Agenda

- Introduction to Almac Diagnostic Services
- Medical Device Lifecycle - Compliance with Regulations
- Compliance with Regulations in Practice - Almac Experience
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Almac Diagnostic Services is a stratified medicine company specialising in biomarker-driven clinical trials
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Discover

Develop & Manufacture
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Discover

Develop & Manufacture

Deliver
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Overview of Medical Device Product Development Lifecycle

Discovery → Development → Performance Evaluation → Marketing
Overview of Medical Device Product Development Lifecycle

- Discovery
- Development
- Performance Evaluation
- Marketing

Regulations
- EU IVDD/IVDR
- US FDA 21 CFR 820 (QSR)
Overview of Medical Device Product Development Lifecycle

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Quality Management System
- Corrective & Preventive Actions
- Production & Process Controls
- Equipment & Facility Controls
- Records, Documents & Change Controls
- Material Controls
- Design Controls
Overview of Medical Device Product Development Lifecycle

Discovery → Development → Performance Evaluation → Marketing

- Regulations
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- Design Controls
- Corrective & Preventive Actions
- Production & Process Controls
- Equipment & Facility Controls
- Records, Documents & Change Controls
- Material Controls
- Quality Management System
- Laboratory Standards
- Laboratory Standards
- Product Development Standards

02 July 2019
Confidential
• Feasibility/proof of concept state
  - Establish clinical relevance of biomarker (diagnosis, prognosis, prediction)
  - Early studies to establish methodologies (wet-lab, dry-lab)
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• Governed by GxP (GLP, GCLP)
  - If using tissue material, ensure consent for use of tissue/data is in place; study may also require review and approval by ethics committee
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Lays the foundation for future product development lifecycle

Recommend early adoption of key principles of Design Control and aspects of product design and development standards such as ISO13485
- Perform studies to allow you finalize what your product is and how to manufacture it
- Recommend studies include clinical samples representative of intended use population to model performance
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Product Lock

Design Specifications

• Perform studies to allow you finalize what your product is and how to manufacture it
• Recommend studies include clinical samples representative of intended use population to model performance

Recommend engaging with regulator (e.g. FDA via pre-submission)/certification body in development stage to outline product development plan and ensure alignment
Discovery → Development → Performance Evaluation → Marketing

Quality Management System

Laboratory Standards
- GCLP: Good Clinical Laboratory Practice
- ISO 15189: Specifies the general requirements for quality and competence in medical laboratories
- ISO 17025: Specifies the general requirements for the competence of testing and calibration laboratories

Product Development Standards

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Laboratory Standards
- GCLP
- ISO 15189
- ISO 17025

Product Development Standards
- ISO 13485
- ISO 14971
- IEC 62304

- Design, development and manufacture of medical devices
- Application of risk management to medical devices
- Life cycle requirements for development of software within medical devices
• Analytical performance of product required to be established and documented

• Sensitivity, specificity, trueness (bias), precision, accuracy, measuring range

• Studies should be performed using material representative of intended use population where possible
  - For rare biomarkers (e.g. fusions) may be able to adopt a representative approach subject to regulator feedback (variant type rather than specific variant)
  - Use of contrived samples can also be utilized where necessary

• Also includes establishing criteria for specimen handling and control of interference
Clinical performance of product required to be established and documented

- Unless otherwise justified (IVDR) must be based upon clinical performance studies (trials)
- Prior to investigational use of device within interventional trial
  - Ethics committee must approve study
  - Within UK
    - Under IVDD device must be CE-marked based upon analytical performance characteristics
    - Under IVDR, must make application to MHRA for clinical performance studies for significant risk devices
  - Within US, FDA must grant investigational device exemption (IDE) approval for significant risk devices

Analytical performance of product required to be established and documented

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Prior to evaluating performance, ensure product lock has occurred to avoid repeat of work and requirement for downstream bridging study.
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Type of validation performed dependent upon characteristics of device.
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Scale of validation performed, proportionate to intended use (e.g. validation to support use in trial vs place on market), risks and device risk class.
Prior to evaluating performance, ensure product lock has occurred to avoid repeat of work and requirement for downstream bridging study.

Type of validation performed dependent upon characteristics of device.

Scale of validation performed, proportionate to intended use (e.g. validation to support use in trial vs place on market), risks and device risk class.

Analytical performance needs to be established in advance of clinical performance evaluation study.
Discovery → Development → Performance Evaluation → Marketing

Quality Management System

Regulations
- EU IVDD/IVDR
- US FDA 21 CFR 820 (QSR)
- US FDA 21 CFR 812, 50, 54, 56

Laboratory Standards
- GCP
- GCLP
- ISO 15189
- ISO 17025
- US CLIA/CAP

Product Development Standards
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- ISO 14971
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Quality Management System

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Post-market surveillance & vigilance (adverse event reporting)

Post-market updates of:
- Risk-benefit determination
- Design and manufacturing information (labelling, IFU)
- Performance and safety specifications
- Update of performance and safety specifications
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Quality Management System within Almac Diagnostic Services

**LABORATORY ACCREDITATIONS**
- UKAS to ISO17025
- UKAS to ISO15189
- CLIA (US Clinical Laboratory Improvement Amendments)
- College of American Pathologists (CAP)

**LABORATORY COMPLIANCE & LICENSES**
- Complies with principles of GLP, GCP & GCLP
- Human Tissue Act UK (HTA License)
- US State Licences:
  - New York (CLEP Permit)
  - Florida
  - California
  - Pennsylvania
  - Maryland
  - Rhode Island

**DESIGN, DEVELOPMENT AND MANUFACTURING CERTIFICATIONS**
- EN ISO 13485:2016
  For design, development & manufacture of in vitro diagnostic nucleic acid technique based assays for gene mutation and expression analysis
- ISO 14971 certification
- IEC62304 certification
Quality Management System within Almac Diagnostic Services

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Almac Diagnostic Services supported Janssen Research & Development, LLC in its development of BALVERSA™ (erdafitinib), a treatment approved by the US Food and Drug Administration in April 2019 for the treatment of patients with advanced metastatic urothelial cancer.
CTA Development
Almac successfully developed and validated a clinical trial assay that could identify patients with urothelial cancer whose tumours have certain genetic alterations in the FGFR2 or FGFR3 genes.

IDE Approval
Following investigational device exemption (IDE) approval by the FDA, Almac then performed screening of patients with metastatic urothelial cancer, within its CLIA and CAP accredited laboratory, using the clinical trial assay, to determine eligibility for enrolment into Janssen clinical studies.

CDx Bridging Study
Following completion of the screening phase, Almac then supported the bridging study between the clinical trial assay and the QIAGEN FGFR Kit which was co-approved as a companion diagnostic test (CDx) by the FDA to identify patients with certain alterations in the FGFR3 gene and guide potential treatment with BALVERSA™.
claraT is a unique software-driven solution, classifying biologically relevant NGS gene expression signatures into a comprehensive, easy to interpret report.

TruSeq® RNA Exome analysis on Illumina NextSeq

3 Immuno-Oncology Gene Expression Signatures

(Public* & Proprietary)

claraT Total mRNA Report

Based on a platform that has been analytically validated for CT use

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* Molecular Signatures Database Hallmark Gene Sets (Liberzon et al. 2015; © 2004-2017 Broad Institute Inc. and subject to the terms and conditions of the Creative Commons Attribution 4.0 International License

TruSeq® RNA Exome analysis on Illumina NextSeq

3 Immuno-Oncology Gene Expression Signatures
(Public* & Proprietary)

Based on a platform that has been analytically validated for CT use

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Thank You

Questions?

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