FDA Regulatory Considerations in the Transfer of Ownership of Diagnostic Technology

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Topics for Discussion

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- Transferring ownership of a 510(k) cleared product
- Transferring ownership of a PMA approved product
- FDA regulatory issues to address during pre-transfer due diligence
- Post-transfer compliance issues and recommendations for successful transfers

Transfer of a 510(k) Cleared Product

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- The FDC Act and implementing regulations are silent on such transfers. However, historically, FDA has permitted companies to transfer ownership of their 510(k)s with little regulatory complexity.
- FDA permits transfer of ownership of a 510(k), with one important caveat
  - Two companies may not manufacture the same device under a single 510(k) clearance.
  - Therefore, if a 510(k) holder wishes to license the right to manufacture a device but also wishes to continue its own manufacturing activity, FDA's policy is to require the licensee to obtain a new 510(k) clearance.

Transfer of a 510(k) Cleared Product

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- Notification to FDA of a 510(k) transfer is not required. However, at a minimum:
  - The transferor should update its device listing to “de-list” the subject device
  - The transferee (recipient) should list the device under its own establishment registration.
    - If the transferee has not previously registered its establishment, it must do so at the same time it lists the device.
  - Many companies submit a letter to FDA to apprise the agency of the transfer.

Transfer of a 510(k) – CLIA Waivers

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- For products that are the subject of a CLIA Waiver, FDA requires notification of a change in ownership.
  - Should FDA fail to learn of the change in ownership, the acquiring company would not be shown in the CLIA Waiver database.
  - Because CLIA Waiver is specific to the product, if an FDA inspector, at the time of an inspection, is unable to locate the product and manufacturer in the CLIA Waiver database, the default categorization of the product would be "high complexity."
- Notification of the change in ownership should be provided to FDA along with:
  - A copy of the product labeling
  - A description of any changes being made in the labeling as a result of the change in ownership (e.g., name of manufacturer/distributor)

Transfer of a 510(k) Cleared Product

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- It should be noted that a new 510(k) may be required if the transfer could significantly affect the safety or effectiveness of the device.
  - If the device will be manufactured at a new site, FDA's position is that a new 510(k) is not required unless the site change could significantly affect the safety or effectiveness of the device.
    - This differs for PMA approved products
  - However, a new 510(k), or documentation that a new 510(k) is not required, should be prepared if the recipient also is making design changes, labeling changes, or process changes.

Transfer of a 510(k) Cleared Product

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- Company A acquires a diagnostic test from Company B. Company A now wants to run the test on its own platform.
  - Transfer of test to Company B does not itself require a new 510(k)
  - However, running test on a new platform may require a 510(k)
  - Similar result if Company A wants to make new claims for Company B's acquired product or significantly change its design

Transfer of a 510(k) Cleared Product

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- Transfer of a 510(k) should be documented
  - Could be in a formal M&A type contract or in a letter agreement
- 510(k) Transfer Agreement should include:
  - A clear description of the transfer that identifies the proper device name and the associated 510(k) clearance number and date of clearance
  - A statement acknowledging that the new 510(k) holder assumes all responsibility to comply with applicable regulations, such as:
    - Quality System Regulation (including complaint handling) – 21 C.F.R. Part 820
    - Medical Device Reporting – 21 C.F.R. Part 803

Transfer of a 510(k) Cleared Product

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- Device Corrections and Removals – 21 C.F.R. Part 806
- Establishment Registration and Device Listing – 21 C.F.R. Part 807
- Determination of whether device modifications require a new 510(k) – 21 C.F.R. Part 807

– A statement prohibiting the transferor from manufacturing or marketing the product after the date of transfer

Transfer of a 510(k) Cleared Product

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- 510(k) Transfer Agreement also should include:
  - A representation and warranty that the transferor has not transferred the 510(k) to another party before.
  - A representation and warranty that the device described in the transfer agreement matches the device described in the 510(k) clearance.
    - For example, the 510(k) holder may have modified the device after clearance without submitting a new 510(k) notice by concluding the changes could not significantly affect safety or effectiveness.
    - It is therefore possible that the existing 510(k) clearance is not legally sufficient to allow commercial distribution of the device the buyer is purchasing.
  - The transfer of all device related documentation to the new 510(k) holder.

Transfer of a 510(k) Cleared Product

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- Documents that should be included in a 510(k) transfer:
  - Device Master Record
  - Design History File
  - Device History Records
  - The complete 510(k), including all correspondence with FDA
  - All documentation pertaining to device/design changes (ECOs, etc.)
  - All CAPAs related to the device

Transfer of a 510(k) Cleared Product

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- Documents that should be included in a 510(k) transfer:
  - Complaint trending and complaint files related to the device
  - All MDRs related to the device (or MDRs from the prior 2-3 years)
  - All documentation pertaining to device corrections or removals, whether reported to FDA or not
  - Any FDA initiated compliance or safety issues (e.g. public health notices, 483s, Warning Letters, etc.)

Transfer of PMA Approved Products

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- PMAs can also be freely transferred, but greater complexity/fees/time/resource required compared to transfer of 510(k) cleared product
  - Two companies can each hold their own PMA based on the same data
- Unlike 510(k), approval is often required in one of several forms
  - Private label distributor PMA supplement
  - Duplicate PMA
  - Alternate or additional manufacturing facility
- Private label distributor PMA supplement
  - PMA holder enters into an agreement with another party to permit that party to distribute the approved device under its own private label.
  - The holder of the original PMA must submit a PMA supplement requesting FDA approval of the agreement.
  - No change in manufacturing location, just distribution.
- Change in trade name also requires a PMA supplement.

Transfer of PMA Approved Products

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- A PMA may be sold to another company at any time, before or after approval.
- At the time of the transfer, the former owner should provide a letter notifying FDA that all rights of the PMA have been transferred to the new owner.
- If the PMA has been approved, the new owner need only report that the transfer of PMA ownership will not result in a change or modification that would require a submission of a PMA supplement or affect the conditions of approval applicable to the PMA.
- If changes are made that require a PMA supplement or affect the conditions of approval, the new owner must submit an appropriate PMA supplement and obtain written FDA approval before marketing the device.

Transfer of PMA Approved Products

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- The above amendment or supplement should also include:
  - the effective date of the ownership transfer;
  - a statement of the new owner's commitment to comply with all the conditions of approval applicable to the PMA; and
  - either a statement that the new owner has a complete copy of the PMA including all amendments, supplements, and reports or a request for a copy from the FDA files.

Transfer of PMA Approved Products

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- If the transfer of ownership occurs before the PMA is approved, the PMA must be amended to include the applicable information and ownership transfer letter described above.
- If the new owner wishes to add its own manufacturing capability, this may require a major amendment to the pending PMA, which can delay approval.
- Often, a subsequent PMA supplement to add a new manufacturing facility may be preferable to avoid PMA approval delays.

Transfer of PMA Approved Products

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- **“Licensing Agreement” PMAs**
- A PMA holder may enter into a licensing agreement with another party to provide that party with permission to reference the data in its PMA.
- The licensee may submit an original PMA that includes, or includes by authorized reference to the holder’s approved PMA, all appropriate information required in the PMA regulations (21 CFR 814.20).
- Upon receiving FDA’s approval, the licensee assumes all the responsibilities of a PMA holder, including the manufacture and distribution of a device that is identical to the licensor’s. Postapproval reporting requirements also apply.

Transfer of PMA Approved Products

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- In addition, following approval of the licensing agreement, licensees may choose to make changes to their product. As for all PMA holders, such changes may require the submission of a PMA supplement.
- After the licensee's PMA is approved, the original PMA holder may not rescind any authorization permitting the licensee's use of information in the original approved PMA.
- Same user fees apply as for new original PMA.

Transfer of PMA Approved Products

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- The PMA submission must include the following:
  - a statement signed by both parties confirming that the original PMA holder has furnished the licensee with a complete copy of all manufacturing information in the approved PMA applicable to the licensee's manufacture of the device;
  - a complete description of a licensee's manufacturing facilities and a listing and explanation of all differences between the original PMA holder's and the licensee's methods and controls used in the manufacture, processing, packing, storage, and, when appropriate, installation of the device;
  - process validation and expiration dating information, where appropriate;

Transfer of PMA Approved Products

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- copies of all required labeling (draft or final) and a description of all differences between the PMA holder's and the licensee's labeling (e.g., a markup of the PMA holder's approved labeling identifying the revisions incorporated in the licensee's labeling;
- a description and the results of all tests and evaluations which demonstrate that the licensee's device is identical or sufficiently similar to the PMA holder's device to the extent that there is reasonable assurance that the licensee's device is safe and effective for the intended use; and
- the licensee's FDA establishment registration number and, if applicable, the dates of the most recent FDA inspection of the licensee's manufacturing facility. (A new inspection may be required prior to approval.)

Transfer of PMA Approved Products

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- Example: Company A decides to phase out manufacture/sale of one of its products that was approved via a PMA. Company B acquires the rights to continued marketing.
  - Initial private label distributor PMA supplement to allow Company B to begin immediate sale using inventory manufactured by Company A
  - Subsequently, Company B wants to manufacture in its own facility exclusively and submits a duplicate PMA with right of reference to the original Company A PMA, including clinical testing
  - If Company B later wants to make further changes, can use its own PMA as basis for future supplements
- Obligations for ongoing postmarket approval studies may require special attention during transfer preparation/negotiation.

FDA Regulatory Due Diligence Prior to Transfer

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- Types of diligence
  - Desk review of documents
  - On-site review of documents (audit)
  - Interviews with key personnel
  - All of the above
- Process
  - Diligence document request
  - Conduct desk review
  - Q&A with target company
  - On-site audit
  - Diligence report
  - Craft representations and warranties and applicable disclosure schedules based on diligence review

Device Due Diligence

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- **Typical documents Requested – Premarket Issues**
  - List of all marketed products and associated clearances or approvals
  - Product Labeling
  - 510(k)s and PMAs
    - Correspondence with FDA regarding submissions
    - All amendments and subsequent submissions (including annual reports)
  - List of all device modifications that have been implemented since clearance/approval
    - Could be a list of ECOs. The reviewer will then select certain changes for a more detailed review.
  - All investigational device exemption applications (IDEs) and any related information, including adverse reaction reports, supplements, annual reports, FDA correspondence regarding open clinical trials

Device Due Diligence

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- **Typical documents Requested – Post-Market Issues**
  - Registration and Listing materials
  - Copies of product labeling and promotional materials
  - Copies of all Form FDA 483s, responses to the 483s and associated Establishment Inspection Reports (EIR)
  - Copies of any Warning Letters and Untitled Letters and responses to them
  - All documentation related to any correction or removals (could be product or date delimited)
  - A listing of all GMP audits (from self-audits and outside audits) within the last four years and a copy of the quality audits from the past 2 years and related CAPAs

Device Due Diligence

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- **Typical documents Requested – Post-Market Issues**
  - Copies of various quality and regulatory documents and procedures including:
    - Quality Manual;
    - Design Controls and Management Controls SOPs;
    - Corrective and Preventive Actions (CAPA) SOP;
    - Complaint Handling and Medical Device Reporting (MDR) SOPs;
    - Advertising & promotion SOPs.
  - Access to complaint files; complaint trend analyses by product over the past 2 years.
  - Import/export documentation

Device Due Diligence

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- **Common Issues**
  - Device modifications made without sufficient support or rationales to support a no-file decision
  - Complaint trends that were not sufficiently addressed (*e.g.,* via a design change or recall)
  - Failure to file MDRs for reportable events
  - Failure to notify FDA of field actions
  - CAPAs that did not sufficiently resolve quality issues (*e.g.*, recurrent quality issues) and/or are "stale"

Device Due Diligence

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- **Common Issues**
  - Labeling or promotional materials that are not consistent with FDA cleared or approved indications for use
  - Clinical evaluation for which an IDE was not submitted (*e.g.*, physician preference evaluations)
  - Failure to follow SOPs
  - Improper or insufficient documentation of quality system information

Device Due Diligence

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- **Common Issues**
  - What will happen to respective web sites with transfer?
  - How will Design History File be reviewed for adequacy/updated/absorbed?
  - What if “catch up” 510(k)s are needed?
  - Who will be responsible if past compliance is found inadequate?

Device Due Diligence

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- **Example**
  - Company A wishes to acquire an IVD product from Company B. Company B obtained a 510(k) clearance for use of the device in 2001 for quantification of an analyte in blood. Company B's web site provides a diagnostic threshold for the analyte.

  - What documents should be requested in due diligence to address this issue?

  - If a conclusion is reached that a new 510(k) would be needed to support a diagnostic claim, who should be responsible for this?

Problems After Transfer
Warning Letter – Philips Lifeline, Inc.

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- Royal Philips Electronics (Philips Lifeline, Inc.) acquired Health Watch Holdings, Inc. in mid-2007.
- In late 2007 FDA inspected the Health Watch facility and identified QSR issues.
- In early 2008, FDA issued a Warning Letter to Philips with a number of findings, including:
  - Failure to ensure that an adequate and effective quality system with oversight by management with executive responsibility
  - Failure to establish and implement written procedures for implementing CAPA, controlling environmental conditions, controlling documents required under the QS regulation.
  - Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints . . and to ensure that all complaints are processed in a uniform and timely manner.
  - Failure to establish procedures for identifying training needs and for ensuring that all personnel are trained to adequately perform their assigned responsibilities.

Problems After Transfer
Warning Letter – Philips Lifeline, Inc.

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- Prior to the Warning Letter, Philips had responded to FDA's inspection observations by stating that Health Watch Holdings, Inc. was no longer a medical device manufacturer
  - FDA disagreed with this because Health Watch was still performing some maintenance activities on existing units (e.g., battery replacement, cleaning and functionality checks).
  - FDA also noted that the company had personnel dedicated to monitoring systems already installed in customer homes and that it was not clear from the company's response how the company planned to ensure that those units would be maintained throughout their product life.

Lessons Learned and Recommendations for Successful Transfers

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- If a previously cleared product is transferred, FDA may hold the new owner accountable immediately for full compliance.
- Inspections can follow rapidly post-acquisition.
- “Inherited” issues are still the acquirer’s problem.
- Careful identification of potential issues during due diligence is critical, preferably allowing resolution prior to transfer or at a minimum a rapid plan of action for resolution after transfer.
- Be certain all prior device modifications are well understood and covered by 510(k) clearance.
- Ensure “institutional memory” regarding limitations of FDA cleared claims is preserved and transferred.

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