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China Dips Its Toes in Disruptive IVD Tech

► By Hrish Poola, Jon Chen, 19 August 2015

THE NUMBER OF CHINESE IVD COMPANIES exhibiting at the 2015 American Association for Clinical Chemistry Annual Meeting (AACC) & Clinical Lab Expo (CLE) was slightly down from last year, but the breadth of diagnostic products and innovations from China appears to be on the up. Hrish Poola and Jon Chen discuss the moves China is making to become a generator of disruptive technologies and reports on the new products and the players emerging from this market

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This year's AACC & CLE, which took place on 27-30 July in Atlanta, Georgia, featured 92 China-based companies, slightly down from last year's record turnout of 98 exhibitors. Over the years, China-based suppliers have diversified far beyond the early days of semi-automated systems, ELISA/MTP offerings, three-part differential hematology, and chemistry reagents. In Atlanta, China-based players showcased a range of clinical chemistry laboratory systems (CCLS), chemiluminescence immunoassay (CLIA), integrated chemistry/immunoassay work cells, and products related to hematology, coagulation, molecular testing, rapid testing, point-of-care (POC), flow cytometry, and urinalysis.

Despite offering expanded product portfolios and increased technology sophistication, China-based vendors still lag behind multinational companies when it comes to quality, service, distribution channels, commercial experience and internal R&D/discovery programs. Nonetheless, China continues to set its

sights at the upmarket end of the IVD industry and stake global ambitions, investing in more disruptive technologies, including molecular diagnostics, or nucleic acid testing (NAT), next-generation sequencing (NGS), mass spectrometry, and liquid cell biopsy products.

Recent moves

Transforming China from a manufacturing to an innovation power has been a top development priority for China's current leadership and a range of reforms in reimbursement, regulation, public financing, and procurement have sought to drive local manufacturer competitiveness. The country's national high-tech development plan lists NGS and mass spectrometry among key R&D focus areas. Molecular and companion diagnostics (CDx) accounted for the majority of new items added to the latest (2013 edition) national clinical laboratory catalog since the previous version (2007). Additionally, the China Food and Drug Administration has provisioned fast-track approval of new and innovative domestic products, including DaAn's NGS Down syndrome test kit (see below). Currently, molecular testing is looking to upend China's traditional serology-based blood processing market thanks to the 2013-2015 national NAT-Blood Processing (NAT-BP) implementation plan; in early 2015, China reiterated its goal of converting provincial and city-level blood centers nationwide to NAT by year-end 2015. In the medium to long-term, NGS may reshape prenatal screening, though high costs, limited reimbursement, undeveloped guidelines, and stringent accreditation processes remain barriers.

Furthermore, to fund such product line expansion and next-generation development, IVD companies have sought public financing, trading on the Shanghai and Shenzhen mainboards or the National Equities Exchange and Quotations (NEEQ) OTC market. A flurry of IPO activities since late 2013, when the

Table 1

Company	Pre-IPO Consultation	Environment Audit	Prospectus	CSRC Review	IPO	Stock Exchange	Main Product Lines
Autobio	Completed	Passed	Filed	null	null	Shanghai Stock Exchange	IA
AVE S&T	null	null	null	null	Completed	NEEQ	Urinalysis
Baibo Biotechnology	null	null	null	null	Completed	NEEQ	Micro
Beijing Strong	Completed	Passed	Filed	Passed	Completed	Shenzhen Stock Exchange	CC Reagent
Clinisciences	null	null	null	null	Completed	NEEQ	CC Reagent
Darui Biotechnology	null	null	null	null	Completed	NEEQ	TRFIA, NGS
DIRUI	Completed	Passed	Filed	Passed	Completed	Shenzhen Stock Exchange	CCLS, hema, urine
EasyDiagnosis	null	null	null	null	Completed	NEEQ	POC
Fenghui	null	null	null	null	null	NEEQ	CC Reagent
HEALTH BioMed	Completed	Passed	Filed	null	null	Shenzhen Stock Exchange	Distribution
HuiZhiKang	null	null	null	null	Completed	NEEQ	CCLS
Hyribio	Completed	Passed	Filed	null	null	Shenzhen Stock Exchange	Gene chip (HPV)
Jiancheng Biotech	null	null	null	null	Completed	NEEQ	Distribution
Kangmei Biotech	Completed	Pending	null	null	null	null	CC Reagent
King Diagnostic	null	null	null	null	Completed	NEEQ	Coag, Spec Protein
Linked-Biotech Pathology	Completed	Passed	Filed	null	null	Shenzhen Stock Exchange	Cytology
Maccura (formerly Sichuan MAKER)	Completed	Passed	Filed	Passed	Completed	Shenzhen Stock Exchange	CC, IAS, distribution
Ningbo Medical System	Completed	Passed	Filed	Passed	Completed	Shenzhen Stock Exchange	CC Reagent
Rayto	Completed	Passed	Filed	null	null	Shenzhen Stock Exchange	IVD systems
Runda Medical	Completed	Passed	Filed	Passed	Completed	Shanghai Stock Exchange	Distribution
SNIBE	null	null	null	null	Completed	NEEQ	IAS
SureXam	null	null	null	null	Completed	NEEQ	Companion Dx
Thalysis	Completed	Passed	Filed	null	null	Shanghai Stock Exchange	Distribution
Tianjin Xinhong	null	null	null	null	Completed	NEEQ	Distribution
Wondfo	Completed	Passed	Filed	Passed	Completed	Shenzhen Stock Exchange	POC
Xincheng Biological	null	null	null	null	Completed	NEEQ	CC Reagent
Zeesan	null	null	null	null	Completed	NEEQ	NAT

Source: Boston Biomedical Consultants Inc

Chinese Securities Regulatory Commission (CSRC) resumed IPO reviews following a 14-month moratorium; four IVD-related companies— Maccura, Ningbo, Runda, Wondfo— completed their IPOs in the first half of 2015, though regulatory reviews were again suspended in the wake of the historic 2015 China market stock crash (see Table 1).

Chinese innovations

China-based disruptive technologies played a marginal role at AACC, with several China-based companies, including CapitalBio, Coyote, DaAn, DiagCor, Fosun, Health Gene, HybriBio, Sansure, Tianlong, and ZJ Bio-Tech (promoted as Liferiver in the US), showcasing molecular offerings. At least two exhibitors— CapitalBio and DaAn— have stepped into the NGS arena with recent product approvals. China-based producers continue, under the steady watch and encouragement of the government, to invest in disruptive technologies on the mainland.

Molecular testing

In molecular testing, PCR, a mature technology, remains the dominant platform for China-based manufacturers, which differentiate themselves through broader assay portfolios, particularly in pathogens and CDx (eg DaAn, Sansure, ZJ Bio-Tech), multiplex capabilities, POC solutions (eg, Coyote, Ustar), alternative amplification methods to PCR, such as isothermal amplification (eg, Randu, Ustar), and biochip/microarray offerings (eg, CapitalBio, Fosun (Yaneng), HybriBio). Overall, however, multinationals have led the way in molecular innovation. For example, Cepheid, in support of China's TB programs, completed a record shipment of >700 GeneXpert systems in China in one quarter (second quarter of 2014) and recently announced additional commercial expansion in the country.

NGS

2014 laid the groundwork for the emerging NGS industry in China when the National Health and Family Planning Committee (NHFP) and CFDA issued a series of new policies and initiatives to regulate and promote the domestic industry. Key measures include new rules on supervising NGS products and services for clinical use, approval of pilot clinical sites for NGS-based non-invasive prenatal testing (NIPT) and cancer diagnostics, and establishment of the national External Quality Assessment (EQA) program for NIPT. In 2014 and 2015, a range of locally-developed NGS products has been cleared by the CFDA, often involving an international partner for the NGS instrument (see Figure 1).

CFDA-cleared NGS analyzers in China include:

- Berry Genomics' NextSeq CN500 (co-developed with Illumina)

- CapitalBio's BioelectronSeq 4000 (based on Life Technologies' ion torrent semiconductor sequencing method)
- DaAn's DA8600 (Life Technologies)
- BGI's BGISEQ-100 (based on Life Technologies' ion torrent semiconductor sequencing method), BGISEQ-1000 (Complete Genomics)
- HYK Gene's HYK-PSTAR-IIA.

Recently, in August 2015, Yantai, Shandong-based Luye Pharma Group acquired Singapore-based Vela Diagnostics and the latter's PCR and NGS portfolio for an estimated \$30m. The deal marks the second M&A transaction involving a China-based company and an overseas NGS developer following BGI's acquisition of U.S.-based Complete Genomics in 2012 (completed in 2013). BGI touts itself as the largest genomics service provider in China (and the world).

Liquid cell biopsy/circulating cell-free tumor DNA

Named one of the top 10 technology breakthroughs in 2014 by the MIT Technology Review, liquid cell biopsy is a brave new field for Chinese researchers, with a handful of China-based companies (none exhibited at AACC 2015) developing related products or partnering with multinational companies. The first product introduced in China was Qiagen's QIAamp circulating nucleic acid kit for research use (distributed by Lianke Biotech). YZY Bio's CTC-Biopsy is an automated system capturing and staining peripheral blood circulating tumor cells (CTCs). Partnerships, investment, and M&A in the space have intensified. In May 2015, Livzon acquired 18% of Cynvenio, a California-based developer of liquid biopsy systems.

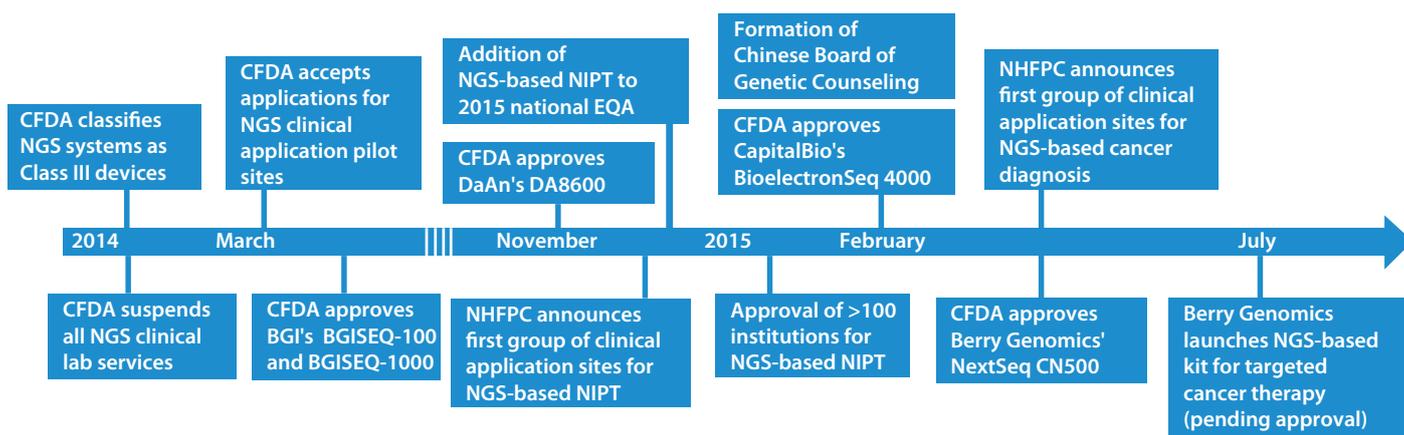
Mass spectrometry

Like NGS, mass spectrometry is blessed by the national high-tech development plan and while three multinational companies— bioMérieux, Bruker, and Waters— have introduced products in China since 2008, only one domestic company, Beijing-based Bioyong has commercialized its own mass spectrometry platform, the CFDA-cleared Clin-TOF. Another Beijing-based company, Biohui recently acquired Advion, a New York-based developer of compact mass spectrometers.

China's IVD players at AACC

CapitalBio, a biochip developer (affiliated with Qinghua University), promoted its LuxScan microarray scanners along with its microarray test kits. The company's R&D focus recently expanded to NGS with CFDA approval of the BioelectronSeq 4000 for trisomy 13, 18, and 21 in February 2015. Notably, CapitalBio's independent clinical laboratory is among the first group of NHFP-approved pilot sites for NGS-based cancer diagnostics. The company's Easy Array 3A integrated microarray workstation

Figure 1. Top NGS Market Events in China, 2014-15



Source: Boston Biomedical Consultants Inc

is pending approval in China and is currently being used to test the company's deafness gene mutation detection array kit in the US.

Coyote is one of a few China-based companies in the POC molecular space. The company showcased its new Instant-Gene portable PCR system and Gel Box portable electrophoresis analyzer, along with the Mini-8 "one-step" realtime PCR cyler and the Theater Slim PCR cyler (all devices have yet to receive CFDA approval). Of note, the Mini-8 has been tested at grassroots community health centers in China and was selected under the WHO procurement program for Ebola testing in February 2015 (used in Sierra Leone during the outbreak). The company's R&D pipeline includes PCR assays for infectious disease, cancer, CDx, and drug-resistant microorganisms.

DaAn, long the market leader in the PCR reagent market, promoted a range of offerings, including a liquid-based cytology system (from LBP Medicine); the company's recently developed automated PCR amplifier, the AFD4800, is pending CFDA approval. While not promoted at the show, DaAn has recently delved into CDx and NGS. In November 2014, DaAn received CFDA approval for the DA 8600 (co-developed with Life Technologies, a Thermo Fisher company) and associated Ion Torrent-based Non-Invasive Prenatal Testing (NIPT) assays for trisomy 13, 18, and 21. In October 2014, Darui, majority owned by DaAn, signed an agreement whereby the latter would transfer to Darui all terms and conditions of the partnership with Life Technologies to co-develop NGS products; in June 2015, DaAn reduced its ownership stake to 47.1% in Darui, which will list on the NEEQ market (DaAn will continue to control Darui's R&D and sales and marketing for NGS).

DaAn's core business remains a broad PCR reagent portfolio, including CDx such as EGFR; a MERS-CoV test kit remains in development.

Fosun promoted products from its whollyowned unit, Long March, as well as from its affiliated companies miacom, Saladax, and Yaneng. Spotlight fell on multiplex PCR kits from U.K.-based GeneFirst, PCR kits for BCR-ABL, BRAF, EGFR, JAK2, KRAS, and PIK3CA, and an HPV multiplex probe amplification kit. Of note, in early 2015, Fosun made an investment (unspecified amount) in GeneFirst and formed a partnership to market and distribute the latter's products. Fosun displayed Yaneng's gene chipbased genotyping test kits (HPV, HBV, and mycobacterium). Fosun, the exclusive manufacturing, distribution, and regulatory partner for Saladax's MyCare assays in China, promoted the MyCare line of personalized diagnostic assays; My5 FU, MyPaclitaxel, and MyDocetaxel assays are currently available in China, with 10 additional tests in development. Additionally, Fosun displayed Germany-based miacom's rapid diagnostic FISH test for sepsis, pneumonia, and other pathogens.

Health Gene, a wholly-owned subsidiary of Health BioMed (one of China's largest IVD distributors), showcased its SureX genotyping test kits (e.g., ADLH2/ADH1B, CYP2C19, HPV (25 subtypes)) and its 5 dyes/6 dyes SureID Human STR Identification Kit (e.g., 21G, PanGlobal, 27Y, Compass).

Hyribio promoted its HybriMax in-flow hybridization biochip technology with its existing HPV genotyping and new thalassemia (alpha and beta) and prenatal/neonatal screening kits (hearing loss susceptibility, G6PD, PAH, and CMV). In July 2015, the company filed for its IPO to be listed on the Shenzhen Stock Exchange with aims to fund R&D, manufacturing, and commercial laboratory services in molecular testing.

Sansure highlighted its PCR reagent portfolio based on one-tube, no-wash magnetic bead technology. The company offers an infectious disease-focused PCR test portfolio and Natch 64 nucleic acid extractor, with PCR combo kits for donor screening (HBV, HCV, HIV) pending clinical trials and CFDA review.

ZJ Bio-tech, promoted under the Liferiver brand in the U.S., highlighted its comprehensive PCR reagent portfolio along with its Autrax 192 nucleic acid extractor (received CFDA approval in 2014) and Life 96 real time PCR system.

As a major domestic PCR reagent supplier, ZJ Bio-tech continues to compete with DaAn in offering the most comprehensive test portfolio. ZJ Bio-tech is one of five China-based companies granted CFDA approval for its Ebola test kits since the outbreak in 2014, with the others being BGI, DaAn, Puruikang, and Tianlong. ZJ Bio-tech's Ebola test kit (also CE Marked) was one of three recommended under the WHO procurement program, the others are produced by Altona (Germany) and Corgenix (U.S.). The company's MERS-CoV test is pending CFDA approval.

Additionally, select China players, while absent from AACC 2015, continue to influence newer IVD technologies in China; of note, the below is not a comprehensive representation.

Amoy offers nearly 10 CFDA-cleared PCR CDx assays. Berry Genomics received CFDA approval for its NextSeq CN500 (co-developed with Illumina) and trisomy 13, 18, and 21 assays for NGS in March 2015. In July 2015, the company unveiled its Onconi CDx kit, detecting ALK, BRAF, EGFR, HER2, KRAS, and TP53 mutations for targeted cancer therapies. BGI offers two CFDA-approved NGS systems, the BGISEQ-100 and BGISEQ-1000 (Complete Genomics), and related NGS assays (trisomy 13, 18, and 21).

The not so distant future

China has clearly made known its long-term ambition as a generator of disruptive IVD technology, particularly with recent product introductions, partnerships, and M&A. Despite its rising investments, China-based suppliers will continue to be challenged by better capitalized and more experienced multinationals offering greater sophistication and downstream support. The future will reveal China's success in the marketplace. These are early days and China-based innovation, while facing steep challenges, will likely draw the spotlight in the not so distant future.

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