Strategic Review of Point-of-Care Diagnostics

By Scientia Advisors
Acronyms

• CC = Clinical Chemistry
• DOA = Drugs of Abuse
• IVD = *In vitro* Diagnostics
• MDx = Molecular Diagnostics
• MRSA = Methicillin Resistant Staphylococcus Aureus
• NPT = Near Patient Testing
• POC = Point of Care
• OTC/PST = Over the Counter/Patient Self Testing
• WW = Worldwide
Point of Care Diagnostics

Definition

• Definition:

POC Diagnostics are composed of approved tests that are performed near the patient and at-home/self-tests (OTC) that require a quick turn around time and do not require permanent dedicated space in a clinical laboratory. This also includes tests performed in STAT* labs

* Small labs near ER/ICUs at large hospitals that perform rapid tests; typically consists of bench-top systems

End-Users

Home  Physician  Hospital
Point-of-Care (POC) Diagnostics
Attractive IVD segment that’s gaining traction

Definition
• POC Diagnostics are composed of tests that are performed near the patient (NPT) and over the counter/patient self testing (OTC/PST) that require a quick turn around time and do not require permanent dedicated space in a clinical laboratory.

Key Trends and Growth Drivers
• Diabetes represents 67% of the market and is primary driver of the POC market.
• Other high growth areas include cardiac, coagulation, blood gas, and infectious disease.
• MDx based tests for infectious diseases such as MRSA and Sepsis that are POC oriented are promising segments that have significant growth potential.
• Adoption of POC takes more time than traditional IVD systems and is highly contingent on physician education and analytical precision, flexibility of technology platform.

The POC Market By Disease ($M)

- Diabetes
- Cancer (FOBT)
- Pregnancy & Fertility
- Infectious Disease
- Drugs of abuse
- Blood gas
- Urinalysis
- CC (incl. Cholesterol)
- Coagulation
- Cardiac
- Diabetes

Source: Scientia Analysis, Company reports
POC market excluding blood glucose & pregnancy testing
Several attractive segments exist within

Key Observations

- Cardiac, Coag. and Infectious appear to be the most attractive segments from a future growth rate perspective
- Although Clinical Chemistry (incl. Cholesterol) is a mature segment, point of care CLIA waived testing exhibits double digit growth
- Urinalysis, and Hematology are relatively mature segments
- Cardiac is the fastest growth sector being driven by overall growth of incidences of Acute Coronary Conditions across the globe as well as launch of new rapid tests (e.g. BNP, Stroke)
- Coag. is the 2nd fastest growing segment being driven by increased monitoring of patients on lifelong warfarin therapy for prevention of stroke, heart attack, DVT, and other conditions requiring long term anticoagulation
- New “disruptive” innovation likely to trigger added growth across various sectors
  - Infectious with multiplexed PCR
  - Cancer with rapid molecular and protein tests for achieving “molecular margin” during surgery

Source: Scientia Analysis

(1) Other includes Allergy, Nephrology, immune, and endocrine testing
(2) Clinical Chemistry Includes cholesterol testing
(3) Red Blood Cells
^ Excludes blood glucose monitoring and pregnancy testing
POC* Competitive Landscape

Fragmented market

2005
Total WW POC Market*: $2.8 Bn

Key Take-Aways

- Roche, Biosite, Bayer, Inverness, and Abbott/i-Stat as well as IL** lead the market
- Market overall is fairly fragmented as different segments have different technology and market requirements
- Roche while #3 overall, leads the Coagulation segment (pioneered this segment) along ITC^.
- Although Inverness owns key patents to lateral flow based infectious disease testing, players such as Quidel are gaining traction through flu and other respiratory disease offerings
- POC oriented Molecular Dx offerings from companies like Cepheid may gain traction when hospitals become more vigilant in screening MRSA in high risk patients
- We expect new entrants particularly in growing segments such as Infectious and Cardiac areas where new technologies are likely to create new markets

Leading players

- Abbott/i-STAT
- Bayer
- Biosite
- bioMerieux
- Cholestech
- IL**
- Inverness
- ITC^,
- Meridian
- Nova Biomedical
- Roche
- Quidel

^ ITC = International Technidyne Corporation, ** IL = Instrumentation Laboratory

Other includes Cozart, Radiometer, Abaxis, Trinity Biotech, Bio-Safe, Qualigen, Cepheid, Matritech, HemoSense, and other emerging players

* Excludes blood glucose monitoring and pregnancy testing

Source: Scientia Analysis, other industry reports, company presentations

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**POC Segmentation by Geography**

*U.S. makes up majority of the market*

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**2005 Total WW POC Market**: $2.8 Bn

**Key Take-Aways**

- Test volume wise, U.S. makes up majority of the market. Due to implementation of tightly regulated CLIA and FDA standards, U.S. is the most amenable to specialized POC.

- EU is growing faster than the U.S. due to the evolution of more and more physician office labs (POLs). However most of these tests tend to be low volume traditional clinical chemistry tests.

- Japan’s highly centralized form of healthcare delivery does not leave much room for POC testing in POLs. However, Japan’s hospitals are increasing their uptake of POC tests for emergency and critical care (especially for Influenza).

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*Excludes blood glucose monitoring and pregnancy testing*

Source: Scientia Analysis, Kalorama, and company presentations

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Geographic regions
- US
- Japan
- Europe
- ROW
Three Key Customer Segments

Hospital critical care units, physician’s office, and home users are key adopters of POC products.

**Key Drivers of POC**

- POC has been accepted as the standard of care in these setting due to the following benefits:
  - Quick Turn-around time
  - Reduction in ER, ICU, and OR length of stay, thus reducing healthcare costs. ICU stays cost $6k-$10k per patient
  - Fewer patients lost
  - Eliminate need for ordering and performing multiple blood draws
  - Avoid other invasive procedures
  - Decrease time to decision-making
  - Improved therapeutic decision-making
  - Reduction in follow up visits
  - Enable better treatment management

Adapted from i-STAT website
### Customer Segments

3 segments exhibit different buyer values for POC

<table>
<thead>
<tr>
<th>Buying Center</th>
<th>Application</th>
<th>Utilization</th>
<th>Quality /Process Improvements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Department</td>
<td>Trauma – Handheld blood gas and chemistry analyzer</td>
<td>Reduction in ED length of stay (LOS)</td>
<td>• Eliminate need for ordering and performing multiple blood draws</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Avoid prophylactic treatments</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Decrease time to decision-making</td>
</tr>
<tr>
<td></td>
<td>Chest pain – Handheld cardiac marker analyzer</td>
<td>Reduction in ED LOS and admissions</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Avoid prophylactic treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decrease time to decision-making</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>Near-continuous, automatic blood gas and chemistry analyzer</td>
<td>Reduction in ICU LOS</td>
<td>• Eliminate need for ordering and performing multiple blood draws</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Initiate critical changes in treatment earlier</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Reduction in re-intubation rates</td>
</tr>
<tr>
<td>Neonatal/pediatric intensive care unit</td>
<td>Near-continuous, automatic blood gas and chemistry analyzer</td>
<td>Reduction in NICU/PICU LOS</td>
<td>• Eliminate need for ordering and performing multiple blood draws</td>
</tr>
<tr>
<td>(NICU/PICU)</td>
<td></td>
<td></td>
<td>• Initiate critical changes in treatment earlier</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decrease neonate blood transfusions</td>
</tr>
<tr>
<td>Operating rooms</td>
<td>Tabletop blood gas, electrolyte and hemoglobin/ hematocrit analyzer</td>
<td>Reduction in OR time</td>
<td>• Avoid prophylactic treatments</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decrease time to decision-making</td>
</tr>
<tr>
<td>Physician office / Urgent Care</td>
<td>Respiratory infections (cold, flu, pneumonia) – Rapid immunoassay test</td>
<td>Reduction in follow up visits</td>
<td>• Improved therapeutic decision-making</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>Congestive heart failure – BNP monitoring in ACE inhibitor therapy</td>
<td>Reduction in follow up visits</td>
<td>• Decrease ED visits and hospital admissions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Improve disease management</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fewer patients lost to follow up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• More timely scheduling of confirmatory or follow-up testing</td>
</tr>
<tr>
<td>Home care</td>
<td>Handheld blood gas, electrolytes and hematocrit analyzer</td>
<td>Reduction in ED visits</td>
<td>• Initiate critical changes in treatment earlier</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decrease need for stat lab work</td>
</tr>
</tbody>
</table>
In the U.S., the FDA is responsible for approving new diagnostics. CMS regulates laboratories and JCAHO accredits hospital workflows and processes.

- **FDA** – responsible for test categorization and approval:
  - Classification drives the level of pre-clinical and clinical testing required for test approval.
  - Point of care testing devices are evaluated on relative accuracy and precision compared to central laboratory tests.

- **CMS** – Clinical Lab Improvement Amendments (CLIA)
  - Regulates all laboratory testing (except research use).
  - All laboratories must be CLIA certified to receive Medicaid and Medicare reimbursement.
  - Laboratory test classifications:
    - **“Highly Complex”—**require specialized scientific and technical knowledge, training and experience to perform accurately, operational steps require close monitoring or control, and extensive independent interpretation and judgment are required.
    - **“Moderately Complex”—**require minimal scientific and technical knowledge and training to perform accurately, operational steps are either automatically executed or easily controlled, and minimal interpretation and judgment are required.
    - **“Waived”—**Non-critical tests which have been approved by the FDA for home use, employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible, or pose no reasonable risk of harm to the patient if performed incorrectly.

- **JCAHO** (Joint Commission on Accreditation of Healthcare Organizations) regulates hospital workflows and processes.
In the U.S., the classification of a new IVD determines the regulatory pathway.

**Class I**
- Represents the lowest risk (e.g., immunohistochemical reagents used as adjuncts to diagnosis)
- Many analyte-specific reagents (ASRs) fall into this category, as do many other types of general laboratory supplies and reagents. ASRs are generally defined to be a single reagent, such as an antibody or nucleic acid probe, that can be used by laboratories in developing a functional clinical assay
- Premarket submissions are not required for class I exempt devices; Class I “reserved” IVDs need premarket notification (510(k)) to provide a reasonable assurance of safety and effectiveness. Reserved IVDs are usually intended for a use of substantial importance in preventing impairment of human health

**Class II**
- Present moderate risk to patients and users (e.g., molecular tests for prothrombin G20210A or factor V Leiden genotyping assay)
- If other tests detecting the same analyte have already been cleared or approved by the FDA, the test will receive the same classification
- Usually utilize the 510(k) process which requires submission of preclinical data and may or may not include clinical data from patient samples depending on how much is already known about the characteristics of the device/analyte combination
- A IVD that is cleared, (i.e., found to be substantially equivalent exhibits similar performance characteristics to previously cleared IVD or reference method to which it has been compared for the same intended use) can be marketed
- The average time between receipt of a 510(k) by the FDA and final decision is just over 3 months

**Class III**
- Corresponds to the greatest risk (e.g., digital image analysis systems for Pap smears or HPV tests)
- Tests for a new analyte (or substance) or which claim a new intended use for an existing analyte that has not been the subject of any previous submission to the FDA are automatically considered Class III
- Requires Pre Market Approval (PMA) process which entails a complete record of the clinical studies performed to support a reasonable assurance of safety and effectiveness for use of the device, as well as information on how the device is designed and manufactured
- Average time between receipt of an original PMA by the FDA and a final decision is around 8.5 months

Source: Mansfield E et al. Journal of Molecular Diagnostics, Vol. 7, No. 1, February 2005; Scientia Analysis
Regulatory frameworks for approving IVDs differ across the major markets

### Comparison of Regulatory Requirements in Major Markets

<table>
<thead>
<tr>
<th>Criteria</th>
<th>EU</th>
<th>United States</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVD Classification</td>
<td>Specific products listed in the IVD Directive</td>
<td>Expert panel decides device by device</td>
<td>By rule</td>
</tr>
<tr>
<td>Conformity Assessment</td>
<td>Notified body for high and medium risk</td>
<td>FDA for high risk, FDA or third party for most medium risk (otherwise FDA)</td>
<td>Ministry of Health, Labor &amp; Welfare (MHLW) for high risk, third party for medium risk</td>
</tr>
<tr>
<td>Essential Requirements</td>
<td>IVD Directive Annex I, not device specific</td>
<td>General and device specific guidance</td>
<td>Will be similar to Global Harmonization Task Force (GHTF) guidance</td>
</tr>
<tr>
<td>Technical Documentation</td>
<td>Technical and design files required</td>
<td>PMA for high risk, 510k for medium risk, plus device master record, device history record</td>
<td>Increasing requirements with increasing risks</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Required in the IVD Directive</td>
<td>Required in the regulations and guidance</td>
<td>Will be required</td>
</tr>
<tr>
<td>Quality Management System</td>
<td>ISO13485:2003 will be harmonized in 2004</td>
<td>21 CFR part 820 as amended describes QSR which is harmonized to ISO13485:2003</td>
<td>Future will see a translation of ISO13485:2003 with adoption in 2005</td>
</tr>
<tr>
<td>Registration Entity and Local Presence</td>
<td>Each EU competent authority, authorized rep</td>
<td>FDA, local agent</td>
<td>License with MHLW, in-country caretaker</td>
</tr>
<tr>
<td>Adverse Event Reporting Requirements</td>
<td>Document vigilance process</td>
<td>Documented processes</td>
<td>Mandatory problem reporting</td>
</tr>
</tbody>
</table>

Source: IVD Technology – Canon Communications
Reimbursement for new IVD tests in the U.S. depends on setting favorable CPT codes.

Procedures for Setting IVD Payment Levels

- **New Diagnostic**
  - **Gap-Fill**
    - New and innovative technology
    - 1- years to obtain new/modified code
  - **New Payment Level Assigned**
    - Varying state fee schedules
    - CLFS-NLA
- **Cross-Walk**
  - 2nd generation technology to replace older technology
  - Map to existing code(s)
  - Obtain Payment for Existing Code
    - May be associated with new payment
- **Payment**
- **Update**
- **Adjustment**
  - CLFS-CPI Updates [infrequent]
- **Addition of new/modified CPT Codes**

Reimbursement Challenges

- **Coding**—New diagnostic tests must be assigned to a particular code which determines the payment level.

- **Coverage**—Policies specify whether or not payers will include a particular technology or service under insured benefits. While US public and private payers typically make coverage and payment decisions separately, payers may anticipate significant financial impact resulting from certain coverage determinations.

- **Payment**—Current coding does not reflect IVD value to patient care. Methods for setting initial payment levels for diagnostic tests and updating existing ones (e.g., cross-walk and gap-fill) are non-standardized and inconsistently applied.

Definitions:
- CLFS—Clinical Laboratory Fee Schedule
- NLA—National Limitation Amount
- CPI—Consumer Price Index

Source: Scientia Analysis; "The Value of Diagnostics" Lewin Group 2005

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POC Technology Overview

Different technologies serve different market segments

- Each assay format is matched to the sensitivity requirements for the analyte being measured
- Each technology has their own set of benefits and limitations
  - No one technology can universally serve all POC markets
- Challenges still exist in getting reliable data in a portable format

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Key conclusions from POC market analysis

• POC Diagnostics market is an attractive area with several segments exhibiting double-digit growth
• Cardiac, Infectious, Coagulation are most attractive segments of POC
• Market is fairly fragmented and is organized based on disease segments
• Critical care types of settings (e.g. Cardiac, Blood Gas), physician office labs (HIV/Infectious), and home users are the primary adopters of POC tests
• Improved turn-around time (immediacy of results) through a portable, simple and reliable test is a fundamental driver of this market
• Lack of skilled labor to perform lab-based tests will continue to fuel demand for POC tests
• Regulatory hurdles remain high for new entrants
• All in all, the POC market is likely to continue its overall growth over the next 5-10 years
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  • core growth
  • white space growth strategy

Customer Strategy

Mergers and Acquisitions
  • strategy
  • acquisition screening
  • strategic due diligence
  • divestitures
  • joint ventures and alliances

Venture Capital/Private Equity
  • due diligence
  • portfolio strategy
  • exit strategy

Emerging Companies
  • post investment growth strategy
  • program prioritization
  • market strategy and positioning
  • valuation
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