Single Site Companion Diagnostic Tests and the Humanitarian Device Exemption (HDE) Pathway

ARUP's experience as a CLIA laboratory

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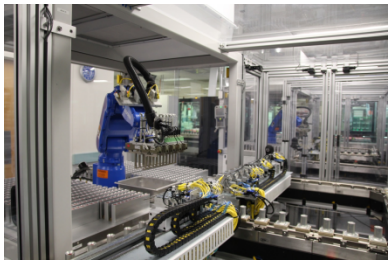
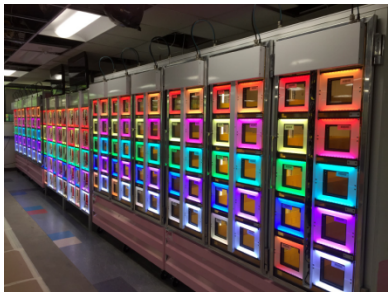
ARUP Laboratories

- ARUP is a non-profit national reference laboratory that offers a broad menu of more than 3,000 tests and test combinations in clinical and anatomic pathology.
- ARUP primarily serves clients in all 50 United States, receiving >40,000 specimens daily.
- Our clients include:
  - university teaching hospitals
  - children's hospitals
  - major commercial laboratories
  - military and government facilities
  - major clinics
  - **pharma, biotech and CROs**

- ARUP is expanding its infrastructure to accommodate specimens originating outside of the US

Routine Laboratory Testing Services





- 55 clinical sections, each with dedicated medical director pathologists
- Existing automation, laboratory and IT infrastructure
- CLIA/CAP quality system compliance
- Optical character recognition camera system
- Automated sample transport and sorting
- Thawing and mixing workcells
- Automated storage and retrieval system
- Collection kits
- Test requisition forms or interfaced ordering
- Access to pathologists with specific clinical and technical expertise

ARUP's PharmaDx Program Activities

ARUP's PharmaDx group provides customized services for the pharmaceutical and biotech industry

- Development of tests under design control in accordance with 21 CFR part 820
- Integration of pharma-sponsored programs with GCLP requirements into existing quality system
- Coordination of efforts between R&D, technical operations, reagent lab, purchasing, Compliance & Quality Systems, executive management
- Project management
- Financial planning, contracting, invoicing
- Interaction with FDA and other regulatory bodies
- Corporate communications

Test Development

- **Customized assay development**
  - Transfer pharma assay to ARUP for use in clinical lab
  - Modification of existing tests
  - *De novo* assay development by R&D staff
  - Validation using residual clinical samples
- **Quality systems**
  - Integration of pharma-sponsored programs with GCLP requirements into existing quality system
  - Development of tests under design control in accordance with FDA regulations (21 CFR part 820)
  - FDA approval for two (2) laboratory developed tests
    - KIT D816V for Gleevec eligibility in ASM
    - PDGFRB FISH for Gleevec eligibility in MDS/MPD

Examples of PharmaDx Collaborations

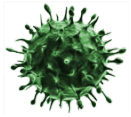
Companion Diagnostics: development of *KIT D816V* and *PDGFRB* FISH assays under design control; FDA submissions and approvals

Oncology: development and validation of molecular, FISH, IHC and quantitative digital pathology assays; test transfer to clinical laboratory

Rare Genetic Disorders: multiple programs in lysosomal storage disorders, other genetic diseases

Therapeutic Drug Monitoring: measurement of Cerdelga (eliglustat) small molecule in blood for Gaucher disease treatment

Gene Therapy: companion diagnostic development for determining patient eligibility



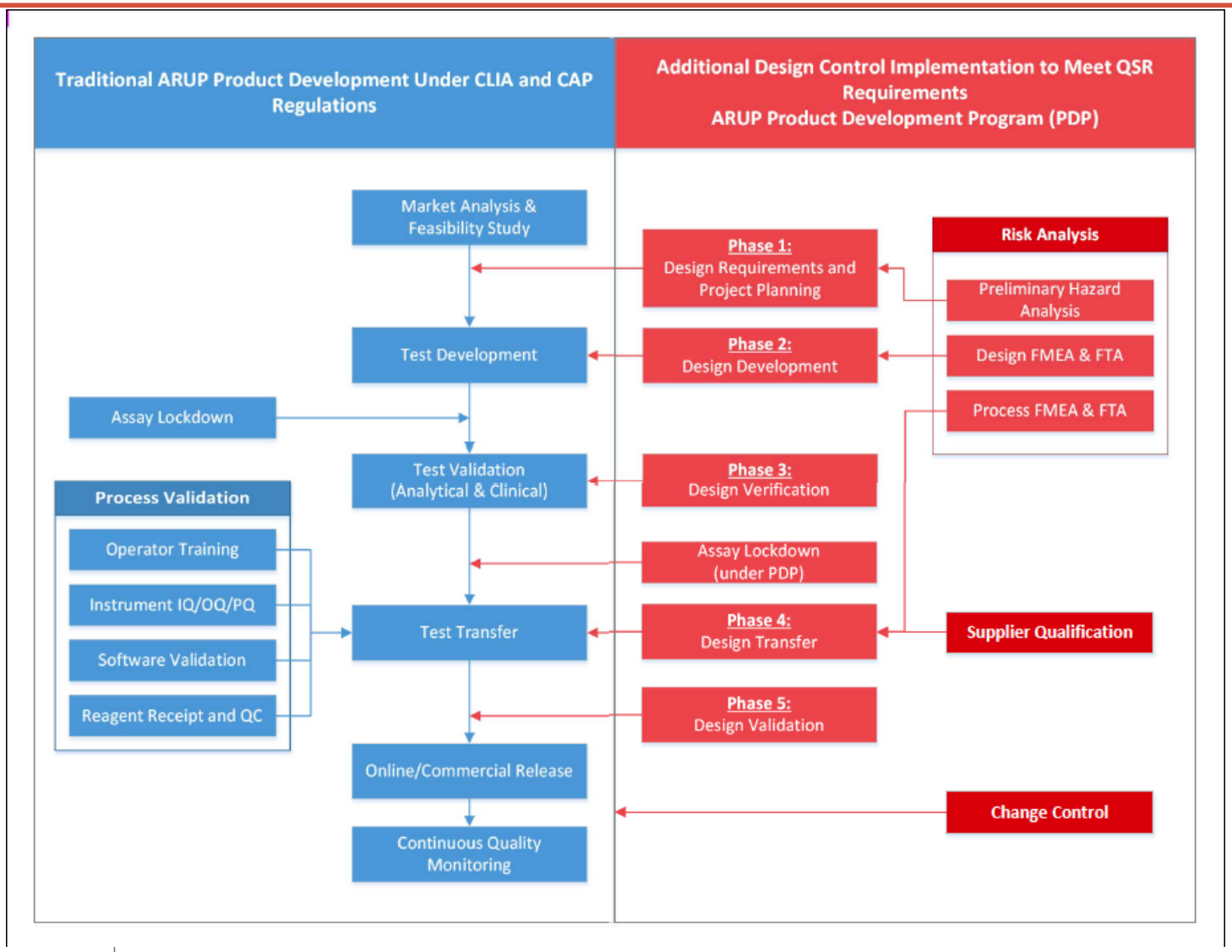
Infectious Disease: molecular and viral culture for global vaccine trial; viral load assay to support anti-viral drug development and registration

How do the Elements of FDA Quality System Regulation (QSR) Relate to ARUP Processes?

Gary Larson

1. For each element of the QSR, ARUP worked with its pharmaceutical partner to understand the meaning of each requirement
2. ARUP mapped each applicable element of the QSR to existing processes and procedures

Design Control – Relationship to CLIA



Quality System Augmentation

- *Each applicable element of the FDA QSR was mapped to an existing ARUP policy/procedure*
- *Documents were organized for easy accessibility and retrieval*

The gaps are closed:

✓ **Design Control** – ARUP *HAS* a formal system to guide and document test development.

✓ **Purchasing controls**– ARUP *HAS* a formal policy to identify/qualify/monitor vendors of critical components, define and formalize component specifications.

✓ **Document archiving** – ARUP policies *CAN* meet the requirements for length of time documents should be archived and readily accessible.

✓ **Complaint handling/medical device reporting** – ARUP *HAS* processes for handling complaints, nonconformances, reporting events to the FDA.

✓ **FDA approvals** - ARUP *HAS* received FDA approval for 2 companion diagnostic tests under the Humanitarian Device Exemption (similar to PMA). Modular format that can be re-purposed for new programs.

Companion and Supportive Diagnostic Tests

KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM)

KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM) is an in vitro diagnostic test intended for qualitative polymerase chain reaction (PCR) detection of KIT D816V mutational status from fresh bone marrow samples of patients with aggressive systemic mastocytosis.

PDGFRB FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD)

PDGFRB FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD) is an in vitro diagnostic test intended for the qualitative detection of PDGFRB gene rearrangement from fresh bone marrow samples of patients with MDS/MPD with a high index of suspicion based on karyotyping showing a 5q31~33 anomaly.

Cerdelga(R) (eliglustat) Panel

For the measurement of drug peak levels in individuals taking Cerdelga® (eliglustat).

Challenges of Being the "Companion"

Relationships may be symbiotic but unequal

Timelines are driven by therapeutic development programs

- Diagnostic development programs often begin late in the process and have to rush to meet drug approval milestones
- Accelerated breakthrough approval of drug could pose extreme challenges to coordinated approval of the CDx

"Legacy" assays developed by pharma partners

- May not be suitable for clinical use
- May utilize undesirable technologies, instruments, reagents
- May be outdated by the time of diagnostic partner involvement
- May require non-routine specimen types
- May not have access to original specimens
- May require untenable turnaround times

Diagnostic success is dependent on therapeutic success

Focus on Rare Disease Diagnostics

Rare diseases may present several challenges

- Diagnostic market too small for kit manufacturer interest
- Few laboratories offer diagnostic test
- Technically complex assays may be required
- Requirement for companion diagnostic to identify patients eligible/ineligible for therapeutic

ARUP has strong interest in rare disease testing

- Proven experience in developing single site companion/supportive diagnostics
- Academic affiliation; medical directors with disease expertise
- Can act as single site for testing by receiving samples from all 50 states and overseas
- Large R&D group with expertise in many technology platforms

Humanitarian Device Exemption

Humanitarian Use Device (HUD) - *a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in <4,000 individuals in the United States per year*

- Similar in form and content to a premarket approval (PMA)
- Exempt from effectiveness requirements
- Not required to contain results of clinical investigations demonstrating the device is effective for its intended purpose
- Device may not pose an unreasonable or significant risk of illness/injury
- Probable benefit to health outweighs risk of illness/injury
- No comparable (FDA-approved) devices are available
- Single site approval; at institution with a local IRB to supervise clinical testing
- Pre-market inspection may not be required

Single Site CDx in ARUP's Lab Environment

- No kits or supplies are used or distributed outside of ARUP
- Test "kits" assembled as needed and consumed at same time
- Most components and methods are general purpose and are not specific to the companion diagnostic assays
- Few assay-specific or critical components
- Modification of existing regulatory processes and assay procedures
- Reliance on surrogate specimens for development/validation
- Reference to past clinical results to predict future clinical setting
  - Prevalence of mutations in general and intended use populations
  - Ability to discriminate positives and negatives

Pros and Cons of HDE Assays

Advantages	Disadvantages
Exclusivity (single site approval)	Small market size/low test volumes
No requirement for establishment of clinical utility	Bridging studies may be challenging
No requirement for pre-approval inspection	No requirement for ordering physician to use FDA approved test
Reliance on surrogate (contrived) specimens	Lack of large numbers/amounts of clinical specimens for development/validation
Niche – no competition from kit manufacturers	Quality & regulatory burden that exceeds CLIA/CAP requirements
No validation requirements for distribution, shipping, label reconciliation	Contractual obligations to sponsor, even in the absence of market interest