Trends in Medical Technologies Innovation in China

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Background on E.A.S.E.-Medtrend

- Equal Access to Scientific Excellence
- Emphasis on Access
- We have been in China for over 10 years
- Our activities center around diagnostics

What is driving innovation in medical (diagnostic) technologies in China

- Health care needs of a large population
- Policy from the central government
- Industry and academia’s response to these forces

Diagnostics Market Dynamics (China)

- There are more than 28,000 hospitals in China

  Class III ~1,400 Class II~6,500 Class I ~8,000

  Unrated ~12,000 Private hospitals>1,000
- IVD market size is US$3 billion in 2013
- Growth in last 7 yrs: 25-30%
- Foreign companies dominate market (Roche, Seimens, J & J, Beckman/Danahar, Sysmex, bioMerieux, Thermo Fisher, Allere)
- Rapid growth of local companes (Mindray, Dirui, Kehua, Snibe, Maker, Leadman, Biosino, Autobio)

Some challenges for hospitals

- Seeking medical care is a tedious, time-consuming and inconvenient process.
- Patients need to travel long distances in many cases.
- Hence the time required to make an accurate diagnosis is important because repeat/follow up visits present a heavy burden.
- Coupled with a large patient load, there is a therefore a strong demand for high throughput tests in most hospitals---much more than in advanced countries.

Influence of the government on medical technologies development

Government policy on coverage & “reimbursement rate” is currently dependant on location, but will be moving towards harmonized rate.

Remimbursement rate for diagnostic tests are also “method/technology” based, and also depends on whether the product is a domestically made or imported one (imported products are allowed a higher rate in most cases because traditionally they represent tests which are not available domestically, or perceived as better in quality)

Reimbursement rates and market factors

- Reimbursement schedule is an effective way for the government to control the prices of commercial tests. To be marketable, manufacturers must produce and sell the tests to the hospitals that allow them to make a profit and still be within the reimbursement schedule. Coupled with China's lower cost of manufacture, and the added cost of transportation for foreign products, this tends to favor "Made-in-China" products.
- This leads to a tendency of foreign companies setting up manufacture in China, and bringing in necessary technology.
- In addition, manufacturers and hospitals favor marketing and prescribing diagnostic tests which are higher in profit.

Example of how profit influences different test use

- Test for Toxoplasma IgG and IgM (reimbursement is currently method based)

Cost of Tests	Reimbursement schedule	Hospital profit
ELISA 15RMB	30 RMB (Shanghai)	15 RMB
CLIA 30 RMB	60 RMB	30 RMB
ELISA 15 RMB	45 RMB	30 RMB
CLIA 30 RMB	45 RMB	15 RMB

Trends in Clinical Chemistry

- This is an area of clinical diagnostics which is most developed with regards to reagents and instruments. There are many players covering the entire spectrum of capabilities.

Trends:

- Dry chemistry for serum/blood based tests (urine chemistry already very well developed)
- Expansion of menu, with emphasis on domestic manufacturing
- Development of homogeneous immunoassay systems and reagents which can use clinical chemistry autoanalyzers
- Development of Reflex Testing capability

Trends in Immunoassay

- Development of high-throughput Random Access instruments with large on-board menus.
- Expansion of menu

(Even medium size hospital labs are demanding Continuous and Random Access and Stat capabilities, 200 Tests/hour with turn around time of 30 minutes or less, and 20+ on board test menu)

There are several manufacturers in China who are marketing such products and generally use magnetic beads as the solid phase because it can be handled by existing liquid handling systems.

The challenge is development of an instrument with these features using traditional microwell format, and to do this without being unwieldy and cost effectively. Since there is a large pool of existing tests, these can be imported directly into this system. (There is at least one company doing this)

Innovative trends in Microbiology

- One of the highest volume and expensive test in microbiology has been blood cultures. Becton Dickinson and BioMerieux are dominant in the Chinese market with their systems which can also determine antibiotic sensitivities. These systems (Bactec in particular) have also been used in TB diagnosis, because of the slow growth of TB and in China they are frequently multiple drug resistant.
- The challenge is two fold for China. These imported reagents and machines are extremely expensive. They provide sensitivity and relative speed, but do not provide identification of the organism.

Chinese companies can now use various methods for real time detection of bacterial growth in individual blood culture bottles, using continuous individual monitoring methods. They are also attempting to use metabolemic data bases to identify the growing organisms, with built in probes that monitor these metabolic products in the bottle.

Innovative trends in Rapid Diagnostic Tests (RDT/POCT) in China

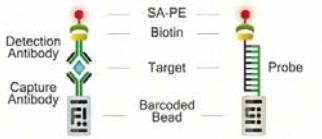
- This is a high growth area with many players. It is easy to produce, easy to use, and easy to sell.
- Actual needs and market forces are driving the price down and also increasing the menu.
- There has been several major areas where advances have been made:
  1. Multiplexing (simultaneous determination of multiple analytes)
  2. Ability to use different specimen types (blood, plasma, serum, saliva, urine)
  3. Semi-quantitative and Quantitative read outs
  4. High-throughput instruments (for tests where there are distinct advantages of RDT over liquid chemistry)
  5. Profile tests for differential diagnosis and monitoring of patients

Trends in Nucleic Acid based testing in China

- Large numbers of small diagnostic companies have sprung up providing a large menu of tests for conventional and RT-PCR, and the number of technologists capable of performing test are rising rapidly. Some of hurdles include the lack of established fee schedules.
- Development trends include:
  1. Diversification of amplification methodology, especially towards isothermal methods.
  2. Increased stability of reagents eg. Glassification of enzymes
  3. Simplification or automation of sample pretreatment/processing
  4. Alternative platforms for doing liquid arrays eg. Nanobar codes

Barcoded Magnetic Beads

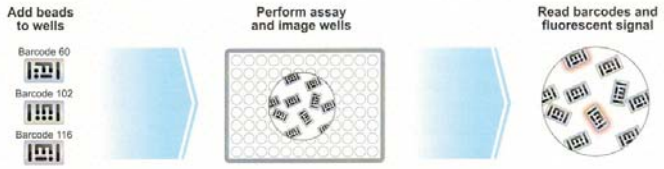
PlexBio's IntelliPlex™ technology utilizes barcoded magnetic beads (BMB). These flat microparticles have photolithographic barcodes and are composed of paramagnetic silicon wafers encapsulated in highly stable biocompatible polymer modified for DNA or protein attachment.



Immunoassays | Molecular Assays

The digital barcodes allow our optical imaging system, the DigiPlex™, to identify each bead under bright field with no ambiguity. The binary encoding principle allows us to offer up to 2^12 (4,096) unique barcodes.

The barcoded beads are chemically treated so that they can bind assay-specific biomolecules through activation of surface carboxyl groups. Biological probes or antibodies can be conjugated to beads so that each barcode corresponds to a particular target. The different barcoded beads are then mixed together with samples and fluorophore conjugate for multiplex DNA/RNA- and protein-based assays. The combination of probe or antibody identification through bead barcodes and target detection through fluorescence intensity results in a powerful, flexible multiplex platform for IVD applications and other research interests.



Results Table

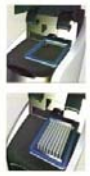
Bead Type	Barcode 60	Barcode 102	Barcode 116
Bead count	44	39	58
Fluorescence	5	2515	1672

Some Advantages

- High classification accuracy
- Flexible multiplexing capability
- Excellent stability
- No fluorescent interference
- Easy to handle

Digital Multiplex Analyzer

The PlexBio DigiPlex™ (Cat. No. 80001) is a robust optical imaging system that is both highly effective and easy to use. The compact machine is simple to maintain – no wash or waste fluid management required – and it accurately decodes beads through high-contrast imaging. The system is compatible with any protein- or DNA-based assays using PlexBio's IntelliPlex™ barcoded magnetic beads.



LED

The DigiPlex™ uses LED instead of complex lasers for both bright field illumination of barcodes and the excitation of the fluorescence reporter, which makes the DigiPlex™ more affordable and compact. Calibration is a quick, simple process with the DigiPlex™ Calibration Kit and takes less than 5 minutes.

CCD Imager

The CCD camera works in conjunction with the moving stage to read each well in a 96-well plate. The imager will autofocus for each well to ensure optimal readings of the beads, then capture images in both bright field and fluorescence. Barcodes and fluorescence measurements are combined for each bead, resulting in reaction intensity data for multiple analytes per sample.

Bright Field Image

Fluorescent Image

Benefits of DigiPlex™ Digital Multiplex Analyzer

Accuracy
Digital barcode classification means no fluorescence interference or gating issues; beads read on well bottom completely eliminates cross-over

Convenience
Intuitive, user-friendly interface with a short installation time, 15-minute startup, 5-minute calibration, and instant shutdown

Small footprint
Not only is the DigiPlex™ compact, but few additional laboratory equipment is needed to perform IntelliPlex™ assays

Efficiency
Run multiple tests with one sample by multiplexing your assays in a compact machine

Low-maintenance
No fluids or probes mean no leaks, no waste bottles, and no fluids to refill

Reliability
Few moving parts and no fluidics mean less downtime, troubleshooting, and servicing

Microfluidics/Lab on a Chip

Over twenty universities and research institutes and commercial companies are actively engaged on various aspects of diagnostics using microfluidic techniques. The explosion in research in this area are witnessed by many recent symposia in China, Taiwan and Hong Kong.

Several factors have helped to accelerate research and development in this area:

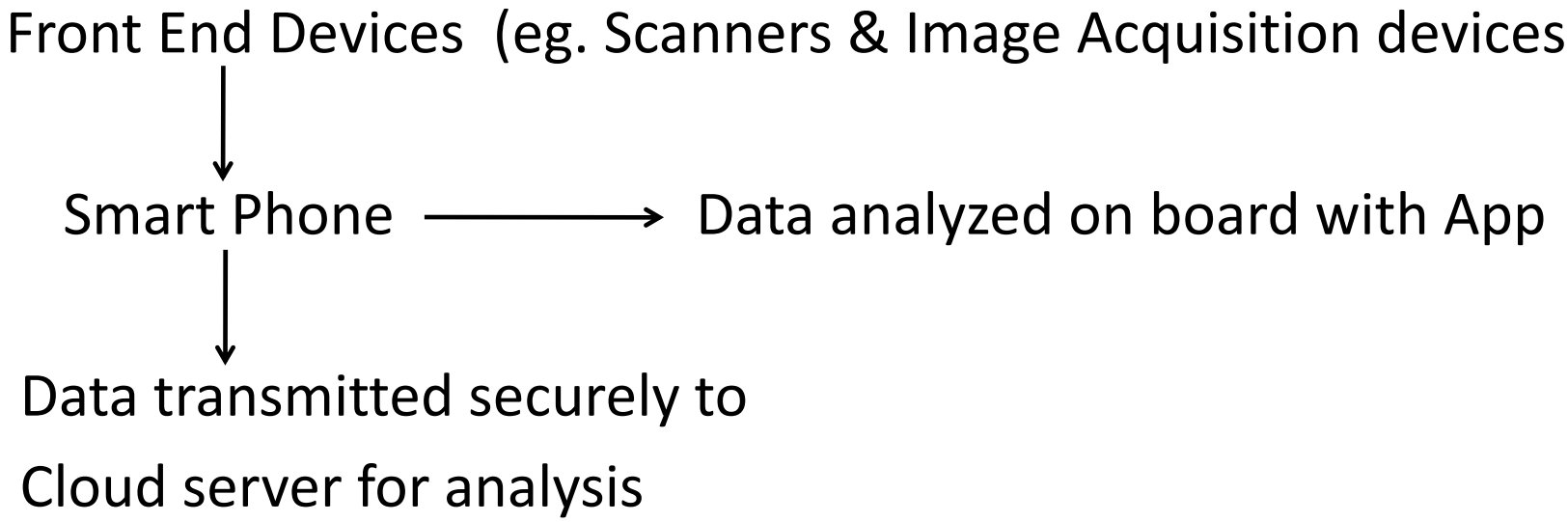
1. Inexpensive photolithography/3D printing
2. Access to specialty polymers a relatively inexpensive price
3. Development in coating technologies and nanopumps in China
4. Collaborative efforts between the life science and engineering disciplines at academic institutions

The Challenges:

Business models for commercialization. Familiarity and acceptance of the methods.

Smart Phone based testing

- An area which holds great promise is the development of test formats and devices which can interface with smart phones.



Making it work!

- EASE of use: minimum training and idiot-proof protocols
- Authenication: Type of test and relevant information on the test
  (eg. Manufacturer, lot no. exp date, calibration etc.)
  Time and location of performance and operator
  (this is done automatically with device ID, GPS etc.)
- Security: Proper encryption of data and controlled access
- Efficiency: Ability to interface with different types of data acquisition devices. (Challenge is to have tests in a format amenable to be “read”)

Planned Applications in China

- Food Safety Monitoring (Testing by field inspectors)
- Epidemiological studies & Outbreak monitoring
- Diagnostic tests in remote areas (eg. Yunnan mountains)
- Home testing (eg. Diabetes, ovulation, kidney function etc. In addition to parameters such as heart rate, blood pressure)

Challenges to Industry:

Business Model: Open system or Closed system?

How to make money on such systems.

How to protect confidentiality of data.

Government Funding and Regulatory trends affect R & D and Innovation

- There is a lot of central and local government funding to industry and local universities for projects that can yield potential commercial products (which in turn leads to increased GDP and tax income).
- This tends to favor products which can easily obtain regulatory approval. In China, Class I products require only notification; Class II products require provincial level CFDA registration and takes several months; Class III products require registration in Beijing (Imported products need to be registered in Beijing even though they may be Class II) and can take up to 18 months.
- Class II and III products require different levels of clinical trials and hence the cost of registration can be quite high depending on the product.

Regulatory Trends

- There has been significant changes in CFDA concerning diagnostic device registration and production regulations in August 2014 which came into effect in October 2014.
- Some products have been moved from Class III to Class II.
- Products which can be proven innovative or is urgently needed will enjoy regulatory relief (How this is defined is not clearly outlined yet)
- More flexibility with regards to outsourcing and contract manufacture. (allows small entities/institutes/universities to bring products to market)

Thank You !

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