Global Trend in Human Subject Protections

Melody Lin, Ph.D.
Deputy Director, Office for Human Research Protections
Director, International Activities
Melody.Lin@hhs.gov

Taiwan

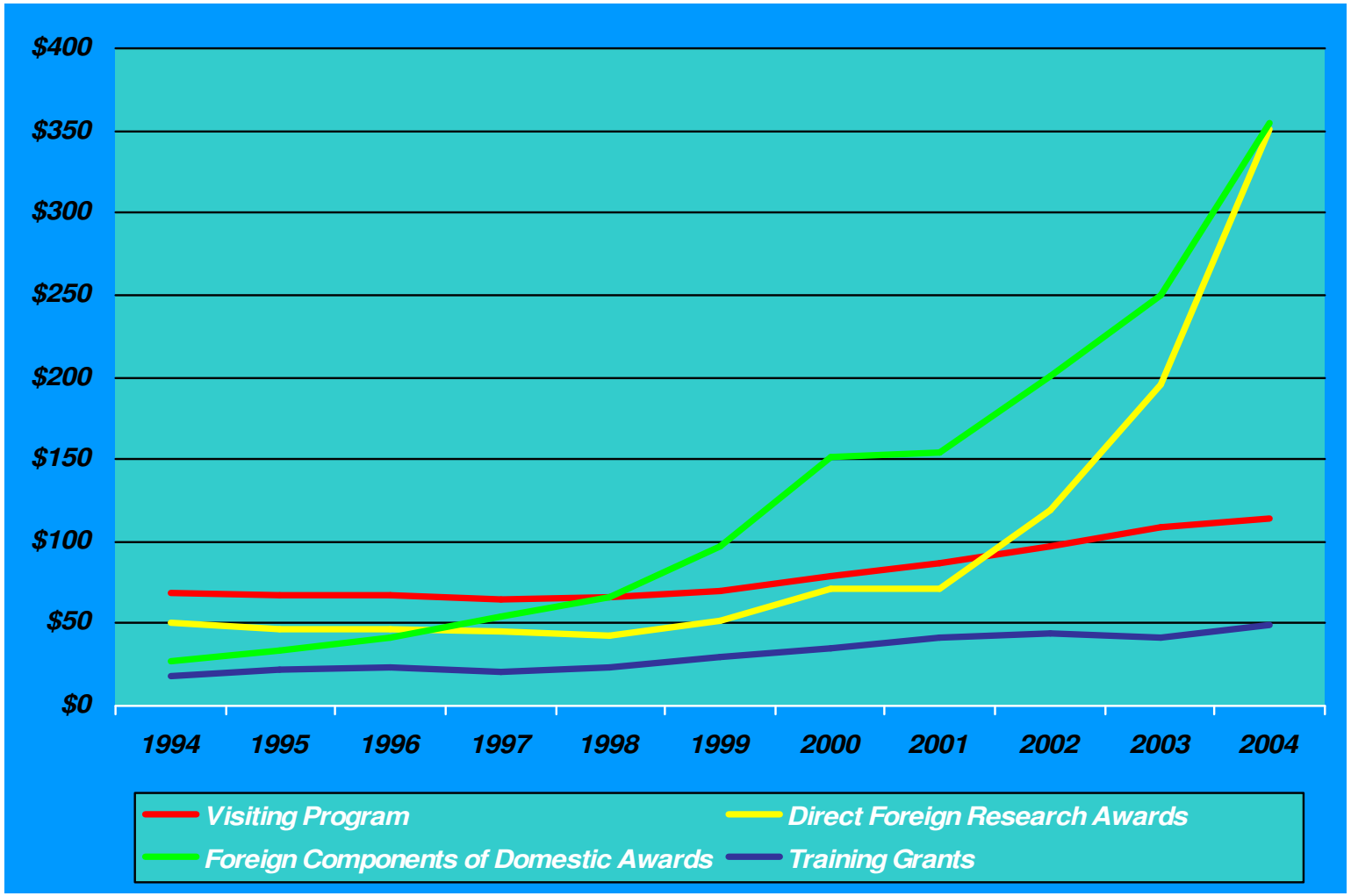
August 2006

Objectives

- Clinical Trials Expanding Globally
- U.S. Expectation
- Lessons Learned – TG1412
- Future Directions

NIH International Research Expenditures

FY1994-2004 (Dollars in Millions)



Recipients of NIH Awards, >$10m

Millions $ in FY2004 (FY1999 in parenthesis)

U.K.
$121.9
($11.1)

Sweden
$14.6
($4.8)

Denmark
$118.7
($3.4)

NL
$13.0
($1.5)

Austria
$46.9
($0.1)

Canada
$95.7
($35.4)

China
$11.7
($6.1)

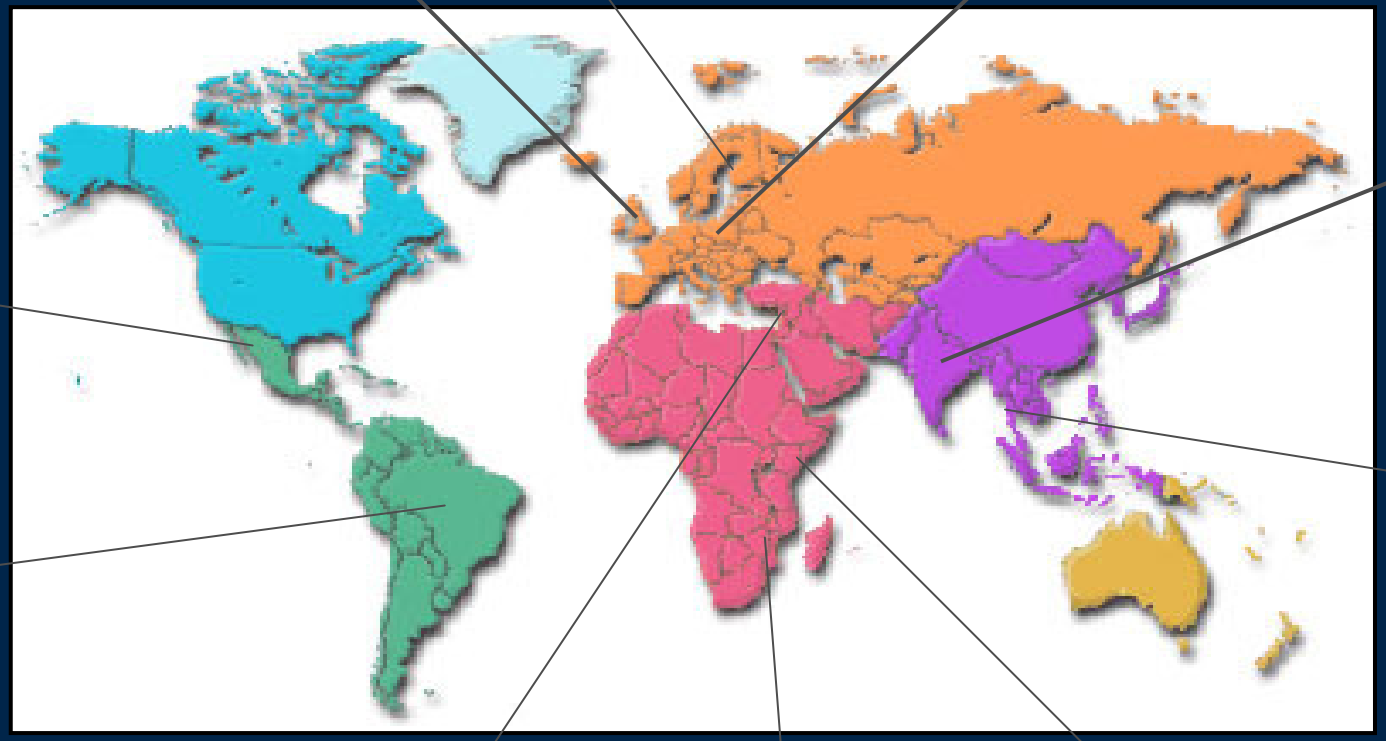
Italy
$11.7
($2.8)

South Africa
$41.3
($2.3)

Australia
$46.4
($7.8)

Recipients of NIH Awards, $5-10m

Millions $ in FY2004 (FY1999 in parenthesis)



France
$9.0
($2.1)

Finland
$9.2
($1.6)

Germany
$8.6
($2.7)

India
$6.5
($1.4)

Mexico
$5.5
($2.9)

Thailand
$6.2
($2.5)

Brazil
$9.5
($3.2)

Israel
$9.9
($4.2)

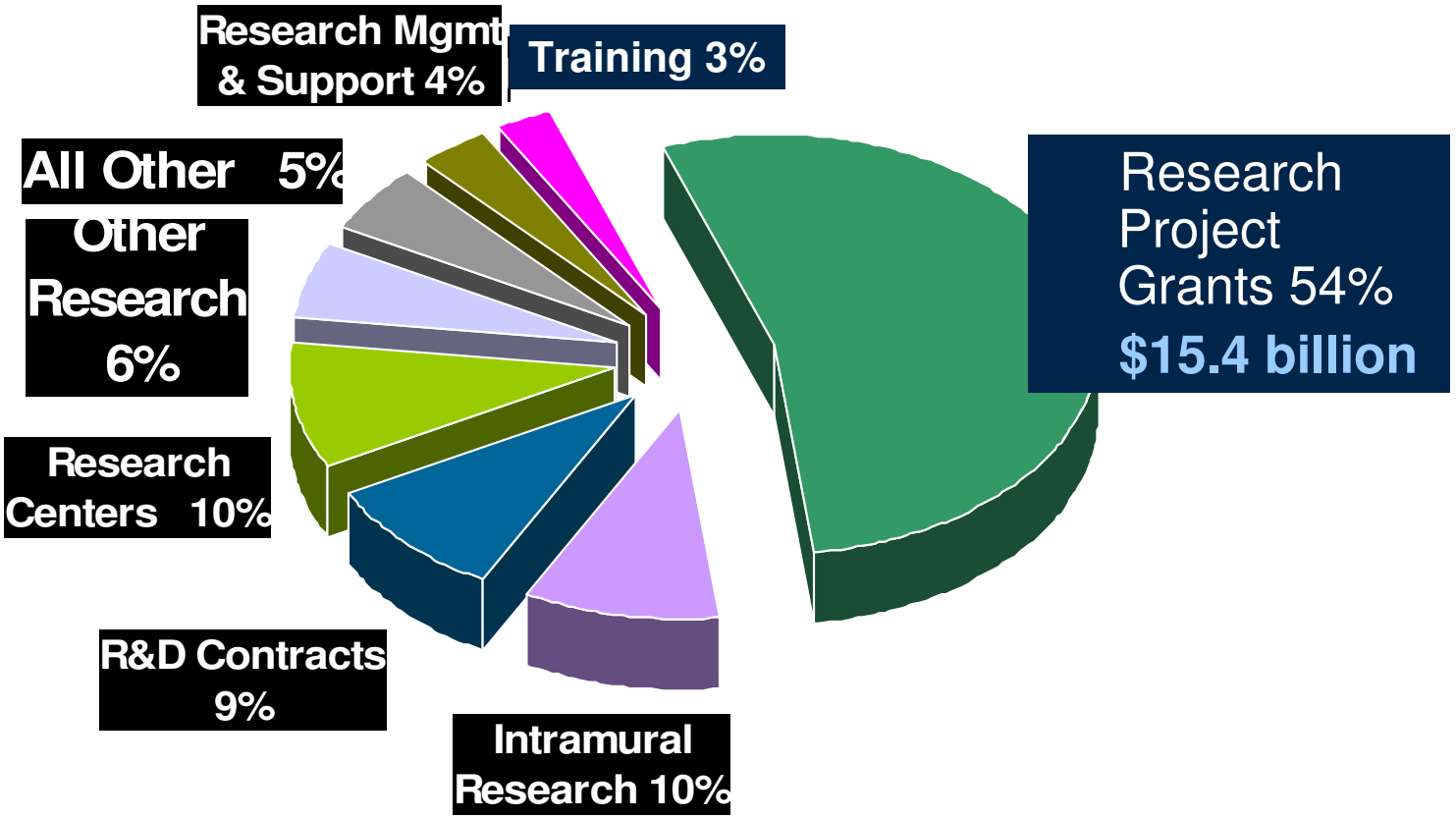
Zimbabwe
$6.8
($3.0)

Kenya
$7.2
($1.4)

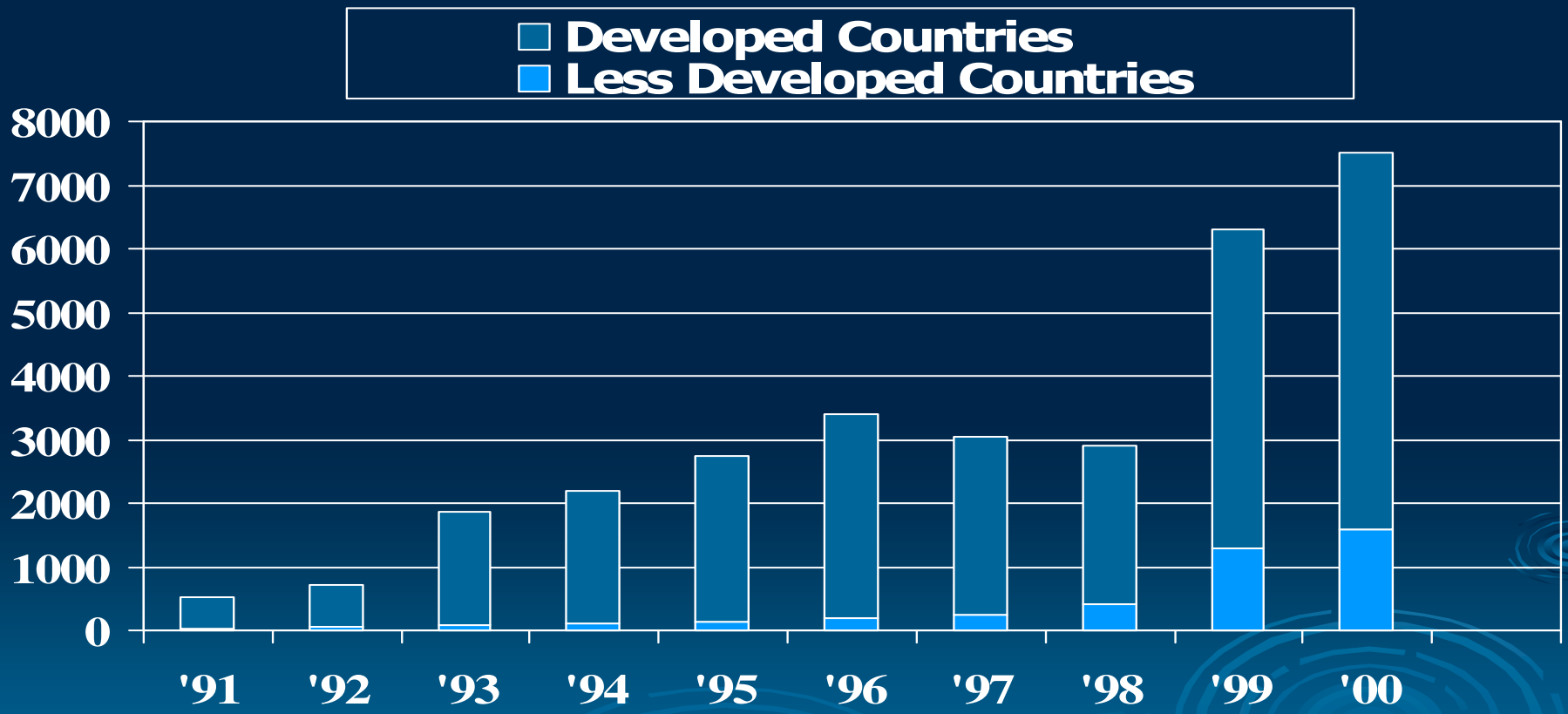
Countries Where NIH Support has Grown at Least Five-Fold: 1999-2004

- Austria: 552.8
- Denmark: 34.9
- South Africa: 18.0
- United Kingdom: 11.0
- Netherlands: 8.7
- Australia: 5.9
- Finland: 5.6
- Kenya: 5.1

FY ‘06 Budget
$28.61 Billion Dollars



Number of Overseas Human Clinical Trials for New Drugs

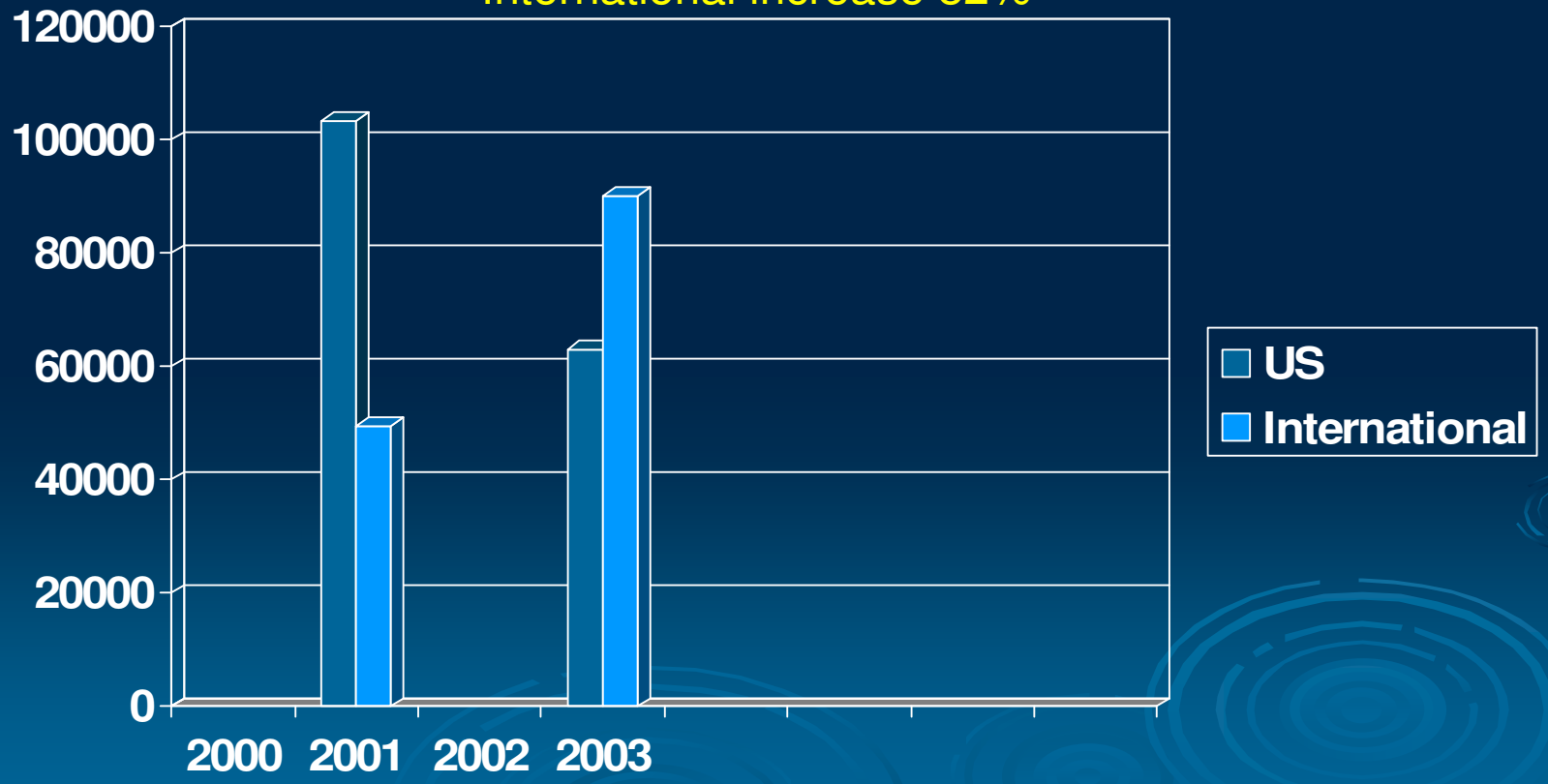


Sources: FDA Biomonitoring Research database; Parexel's Pharmaceutical R&D Statistical Sourcebook 1999; Aculaunch; Washington Post Research

Human Subjects in Clinical Trials

US decrease 40%

International increase 82%



Cost, regulations move more drug tests outside USA

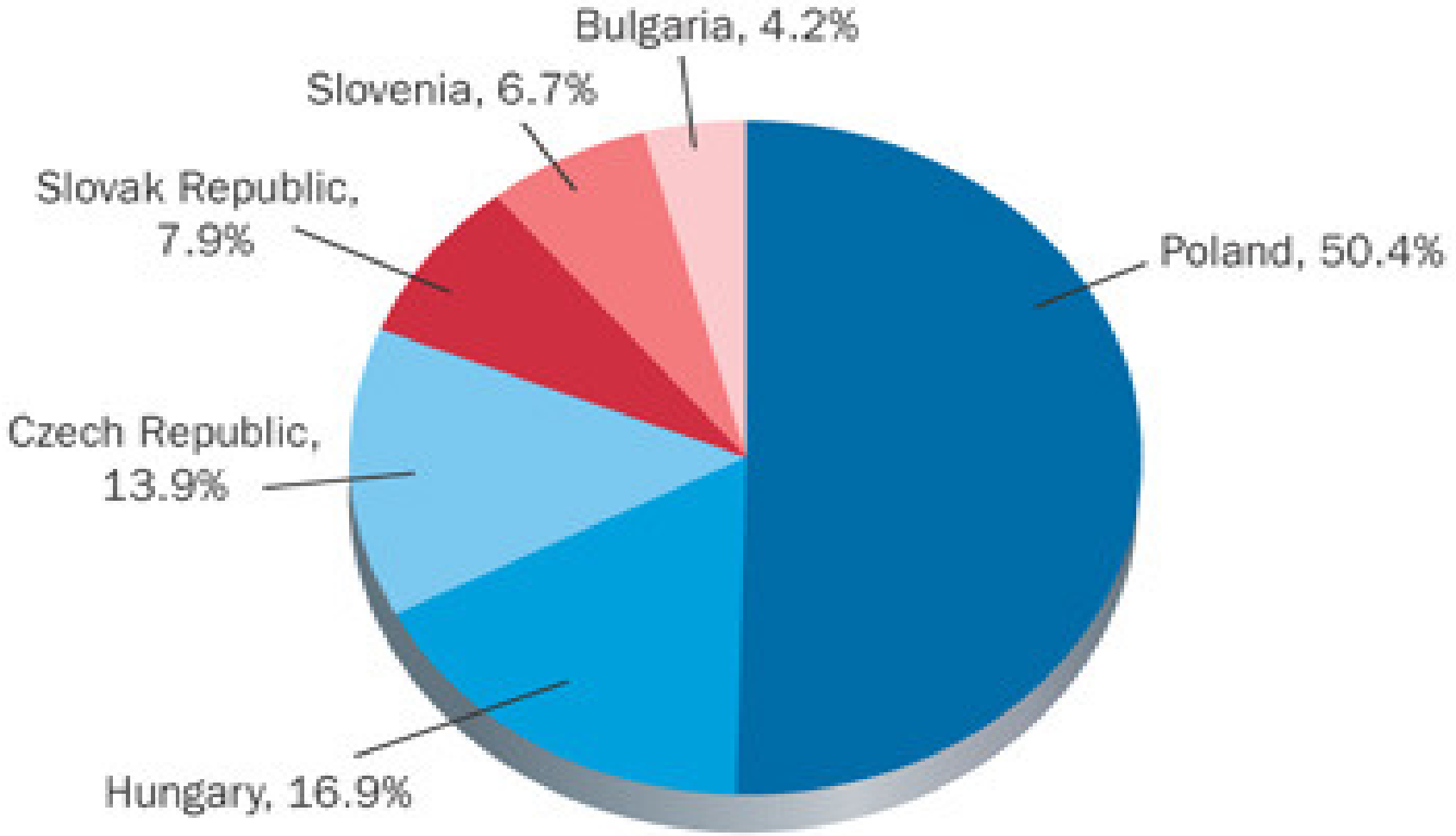
	2004	2006
Wyeth Pharmaceuticals	50%	70%
Merck	50%	
GlaxoSmithKline	29%	50%

http://www.usatoday.com/news/health/2005-05-16-dru-trials-usatx.htm_

CRO

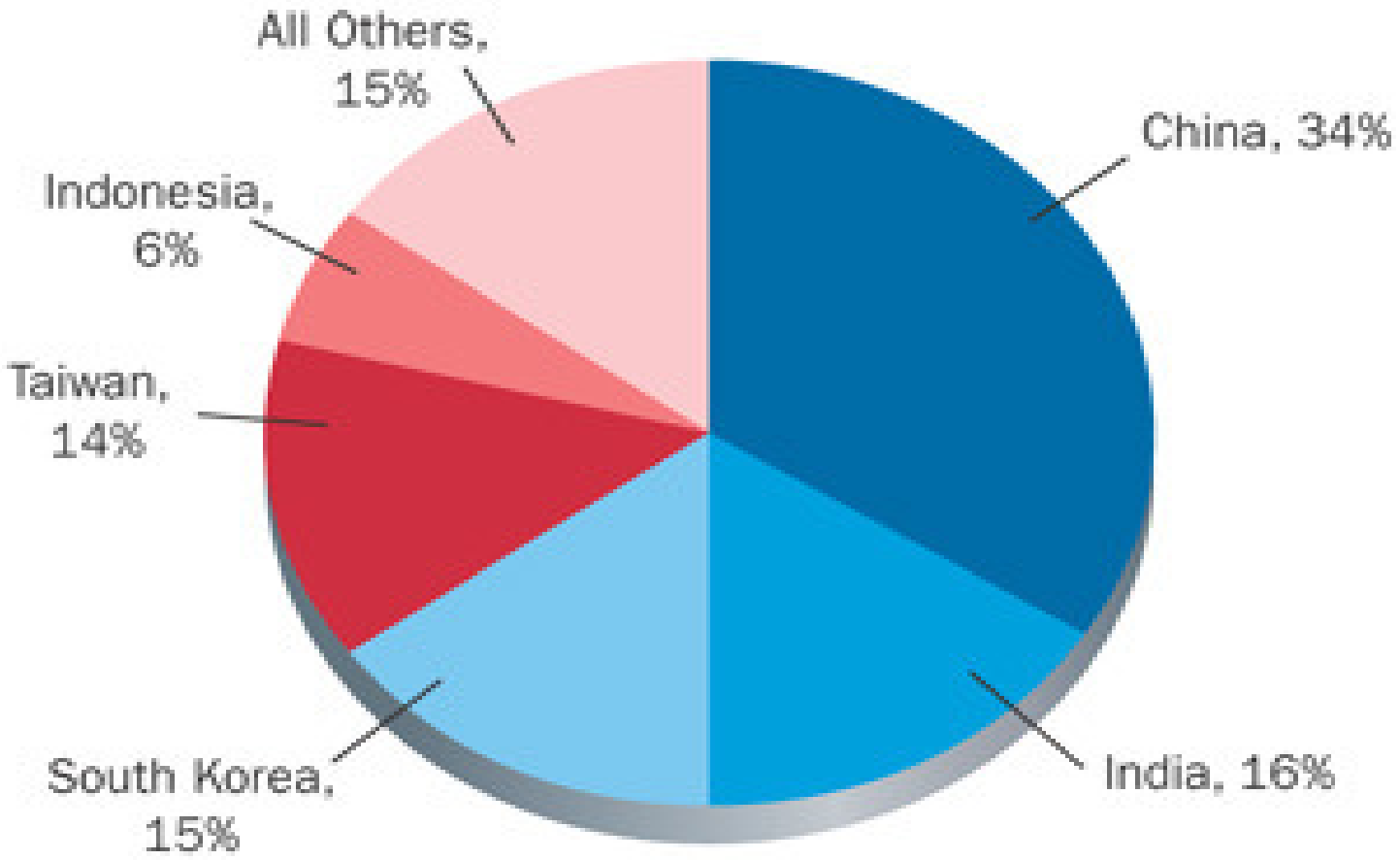
North America	400
Europe	450
Others	150
Worldwide	1000

Thomson Center Watch



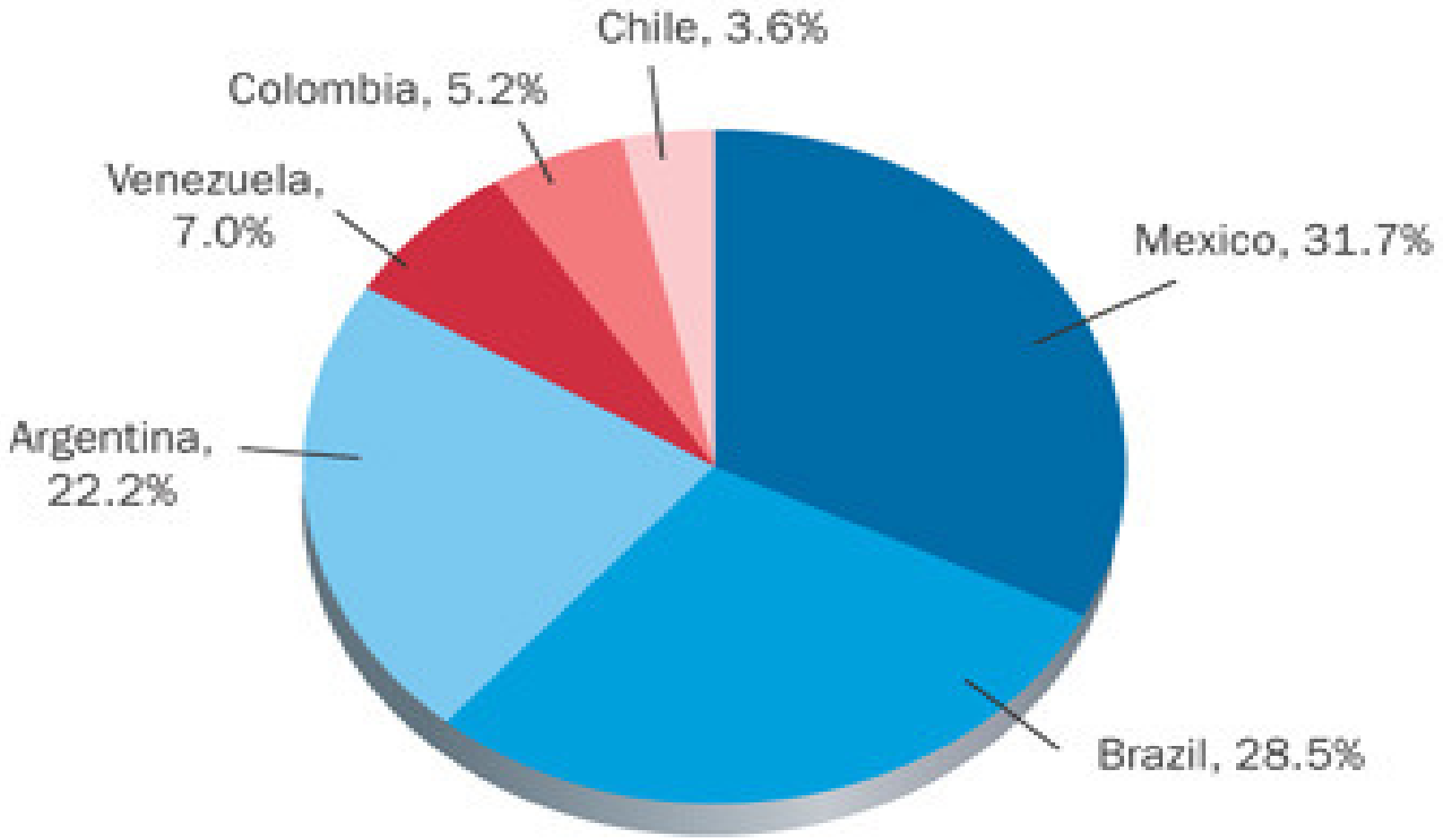
Source: *IMS-Global, 2003*

Figure 2. Share of $7.9 billion Central/Eastern European pharmaceuticals market.



Source: *IMS-Health, 2003*

Figure 3. Share of $22 billion Asian pharmaceutical market.



Source: *IMS-Global, 2003*

Figure 4. Share of $30 billion Latin American pharmaceutical market.

U.S. Expectation

Department of Health and Human Services

Regulations:

45 CFR 46

Food and Drug Administration

Regulations:

IRB - 21 CFR 56

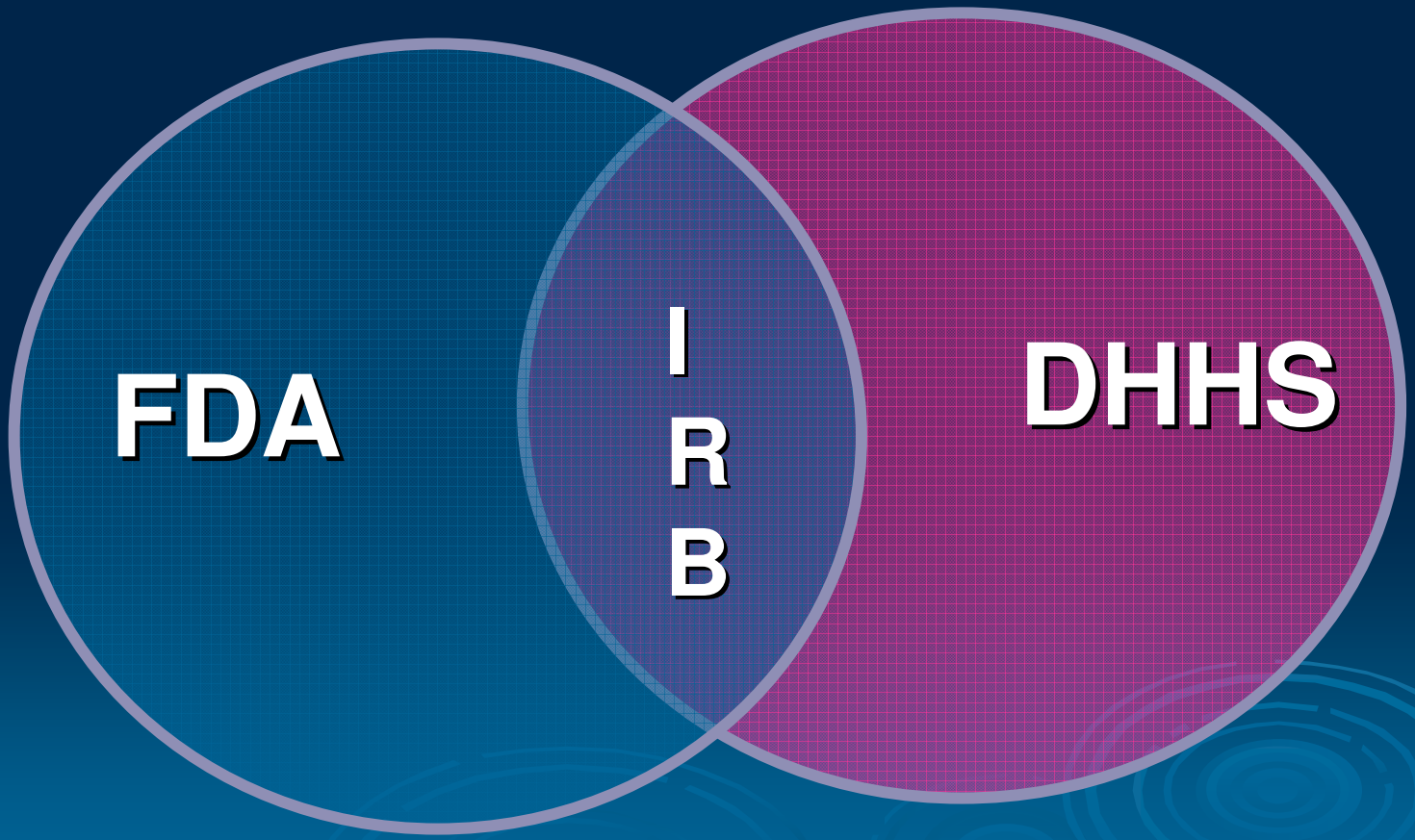
Informed Consent - 21 CFR 50

Health and Human Services (HHS) vs. FDA Regulations

- **Basic requirements** for IRBs and for Informed Consent are **congruent**

- **Differences** center on differences in **applicability**
  - HHS regulations based on **federal funding** of research
  - FDA regulations based on use of FDA **regulated product**: drugs, devices, or biologics

HHS vs. FDA Regulations



What is TGN 1412?

- Monoclonal Antibody
- Boosts the activity of human immune system protein

TGN 1412: What happened?

- First time in man
- Phase I March 13 2006
- 8 subjects in first cohort
  - < 40 healthy male volunteers
  - 2 placebo
  - 6 active
- All 8 treated in rapid succession
- $4,000

Daily Mail
24 HOURS A DAY

Hell of human guinea pigs

How the drug trial horror unfolded

By MICHAEL SEAMARK, Daily Mail 17th March 2006

We saw human guinea pigs explode

Victims tearing at shirts

By NICK PARKER, EMMA MORTON and JACQUI THORNTON

16th March 2006

SUN: A VOLUNTEER who escaped the drug test disaster told last night how he saw six healthy young men turn into wailing wrecks within minutes.

Human guinea pig *Raste Khan* — who did not know he had been given a harmless placebo in the test — said it was like a horror film unfolding before his eyes.

RASTE KHAN

"The test ward turned into a living hell minutes after we were injected. The men went down like dominoes. *First they began tearing their shirts off complaining of fever, then some screamed out that their heads felt like they were about to explode"*

"After that they started fainting, vomiting and writhing around in their beds"

"It was terrifying because I kept expecting it to happen to me at any moment. But I felt fine and didn't know why. An Asian guy next to me started screaming and his breathing went haywire as though he was having a terrible panic attack"

RASTE KHAN

"They put an oxygen mask on him but he kept tearing it off, shouting '*Doctor, doctor, please help me!'* He started convulsing, shouting that he was getting shooting pains in his back."

TGN 1412: What went wrong?

- Rapid onset
  - Cytokine Release Syndrome
  - Angioedema
- Testing continued
- Multiple Organ Failure
- 6 subjects admitted to ICU
- Prolonged immunosuppression

TGN 1412

Medicines and Healthcare Products Agency (MHRA)

- **Suspended CTA**
- **Immediate Inquiry**
- **Released**
  - **protocol, review and inquiry**

UK Government announces expert inquiry

TGN 1412

Expert Inquiry (Terms of Reference)

- What may be necessary in transition from pre-clinical to first-in-man Phase 1 studies, specifically:
  - Biological molecules with novel mechanisms of action
  - New agents with highly species-specific action
  - New drugs for immune system targets
- Interim report May 4, 2006
- 22 Recommendations

Recommendations

- Drugs that involve immune system should not be administered to healthy volunteers
- First dose to one person only
- Set up specialist centers for Phase I studies on high risk research
- Dialogue between drug maker and regulatory agency about safety data
- Use an alternative first dose assessment if the drug involves novel agents
- Conduct clinical trials at hospitals that has ICU

Lessons Learned
TGN 1412 (*1*)

- Recruitment
  - Financial Incentives
- Adequacy of Information
- Choice of Subject in Phase I
- Number of Subjects
- Timing of Administration

Lessons Learned
TGN 1412 (*2*)

- Sources of Information Reviewed
  - Regulatory Review
  - Ethical Review
- Independent Expert Review
- Relevance of Preclinical Testing
- Transparency in Development
  - Publishing preclinical work
- Response to Disasters

The Relevance of Animal Testing

- Need to establish validity
- Staggered timing
- Microdosing
- Ex-vivo

Future Direction for Human Subject Protections

Investigator's Qualification

vs.

Investigator's Certification (GCP)

IRB Registration

vs.

IRB Accreditation

Institution Commitment

&

Accreditation of HRPP

Monitoring of Consent Process

- Research Intermediate
- Consent Auditor

Sponsor

- Government – NIH
- Industry – Pharmaceutical & Devices
- Training IRB and Investigators

HUMAN SUBJECT PROTECTIONS