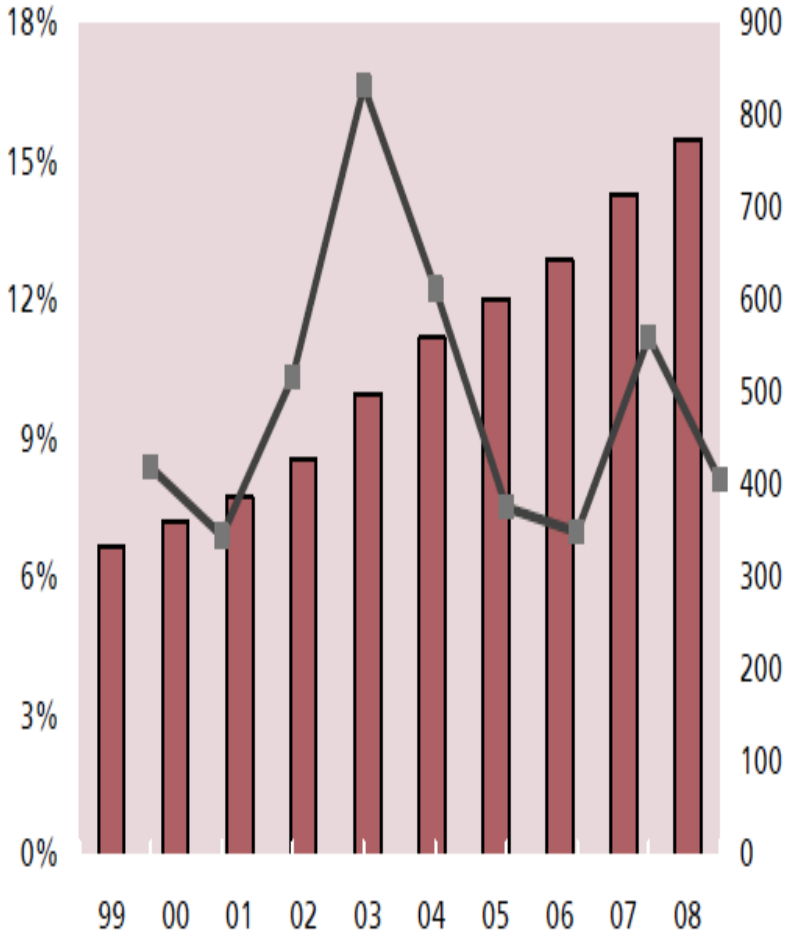
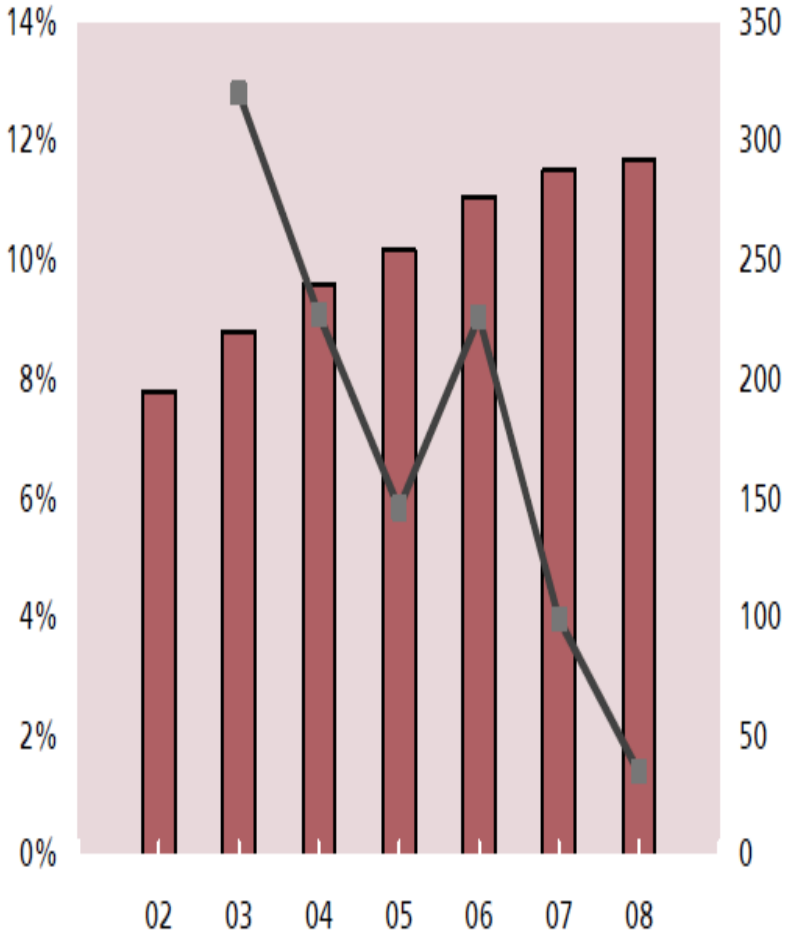
World pharmaceutical sales
(growth on left-hand scale, USDbn on right scale)



US pharmaceutical sales
(growth & USDbn as per World, source: IMS for both)



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Pharmaceutical Markets

- Growing markets
  - Pharmemerging markets (China, India, Brazil, Russia, Mexico, Turkey, S. Korea)
  - Rest of World
- Stagnating (but LARGE) markets
  - US
  - Europe
  - Japan (2nd largest market)

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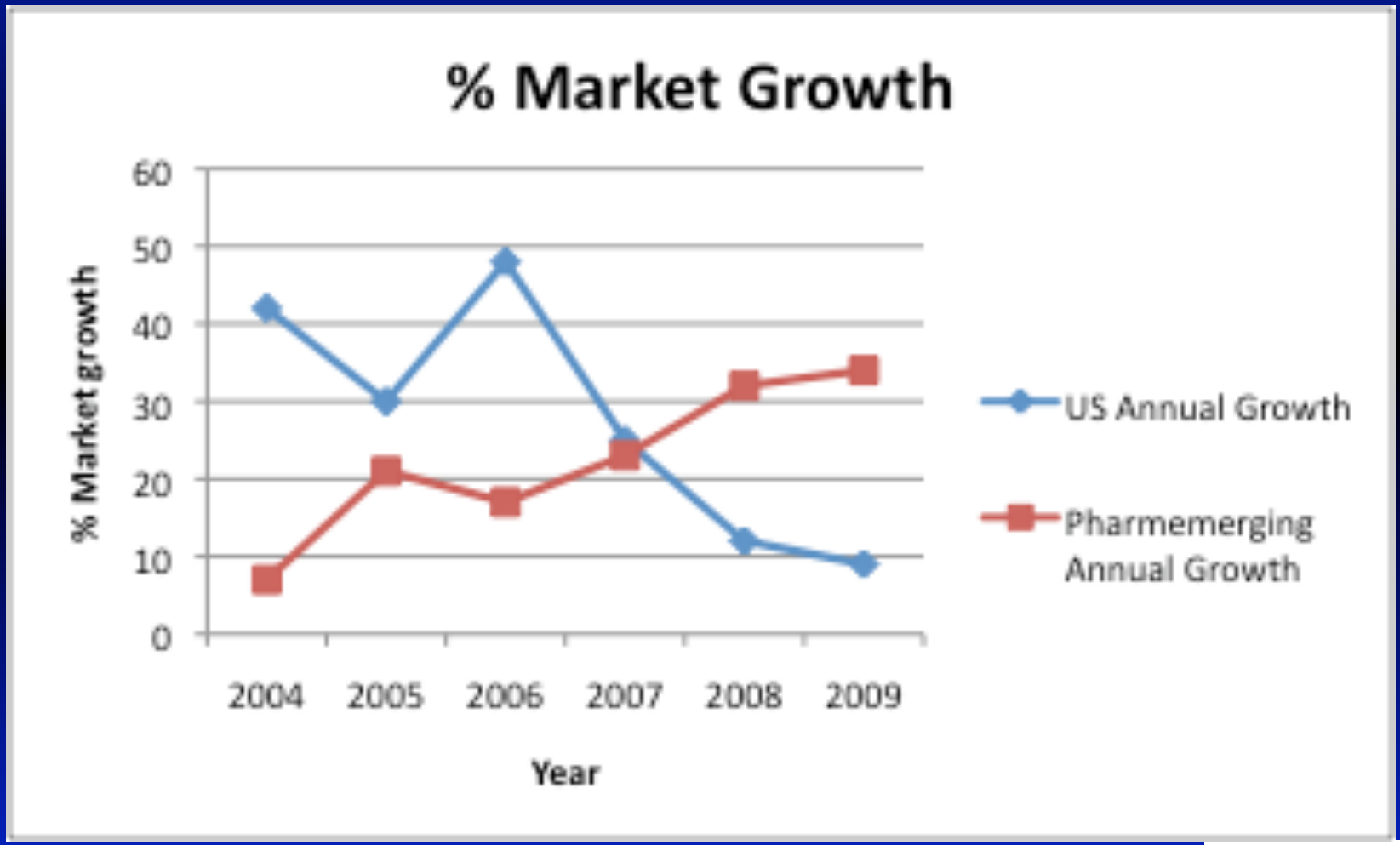
Contribution to World Market Growth



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Drivers of Lack of Growth in US

- Generic Intrusion + Lack of New Products
- Generic Intrusion + Lack of New Products
- Generic Intrusion + Lack of New Products
- Generic Intrusion + Lack of New Products

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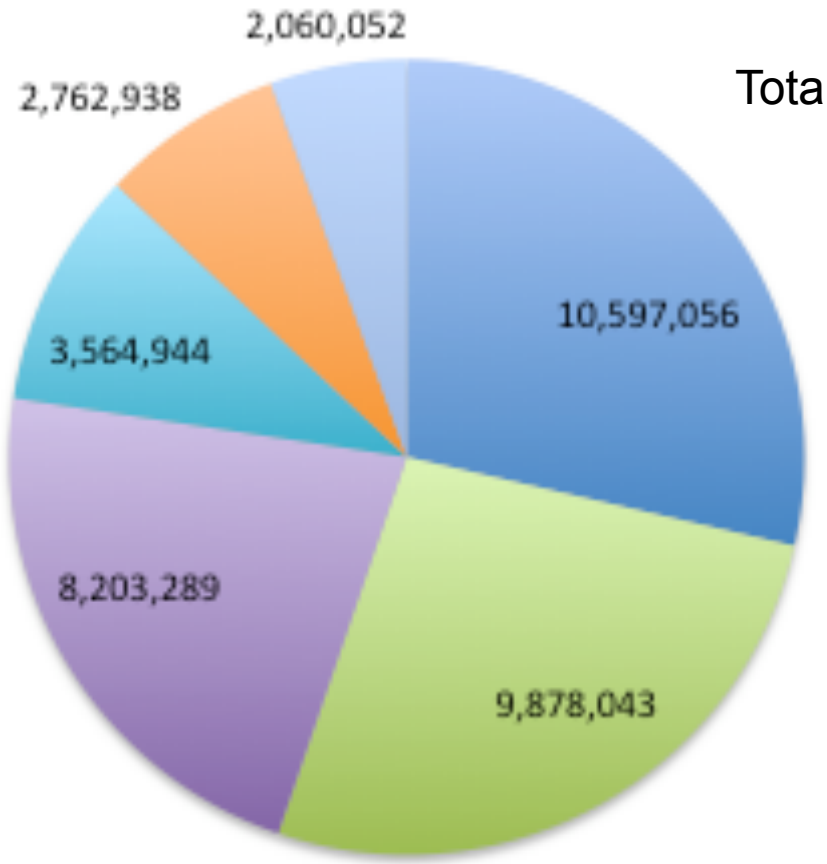
Antibacterial sales 2010



Total sales = $37.5B

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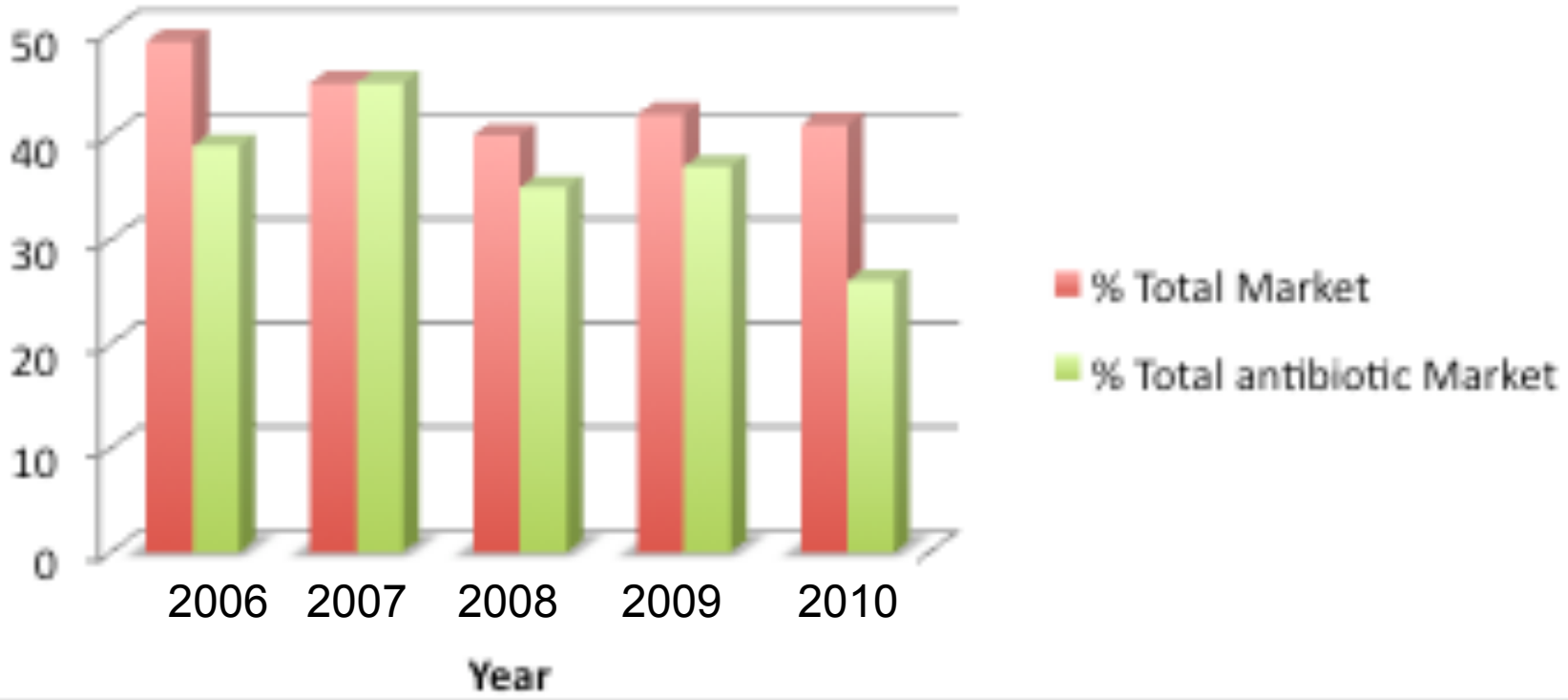
Pharmaceutical and Antibiotic Market - US Share



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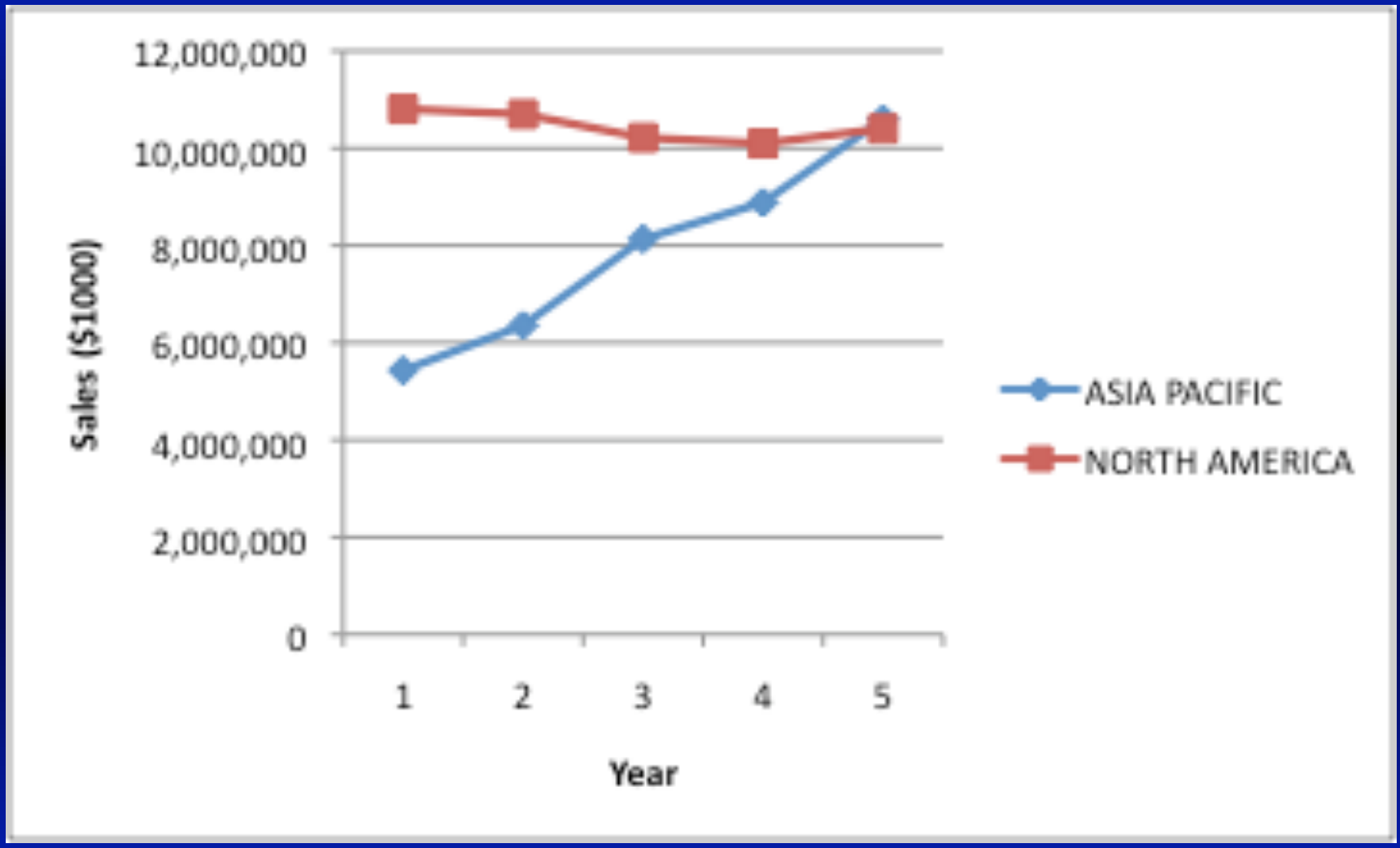

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Large pharmaceutical companies active in antibacterial research in 1990	Companies active today	Companies not pursuing antibacterial research today
Abbott	Pfizer-Wyeth →	Abbott
Bayer	Astra-Zeneca	Bayer
Bristol Meyers	Glaxo SmithKline	Bristol Meyers Squibb
Ciba	Novartis	Lilly
Glaxo	Merck-Schering Plough	Roche
Hoechst		Johnson & Johnson
Johnson & Johnson		Sanofi-Aventis
Lederle		
Marion Merrell Dow		
Merck		
Parke-Davis		
Pfizer		
Roche		
Rhone Poulenc		
SmithKline Beecham		
Squibb		
Upjohn		
Zeneca		

The Future

- We continue down the same path.
  - Nuclear option
    - The US market becomes less relevant.
      - Companies register their drugs outside the US.
  - The off-label use option.
    - Some companies may register their drugs for feasible indications (ABSSSI) and obtain sales from off-label use in the US.
  - Companies give up (e.g. J&J and Pfizer).
  - All of the above.
  - In any case – off-label use of new antibiotics will increase.

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What Else Can We Do?

- Incentives (somebody must spend $$$)
  - Wild card exclusivity
  - Push-Pull
- Disincentives
- All of the above . . .
- Next talk . . .

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A New Future

- The FDA provides ***feasible*** guidance
  - More general guidance (e.g. EMEA).
  - Totally revamps the recently released guidance documents.
- FDA thinks totally out of the box –
  - Bayesian approaches
  - FEASIBLE superiority designs
  - Conditional approvals based on non-powered trials in populations of high medical need.
    - Increasing use of REMS means we are already doing this to some extent based on safety concerns.

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Out of the Box

- Must be done by a totally different group than currently exists.
  - Must include industry.
  - Special OOTB Committee that reports directly to the Sec. HHS (best).
  - Special OOTB Committee that reports directly to the Commissioner (preferred).
  - Special OOTB Committee which then presents to anti-infectives division (WOT).

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Backups

2003 Pharmaceutical Company	Number of original companies since 1980
Aventis[1]	17
Bristol-Meyers-Squibb	8
Glaxo Smith Kline	12
Novartis	7
Pfizer	12
Wyeth	14

[1]Now Sanofi-Aventis

Pfizer has now purchased Wyeth.

Not shown: Merck has now purchased Schering Plough.

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FDA Approvals of New Antibiotics

Antibiotic NDAs 2007-10

	Approved
Iclaprim	No
Oritavancin	No
Telavancin	Yes – cSSSI, NOT HAP/VAP
Doripenem	Yes - cUTI, cIAI, NOT HAP/VAP
Cethromycin	No
Ceftibiprole	No
Ceftaroline	Yes - CABP, cSSSI

Approval rate 43%

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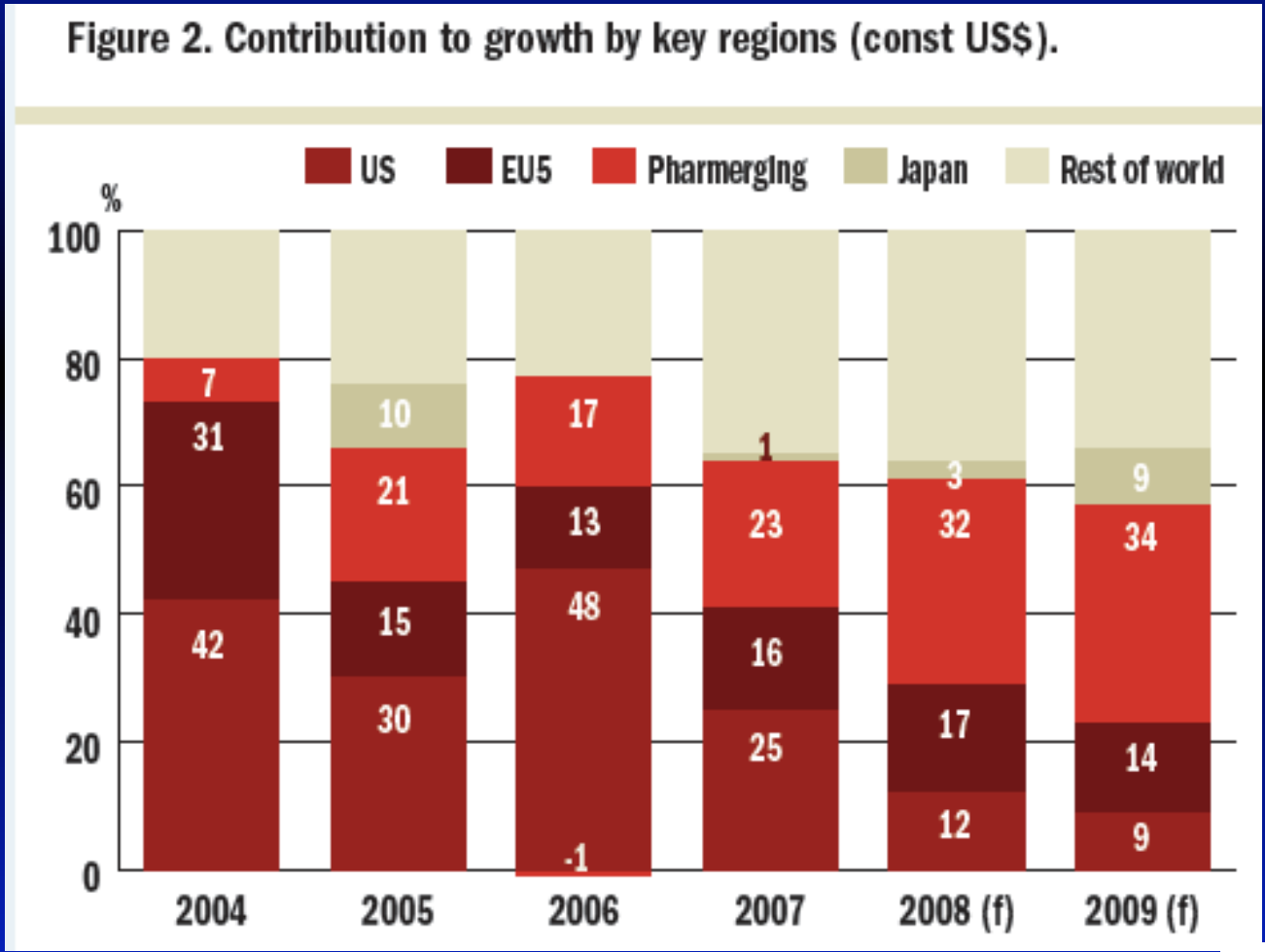
Pharmaceutical Markets



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