FDA PRVs – The Potential Can be Realized

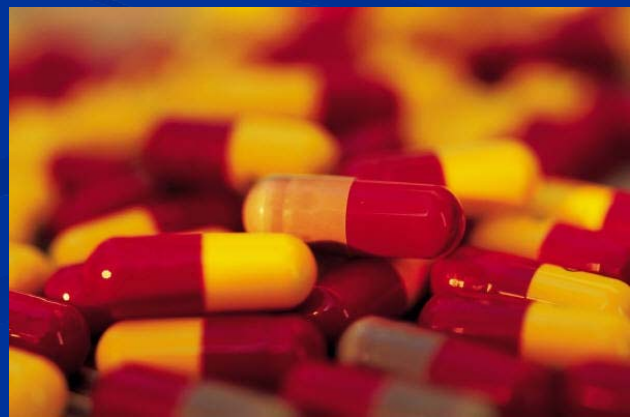
Colin Ohrt, MD, MPH
COL, MC
Division Experimental Therapeutics
Walter Reed Army Institute of Research

Disclaimer

- The opinions presented in this lecture are those of the author and do not reflect the official views of the US Army, the US Department of Defense, or the US Government.
- I have no financial conflict of interests to declare.
- In the interest of full disclosure, I have been leading or supporting tafenoquine, intravenous artesunate and other tropical diseases product development for the last 10 years.

Agenda

- Background
- Consider removing diseases from the list
- Consider adding diseases to the list
  - One obvious that should be added
  - Poll of physicians
- Suggestions for the potential **to be realized**
- Conclusions



The Problem

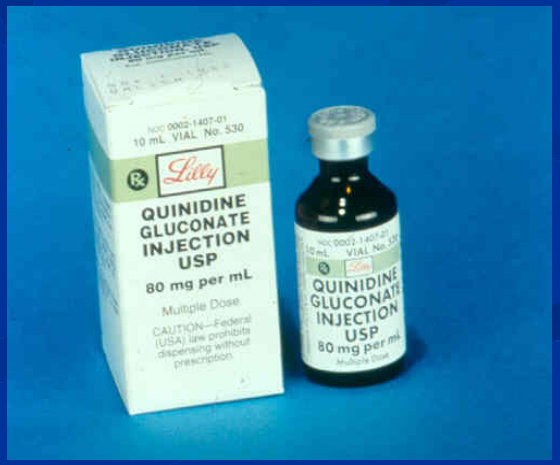
- $125 billion spent yearly on pharmaceutical R&D
- 1% of NCEs in last 3 decades for tropical diseases
- Tropical diseases 11% global disease burden
- Very limited commercial market
- US military and citizens living abroad at risk

Experience

- US Army targets tropical infectious diseases
  - Malaria
    - Intravenous artesunate
    - Tafenoquine
    - Primaquine
    - Azithromycin
  - Cutaneous leishmaniasis
    - Topical paromomycin-gentamicin
    - Sodium stibogluconate
  - Dengue (vaccine)
  - Japanese encephalitis (vaccine)

Always a Struggle

- Identify co-development partners
- Achieve FDA approval
- Sustain products after approval

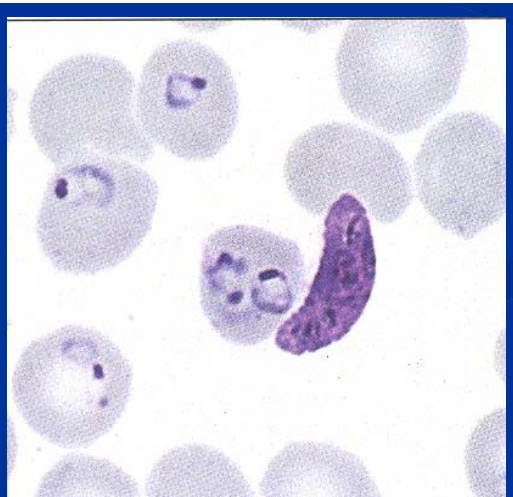


October 17, 2007

Bill and Melinda Gates Call for New Global Commitment to Chart a Course for Malaria Eradication

New resources and scientific progress help pave the way toward malaria eradication

U.S. presidential candidates urged to sustain and expand President's Malaria Initiative



Designating Removals

- Some of the diseases on the list
  - Do not immediately appear to require new products
    - Trachoma
    - Yaws
  - Suggest
    - Systematic review
    - Expert advisory board recommendations
    - Prioritize if remain on list??
- Diminished focus
- Decreased voucher incentive

Designating Additions

- Primary intent of this hearing
- Most obvious
  - Chaga's Disease
  - Listed in Ridley article, but not included
  - ~8-12M infected in South America
  - Clearly inadequate treatment
  - No dedicated development in industry

D. Ridley *et al*, Health Aff. 2006 25(2):313-24.

Designating Additions

- Questionnaire sent to DoD Physicians and EID list server
- Example additions suggested:
  - Monkeypox
  - Meliodosis
  - Japanese encephalitis
- Suggest expert advisory panel(s)
  - To identify additions
  - To endorse additions
  - Provide on-going review

Designating Additions

- Law supports additions at later time
  - Forgotten diseases
  - Newly emerging diseases
    - HIV
    - SARS
    - Avian influenza

Priority Review Vouchers (PRV) = Game Changer?

- We believe so!
  - Access/Speed delivery to soldiers at risk
  - Overcome emerging pathogen resistance
  - Fill missing gaps
  - Ultimately, control and elimination
- Unprecedented incentive
- Seeing intense interest
- Pharmaceutical industry essential

Draft PRV Guidance

- Limited or potentially negative impact as written
- Can achieve intended outcome
  - Guidance
  - Regulations
- Model in Orphan Drug regulations

Current Limitations

- Combination products
- Ultimate availability of product
- Priority review qualification
- Priority Review Voucher (PRV) qualification
- Orphan or neglected requirement
- Multiple indications needed
- 505(b)(2)

Combination Products

- Background: Potentially excludes TB and is problematic for malaria and other diseases
- Law: "for a human drug, no active ingredient which has been approved"
- Guidance: "Product contains any active ingredient previously approved, not eligible"
- Issue: Combinations must be standard of care to prevent emergence of drug resistance
  - Standard drugs
  - Fixed-dose

Suggest for Combination Products

- Guidance
  - Clearly state combinations and fixed-dose combinations are acceptable
  - Only if added benefit of the new ingredient has been clearly demonstrated

Availability of Product

- Law: No requirement
- Guidance: "Not matter if sponsor decides to market the product"
- Issue: Companies that receive a PRV
  - Will usually control the availability of the product with **Intellectual property (IP)**

Suggest for Availability of Product

- Guidance
  - Company receiving the PRV must market in a manner that ensures access
    - Include in qualification for priority review
    - Provisional approval with right to withdraw
    - Transfer of IP and technical expertise to:
      - 3rd party
      - Generic manufacturer

Priority Review Qualification

- Background: Drug for neglected disease must qualify for “Priority Review”
- Law: "Secretary deems eligible”
- Guidance: "significant improvement on marketed products“
- Issue: Current Review Classification Policy
  - Vague
  - Incomplete

Suggest for Priority Review Qualification

- Guidance
  - More specific
    - For each disease
    - By indication
    - Specifically addressing resistance
  - Driven by Target Product Profiles (TPP)
  - On-going expert advisory committee approval
    - Ideal characteristics
    - Minimal acceptable characteristics
    - On-going assessment

Example Partial TPP

Key Performance Parameter	Ideal	Acceptable Threshold
Drug Resistance	**Ideal**	**Threshold**
Genotypic: *Point mutation possible*	complex	> 1 single point mutation
Phenotypic: *Resistance induction*	Resistance not easily induced in vitro/mice	Resistance not easily induced in vitro/mice
Cross Resistance	None	Limited clinical relevance
Regulatory/Business Issues		
Ease of approval	FDA approved; sNDA	New antimalarial class
Availability in other countries	505b2	New chemical entity
Co-development partner	Yes	None identified
Likelihood of NGO partnership	Yes	No
Summary of Dosage & Administration		
Utility for short-term prophylaxis	Both	Only
Utility for long-term prophylaxis	Both	Only
Recommended route of administration	oral	transdermal / parenteral
Dosing, clinical endpoints	weekly/monthly	daily
Human prophylaxis dose prediction	< 500 mg/wk	< 1 gm/day
Other Indications	All	Malaria treatment or Radical cure

PRV Qualification

- Law: No requirement
- Guidance: "Agency will not make voucher determinations until the time of application approval"
- Issue: Lack of clarity about which products /indications may qualify will lead to
  - Incorrect conclusions
  - Unwillingness to invest

Suggest for PRV Qualification

- Guidance
  - Clarify that a company may seek early FDA input
  - Given drug for a planned indication would likely qualify for a PRV
  - Similar to 45 day review for a pivotal study

Orphan or Neglected Requirement

- Law: "prevention or treatment"
- Guidance: "prevention or treatment"
- Issues:
  - US traveler population
    - exceeds the orphan requirement
    - not large enough to attract product development
  - Can be interpreted as not eligible

Suggest for Orphan or Neglected Requirement

- Guidance
  - Clearly state that indications that are not orphan can be acceptable
  - If added benefit of the new ingredient has been clearly demonstrated
  - Needs of US citizens will be considered

Multiple Indications Needed

- Background Example Malaria:
  - 7+ unique indications
  - Many requiring a different formulation and series of clinical trials to support an sNDA or ANDA
  - Artesunate example
- Law: "for a human drug, no active ingredient which has been approved"
- Guidance: "Product contains any active ingredient previously approved, not eligible"
- Issue: Currently law will require new NCE for each indication.

Suggest for Multiple Indications

- Law & Guidance
  - PRV for important new indications with existing drugs
  - Indications should be driven by appropriate **Target Product Profiles**
- PPP's
  - Could fund additional indications
  - Need ability to modify labeling

505(b)(2)

- Background: Rely on data not developed by the applicant for NDA
- Law: "application submitted under section 505(b)(1)"
- Guidance: "application must be submitted under section 505(b)(1)"
- Issue: Superficially appears 505(b)(2) not qualify

Suggest for 505(b)(2)

- Guidance
  - Clarify that Section 505(b)(2)
    - Is submitted under section 505(b)(1)
    - Therefore eligible

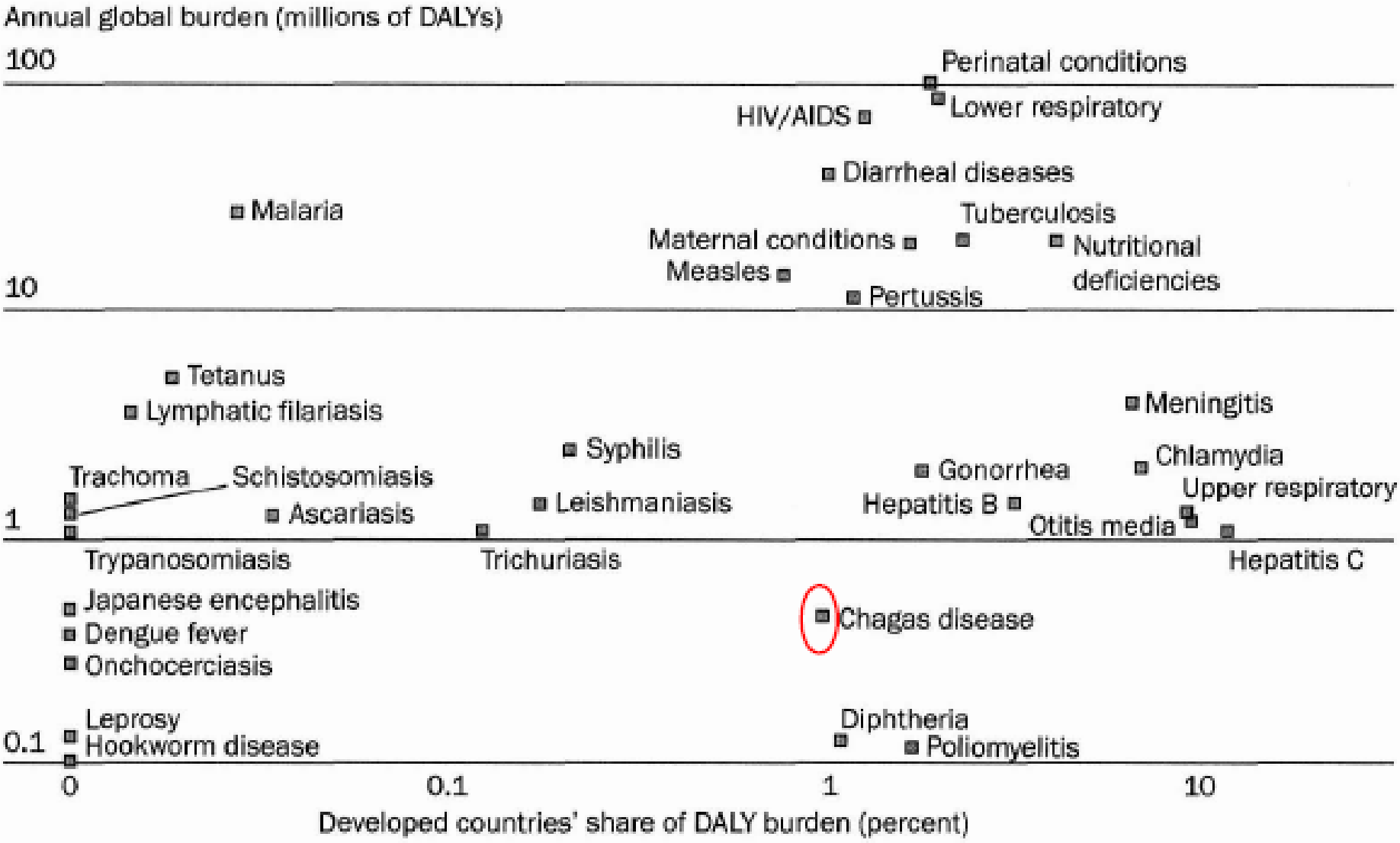
Other Points

- Pediatric (pediatric rule)
  - Formulation
  - Appropriate dosing
- Products already approved outside of USA
  - Relatively low cost
  - Good for US citizens
- Too many PRV awards will decrease their value

?? Questions

Comments ??

EXHIBIT 3
Distribution Of Global Disease Burden, 2004



SOURCE: Authors' calculations based on World Health Organization, *World Health Report* 2004.
NOTES: Data are plotted using a log scale. DALY is disability-adjusted life year.

D. Ridley *et al*, Health Aff. 2006 25(2):313-24.