The landscape of TB diagnostics in India and barriers to innovation

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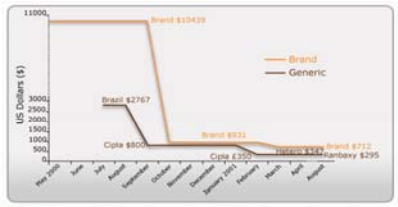
TB control in India

- Scale up of DOTS in India is one of the greatest public health accomplishments in our generation
- Yet undiagnosed and poorly managed TB continues to fuel the epidemic such that India continues to have the highest number of TB cases.
- Recognizing these challenges, the GoI has set an ambitious goal of providing universal access to quality diagnosis and treatment for all TB patients in the country.
- **Innovative technology and innovative delivery** systems that engage both public and private sectors are essential for reaching this goal.
  - Improved TB diagnosis and new technologies are therefore critical

India

- Strong and growing economy
- Globally competitive
- Increasing purchasing power
- Megamarket for almost every product or service
- Ability to dramatically reduce cost structure increase access (e.g. generic drugs and low-cost vaccines)
- Strong science and R&D skill base for innovations (e.g. innovations in IT, biotech, telecom)
- Huge economies of scale in R&D and manufacturing
- Strong and thriving private sector
- Potential for public-private partnerships
- International donor support (BMGF, GFATM, UNITAID, USAID, DFID, Wellcome Trust, etc.)
- There are several successful examples and precedents

Success story with drugs: ART



India is the largest supplier of generic ARVs to low- and middle- income countries, exporting two thirds of the drugs it manufactures[3]. Brazil, Thailand and South Africa also produce a significant amount of generic drugs and a number of African nations - such as Zambia, Ghana, Tanzania, Uganda and Zimbabwe - have developed local AIDS drug manufacturing facilities[4].

Rapid action in India for low cost flu vaccines, drugs and diagnostics


Business Standard

ICMR to launch low-cost swine flu diagnostic kit


THE TIMES OF INDIA

'India developing indigenous swine flu vaccine'


The New York Times Technology

We invite you to compare.

The Ally High Interest TFSA

Other bank TFSAs

Indian Company to Make Generic Version of Flu Drug Tamiflu


GLOBAL DIAGNOSTICS

China, Brazil, and India: Crashing the gates of the top ten IVD markets

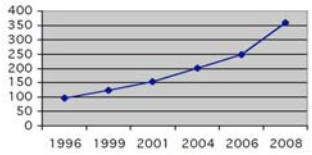
A look at the recent past, the present, and the near-term future of these emerging markets. BY CARL MCEVOY AND MICHAEL FARMER

ivdtechnology.com IVD TECHNOLOGY | SEPTEMBER 2008 27

Indian IVD market

Sectors	Crores	Rupees	US Dollars	
Chemistry	645	6,450,000,000	$150,000,000	42%
Hematology/Flow Cytometry	215	2,146,775,000	$49,925,000	14%
Coagulation	33	332,175,000	$7,725,000	2%
Immunochemistry	495	4,953,600,000	$115,200,000	32%
Molecular Testing	21	207,260,000	$4,820,000	1%
Other *	129	1,290,000,000	$30,000,000	8%
Exchange Rate	43.00			
Total Market	1,538	15,379,810,000	$357,670,000	100%

~350 million US$
Growing at ~15%



http://www.mcevoyandfarmer.com/

Indian IVD market

- Exact size is unknown (estimates vary a lot)
- But everyone agrees that it is a growing market (~20% annual)
- Everyone agrees that market is highly fragmented/segmented
  - Diagnostic companies: MNCs, Indian manufacturers, distributors (traders), intermediaries
  - Public vs. private
  - Urban vs. rural
  - Types of tests: Biochemistry, hematology, pathology, microbiology, etc.
  - Labs: large, medium, small
- Cost-conscious and highly competitive

Indian TB diagnostics market

- About 2 million active TB cases are reported each year
- Conservatively, about 10 million TB suspects need testing for TB every year; ~1 million need MDR screening
- In addition, testing for latent TB (e.g. TST, QFT), and extra-pulmonary TB will increase numbers that would need TB testing
- Exactly $ value of expenditure on TB diagnostics not known
- Indian-made tests have a large potential export market
- About 60 – 70% of testing is likely to happen in the private sector
- TB tests on the Indian market:
  - Smear microscopy (mostly direct ZN; underused in private sector)
  - Chest x-rays (widely overused for active TB)
  - Solid culture (mostly in referral labs and medical schools)
  - Liquid culture (e.g. BACTEC, MGIT 960, BacT) [offered also in path lab networks]
  - Molecular NAATs for active TB (mostly in-house; rarely GenProbe or Roche; mostly private sector)
  - Hain Genotype LPA (recently introduced in RNTCP; also entering private lab market)
  - TST (used mostly in children)
  - QuantiFERON-TB Gold In Tube (being used for active TB)
  - Serological antibody-based tests (very widely used in private sector)

Indian diagnostics market is miniscule in comparison to pharma


THE TIMES OF INDIA India Business

Drug patents worth $60bn to expire in 4 years

Make your Money work for you
iFOREX

CHENNAI: Nearly $60 billion worth of patents for drugs is set to expire in the next four years across the world and Indian pharmaceutical companies are now in a position to take a major share of this pie, industry members said.

Already, India is the No. 1 exporter of generic drugs in the world with exports to the tune of $8 billion in 2008-09.

Pharma is ~10 billion $

Diagnostics <5% of pharma size

Pharma not interested in diagnostics

Those who tried, mostly gave up

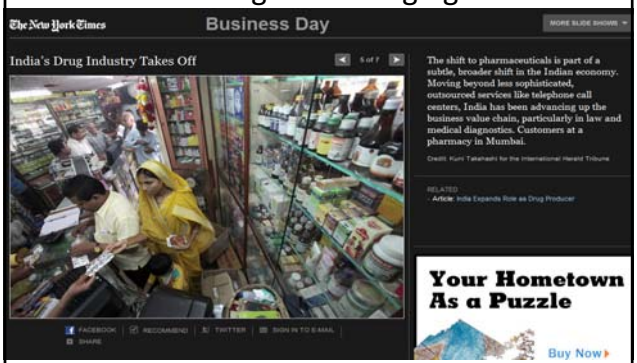
Biotechs are mostly into drugs, biologics and vaccines

Important points to note early

- No new drugs from India
- Probably no new vaccines
- Very few new diagnostics (see later)

- India is strong in generics, but weak in R&D

But things are changing...


The New York Times Business Day

India's Drug Industry Takes Off

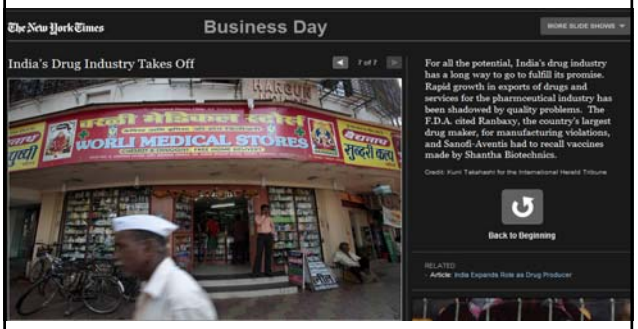
The shift to pharmaceuticals is part of a subtle, broader shift in the Indian economy. Moving beyond less sophisticated, outsourced services like telephone call centers, India has been advancing up the business value chain, particularly in law and medical diagnostics. Customers at a pharmacy in Mumbai.

Your Hometown As a Puzzle

Buy Now

"Moving beyond less sophisticated, outsourced services like telephone call centers, India has been advancing up the business value chain, particularly in law and medical diagnostics. Now it is showing a flair for manufacturing, particularly in goods demanding high-skill production and superlow prices..."

Quality remains a big concern



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Indian IVD companies

- ~50 or so, but not including small distributors
  - Only a handful of these are manufacturers
- All major MNCs have India offices:
  - Roche, Abbott, Bio-Rad, bioMerieux, Inverness, BD, Beckman Coulter, Siemens, ThermoFisher/Qualigens, Qiagen
  - Mostly act as distributors (very little local manufacturing; hardly any local R&D)
- Major Indian manufacturers (strong in generic rapid tests and ELISA):
  - Tulip Group, Goa
  - Span Diagnostics, Surat
  - J Mitra, Delhi
  - Transasia, Mumbai
  - Himedia Labs, Mumbai
- Smaller/boutique/start-up companies:
  - ReaMetrix, Xcyton, bigtec labs, etc.
    - Some of these are trying innovations and are keen on R&D

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LABS IN INDIA

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Labs in India

- Widely varying numbers (20,000 – 60,000!)
  - Depends on how one defines a "lab"
  - Very few large labs
  - Most labs in cities/towns
- Only 100+ have some sort of accreditation/certification (ISO, NABL, CAP)
  - Anyone can start a lab in India
  - Hardly any data on quality of lab services
  - Several anecdotes suggest poor quality assurance
  - Hardly any attempt at EQA
  - Certification based on documentation and processes, not on validity/reliability of tests offered

  – Key question: if quality cannot be assured, how will it impact scale-up of new TB technologies??

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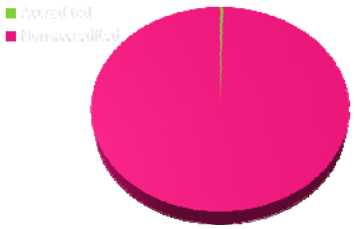
Accredited / certified labs in India

NABL
ISO
NABH
CAP
JCI
< 200 labs certified

Total no. of labs – estimated 50,000



John Kenneth, SJRI

REGULATORY ENVIRONMENT

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Regulatory environment

- Fuzzy and not transparent for diagnostics
- Diagnostics are hardly mentioned in the Indian Drugs & Cosmetics Act
- No clear documentation of what exactly is needed by DCGI
  - Sometimes, DCGI regulates diagnostics like they regulate drugs
- Importing is usually straightforward
  - No clarity on acceptable test performance
- Manufacturing is a state-level issue (takes longer and requires site inspection)
- No system for withdrawing bad tests
- TB is classified as a "non-critical" test and therefore poorly regulated
  - No attempt to revisit the critical/non-critical list (which was put together when HIV emerged, esp. blood bank screening)

  - Key question: how can regulation of TB diagnostics be improved??

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The difference in regulations for critical and non-critical diagnostics devices has led to lack of quality control

Regulatory process for diagnostics equipments

Source: Fingro "Diagnostic Center Feasibility Study – India", Nov 2008

MEDICAL DIAGNOSTICS – INDIA.PPT 17

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Medical Diagnostics - India. By: Netscribes (India) Pvt. Ltd

SUBOPTIMAL DIAGNOSTICS

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TB serology in India

- TB serology (mostly ELISA) is very widely used in the private sector
- Market for serology exceeds microbiological methods in almost all the labs
- Irrational testing practices are widespread
- All major service labs offer serology
  - Most widely used test is ANDA (France)
  - Brings in big revenue
  - >1.5 million tests done every year
  - >$15 million may be spent on serologies in India every year

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Serological Testing for Active Tuberculosis in India is More Costly and Less Effective than Sputum Smear Microscopy

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Dowdy D et al. Under review

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Hypothetical "Study Population"

- 1.5 million TB suspects
  - Conservative estimate of annual volume of serologic tests in India (sensitivity analysis on 3 mil)
- 1 in 7 actually have TB
  - Estimate from FIND, comparable to other studies
- Among TB patients, 53% are "highly infectious"
  - Would be diagnosed with 2 sputum smears in an ideal lab
- 5% HIV prevalence
- ANDA (from updated meta-analysis [Steingart K et al. PLoS Med 2007]:
  - Sensitivity = 76% highly-infectious
  - Sensitivity = 59% less-infectious
  - Specificity = 87%
  - Loss to Follow-Up = 15%
  - Cost = $20

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Costs of diagnosing and treating 1.5 million TB suspects in India.

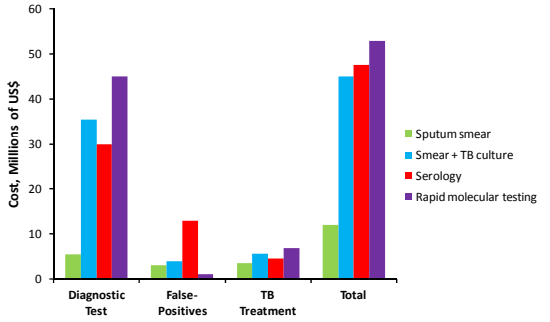

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Table 3. Cost-effectiveness of diagnostic strategies for 1.5 million TB suspects in India, relative to no microbiological testing.

Diagnostic Test	Cost (US$)	Additional TB Cases Treated	Additional False-Positive Cases Treated	Secondary Cases Averted	DALYs Averted	Incremental DALYs Averted	Incremental Cost per DALY Averted
Sputum smear microscopy	$11.9 million	44,000	36,000	443,000	622,000	622,000	$19
Sputum smear + TB culture	$45.0 million	71,000	48,000	555,000	752,000	130,000	$255
Serological testing	$47.5 million	58,000	157,000	411,000	520,000	(dominated)	(dominated)
Rapid molecular testing	$52.8 million	86,000	12,000	629,000	789,000	37,000	$209

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Summary of findings

- If used instead of sputum microscopy, serology would result in an estimated 14,000 more TB diagnoses and 121,000 false-positive diagnoses.
- However, by detecting more-infectious cases, smear would avert an estimated 102,000 more DALYs and 32,000 more secondary cases than serology, at approximately one-fourth the incremental cost ($11.9 million vs. $47.5 million).
- Addition of culture to sputum smear would avert 130,000 incremental DALYs at a cost of $255 per DALY averted.
- Relative to smear plus culture, molecular testing would avert 37,000 additional DALYs at $209 per DALY averted.
- Serology was more costly and less effective than smear microscopy in all sensitivity analyses.

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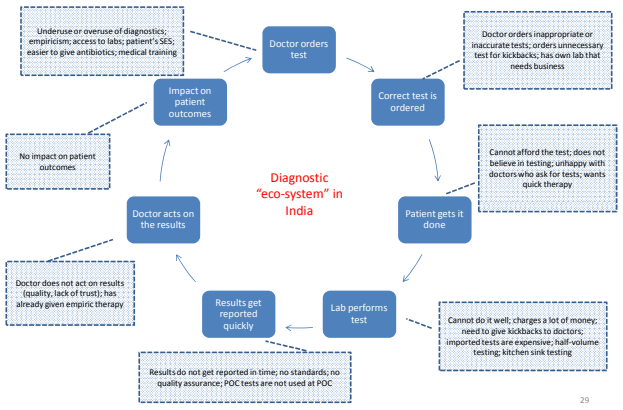

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2010: negative policy from WHO

- Commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes.
- Overall data quality was graded as very low and the Expert Group strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB.

World Health Organization TDR For research on diseases of poverty

COMMERCIAL SERODIAGNOSTIC TESTS FOR DIAGNOSIS OF TUBERCULOSIS

http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf

Other statements

- International Standards for TB Care discourages use of TB serology
- IAP has discouraged TB serologies
- RNTCP is planning a consensus statement against these tests
- IAMM is planning a position statement

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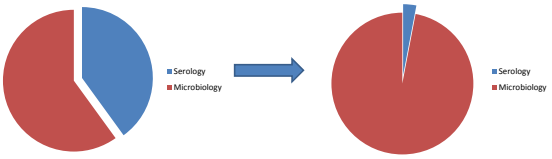
How can we roll-out new tests if bad tests 'eat up' the diagnostic space, and prevent us from using good tests?



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VALUE CHAIN FOR IVD DIAGNOSTICS IN INDIA

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First need to understand the value chain for diagnostics in India:

STATUS QUO: 3 VALUE CHAIN MODEL, WITH MODEL #1 DOMINATING

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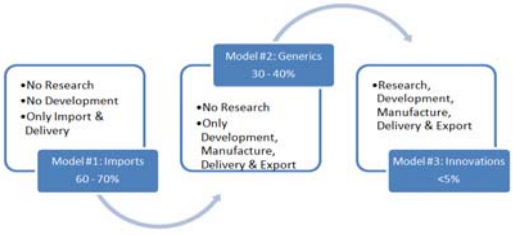
WHERE WE WANT TO GO: MODEL #2 AND #3 DOMINATING



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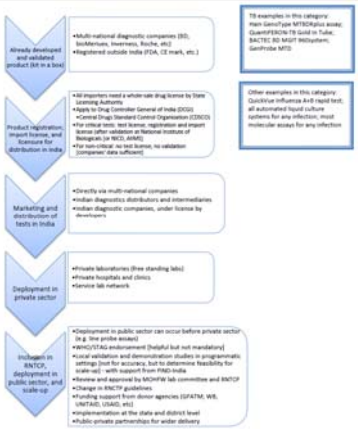
Model 1
Imports



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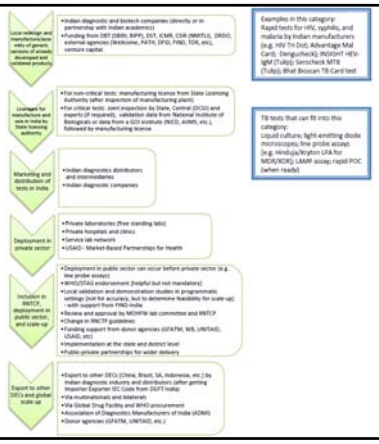
Model 2
Generics



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Model 3
Innovations

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To move from Model#1 to #2

Barrier

- No good TB tests to copy (until recently)
- Concerns about IP (recent phenomenon)
- Concern that market might not be profitable enough
- Concern that TB implies dealing with GOI/RNTCP [infamous "L1 tender"]
- Lack of funds for development (even if R is not needed)
- Even if DBT/DST/DHR funding is available, takes time and process not clear
- Perception that GOI is not private industry friendly
- Difficult regulatory environment
- "Made in India" is equated with "low quality"
- Severe competition results in cost cutting and compromised quality
- Tough to compete with low-cost generics from China

Enabler

- Success and experience in generic drugs and vaccines is helpful
- Generic diagnostics are already being made
- Manufacturing capacity is fair (but quality is an issue)
- Can be done with limited funds by major players (because R is not needed)
- Megamarket for any product and attractive to industry
- Until recently, IP was not an issue (nobody was checking)
- Even now, perception that IP is not a problem, unless patent held in India

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To move from Model#2 to #3

- Industry not strong in R&D (while strong in trading and generics)
- Academics do not understand product development (content with publishing)
- Academic-industry partnerships uncommon, weak
- Needs significant resources
- Time consuming and requires sustained commitment
- Difficult regulatory environment
- Lack of industry interest (TB market not worth the effort)
- Investors, industry and academics lack patience and are risk averse
- Industry lacks access to specimen banks, clinical validation
- Failure not tolerated and therefore not conducive for innovations
- Poor bench science facilities (e.g. very few BSL3 labs)
- Much of the innovative research is out-sourced work from outside India
- No serious commitment from philanthropic foundations, politicians or celebrities

- Strong and growing economy; thriving private sector
- Increasing funding via DBT, DST, DHR, etc.
- Special initiatives for industry (SBIRI, NMITLI, etc.)
- Several academic institutions involved in TB
- Clinical studies can be easily done with high case load
- Emerging culture of start-ups and biotechs strong in R&D
- Smart researchers, including returning Indians
- Success in IT has inspired entrepreneurs
- Non-conventional players are engaged (engineers, chemists, biotechs)
- Innovations are happening, but in bits and pieces (but no focused, concerted plan; no real collaboration)

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No doubt that India can innovate...

- "We found terrific scientific, engineering and administrative talent in India that today serves almost every business at GE" - Jack Welch, General Electric Co

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But can innovations happen without external push/resources?

- There are good examples of:
  - "out-sourced" innovations and "off-shored" R&D (e.g. John F. Welch Technology Centre, Bangalore; AstraZeneca´s Bangalore Research Institute)
- But they have been externally initiated/supported
- Will need a strong internally initiated and supported effort for diagnostic innovations

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More resources are now available in India and this might help with innovations

- DBT grants
- Technology Development Board
- CSIR/DST
- GOI partnerships with Wellcome Trust, etc
- Grand Challenges Explorations (GCE)
- Grand Challenges Canada
- X Prize Foundation
- Philanthropic groups

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Key questions for our group discussion

- How can we change diagnostic behaviors and replace bad tests with good technologies?
- How can we ensure quality in lab testing to support roll-out of new technologies?
- Despite the high TB burden, why is India yet to produce innovative TB products (diagnostics, drugs or vaccines)?
- What are the most important barriers for innovation?
- Should India stick to its strengths and focus only on generics?
- Why is the Indian industry not interested in TB (despite the market)?
- Why are academia-industry partnerships so weak in India?
- What are the sources of funding for TB innovations?
  - How can we convince GOI, Indian industry, VC and philanthropists to support TB innovations?
  - Has the grant model worked?
  - Will a prize model work in India?
- How can successes in sectors such as IT be replicated in health technologies?

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