Regulatory Requirements for Diagnostic Oligo Manufacturing

The Value of GMP Compliance

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I. GMP quality management for IVD oligonucleotide manufacturing

II. TO GMP or not to GMP.....
   • Regulatory perspective
   • Quality perspective
   • Risk management perspective
   • Financial perspective

III. Summary
Good Manufacturing Practices

- IVD Manufacturer needs QMS in compliance with GMPs:
  - FDA QSR (21 CFR 820)
  - IVD Directive 98/79 EEC: CE marking
- ISO 13485 standard is highly similar to QSR.
- Presumption of conformity:
  - Compliance to harmonized standard ISO 13485
    🚦 100 % Compliance to IVD Directive 98/79 EEC
    🚦 > 90% Compliance to FDA QSR
To GMP or not to GMP

Do manufacturers of molecular diagnostic assays need to source from GMP-compliant suppliers?

- Regulatory perspective
- Quality perspective
- Risk management perspective
- Financial perspective
GMP for IVD Oligos

Regulatory/authorities

• Manufacturer needs to ensure that IVD Oligo supplier uses appropriate QMS.
• Suppliers are encouraged to be in compliance.
• In case of FDA inspection related to PMA filing or for cause, control over supplier is likely to be reviewed intensively.
• In practice: manufacturers require critical components to be made under GMP.
Pharmaceutical Affairs Law
(Apr./2005, revised, Yakuji-hou)

- IVD Manufacturer needs QMS in compliance with MHLW Ministerial Ordinance No. 169.
- ~ Equivalent to ISO13485 + additional guidelines.
- IVD Oligos, no QMS is defined.
- Interpretation: GMP is not needed for IVD oligos.
To GMP or not to GMP

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Quality

- FDA (§ 820.50): Quality of a product is achieved through proper control of the manufacture of that product.
- WHO: Good quality must be built in during the manufacturing process; GMP prevents errors that cannot be eliminated through quality control of the finished product.
- Quality cannot be fully tested into products afterwards!
Oligo quality

- Oligo quality is critical for IVD assay performance.
- Variations in oligo quality result in variations in detection limit, specificity ……
- Extent of control on oligo production should therefore be maximized.
- **GMP oligo manufacturing is required from a quality point of view.**
Incoming QC
Inadequacy

- Sequence errors: ACGT/AGCT
- Impurities
- A > T change (9 Da)
- Traceability (documentation) errors
To GMP or not to GMP

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To GMP or not to GMP
Risk Management

- ISO 14971 lists hazards associated with medical devices in normal/fault conditions.
- Hazards like non-specificity, or reduced sensitivity may impact patient health.
- Manufacture of critical assay components with a GMP process will reduce that risk.
- Absence of GMP will increase the risk.
- GMP oligo manufacturing is an effective measure to reduce the medical risks associated with IVD use of MDx assays.
GMP IVD Oligonucleotides

Assuring highest quality throughout entire process

- Not the highest purity.
- Not just Quality Control at the end.
GMP IVD Oligonucleotides
Eurogentec’s Quality Management System

- QMS compliant with ISO13485 & QSR
- Rigorous risk analysis, to reduce risk for end user.
- Documented procedures, validated & optimized methods, qualified equipment.
- Process control through use of checklists and, followed by sign-off of every step.
- Full traceability (equipment, facility, raw materials..).
- Training and qualification of personnel.
- Release of product by QC-authorized person.
- Environmental control to eliminate contamination risk.
Many IVD oligo suppliers claim compliance.....

GMP certification is not possible, but ISO 13485 certification is possible by independent accredited organization.

Further credibility if certification body is accredited by FDA and others to perform inspections.
Eurogentec Belgium is ISO 13485 certified for production and sales of IVD oligonucleotides!
GMP IVD Oligonucleotides
Eurogentec’s clean room facility

- Classified clean rooms for all steps
- Options: class 10,000/100,000
- Restricted card-key access via airlocks
- Specific gowning
Strict segregation Research-GMP
- Restricted card key access
- Overpressure
- HEPA air filters
- Classification
Airlocks and gowning area
Purification room, class 100,000
Class 10,000 room & class 100 cabinets
Gowning
Three Manufacturing Sites

Redundancy & harmonization: uninterrupted supply

San Diego

Belgium

Japan
Three Manufacturing Sites

Redundancy & harmonization: uninterrupted supply

- **Belgium**: Full GMP, ISO13485-certified, classified clean rooms.
- **USA**: GMP-capable facility, ISO13485 certification and classified clean rooms by end of 2009.
GMP IVD Oligo Manufacturing
seamless solutions from R to D to C

1st Ideas  Feasibility  Prototyping  Validation  Commercialization

Research Oligos

Pre-Diagnostic Oligos

Diagnostic Oligos

Classified clean rooms (ISO 7/8)

IVD validated methods, qualified equipment

Full batch record,
Full traceability, ISO13485
GMP IVD Oligo Manufacturing

RDC solutions Japan

1st Ideas → Feasibility → Prototyping → Validation → Commercialization

Research Oligos → Traceable Oligos

Reliable & Traceable Oligos in dedicated IVD rooms

Batch record & Full traceability

IVD validated methods qualified equipment, ISO13485
To GMP or not to GMP

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To GMP or not to GMP

Financial

GMP vs. non-GMP 40-mer FAM beacon: Costs

nmol final yield

Cost

0% 20% 40% 60% 80% 100% 120%

1 10 100 1000

GMP non-GMP
Summary (I)

- GMP manufacturing of IVD oligos: QMS + facility assuring highest reproducible quality throughout entire manufacturing process.
  - ISO 13485 & FDA QSR compliant QMS.
  - Classified clean rooms.
- Incoming QC cannot replace GMP process.
- ISO 13485 certification gives highest assurance that Oligo supplier is truly GMP compliant.
Summary (II)

IVD oligos, to GMP or not to GMP

• **Regulatory/authorities**: GMP compliance is the practice in EU and USA, but not in Japan.

• **Quality**: GMP compliance is a requirement.

• **Risk management**: GMP compliance is a requirement.

• **Financial**: Increased GMP costs are minimal at higher quantities.