FDA/CDER's Division of Project Management Office of Regulatory Operations Office of Generic Drugs

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April 13, 2016

"How an ANDA Gets Reviewed"

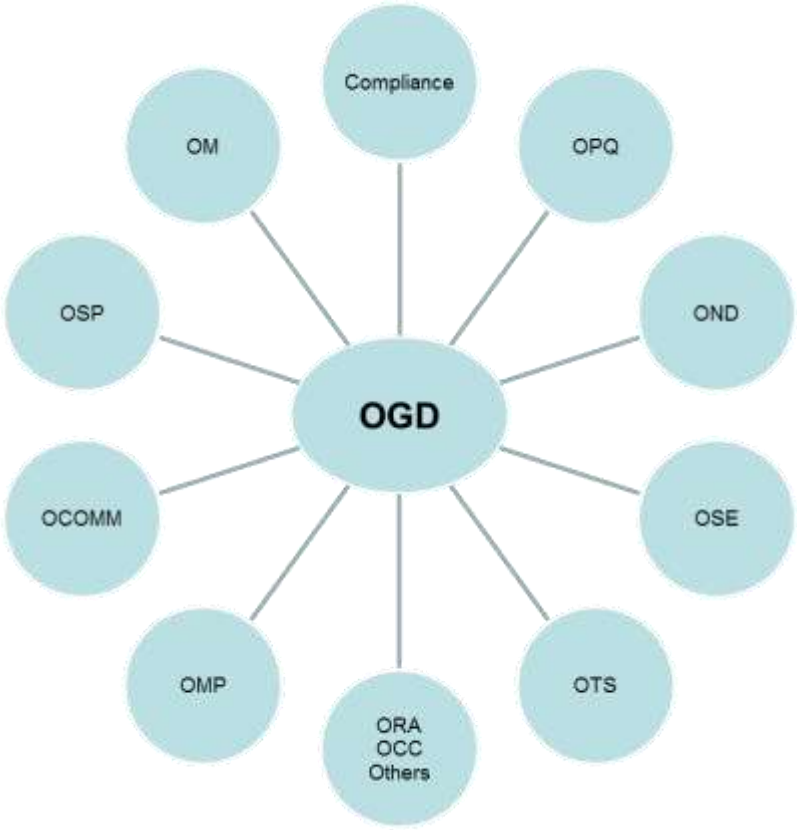
Topics Covered

- **Overview of the disciplines involved in the approval process**

GENERIC DRUG PROGRAM

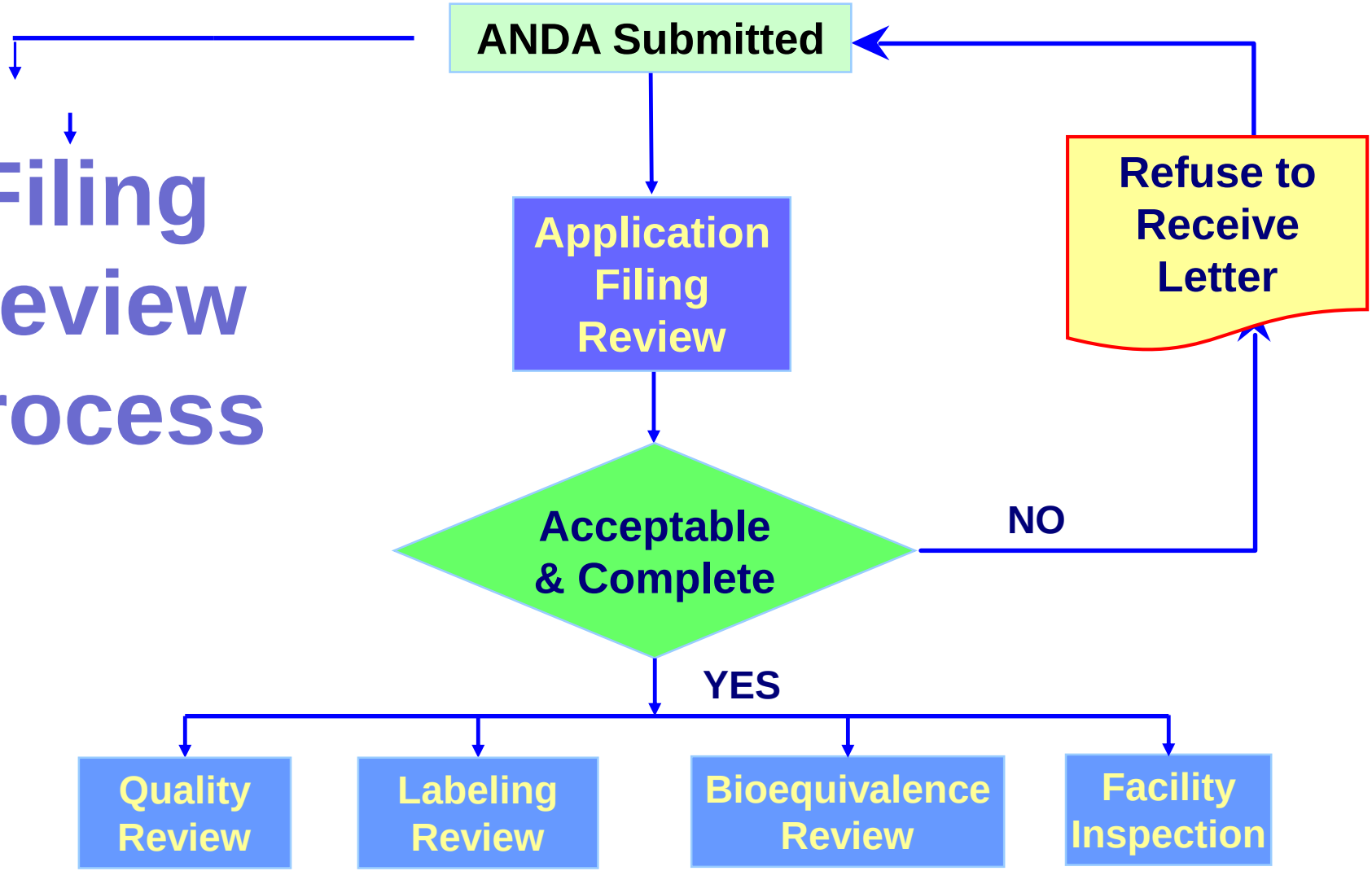
- **Not just OGD**
- **All of CDER**
- **Other FDA units:**
  - **ORA**
  - **Office of the Commissioner**
  - **CBER, CDRH**

- **OGD is the interface for ANDA applicants to interact with the Generic Drug Program**



FILING STAGE

Filing Review Process



Filing Review

- **Will verify Drug Master File (DMF)has been received by the FDA**
- **Will Determine Fees are paid in full**
- **Verifies application is suitable for review**
  -not a determination of approvability

Acceptable for Filing

- **Acknowledgement letter including Goal Date issued to applicant**

- **Goal Date – Date by which Action Taken**
  - **Complete Response Letter**
  - **Tentative Approval letter**
  - **Approval Letter**

Questions

- **Any questions related to filing may be directed to ANDAFiling@fda.hhs.gov**

REVIEW STAGE

Regulatory Project Manager (RPM)

Regulatory Project Manager

- **Oversee the review of ANDAs**
  - **Provide oversight across all review disciplines**
  - **Work to ensure all reviews are complete**
  - **Work to ensure OGD meets GDUFA goal dates**

- **Triage all amendments from receipt of ANDA to approval**
  - **Assign received amendments to the applicable disciplines**

- **Communicate key events in the approval process**
  - **MAPP 5200.3 Rev. 1**

- **Serve as point of contact**
  - **All communications will go through RPM**
  - **Exception: responding directly, as requested by a discipline**

Communications

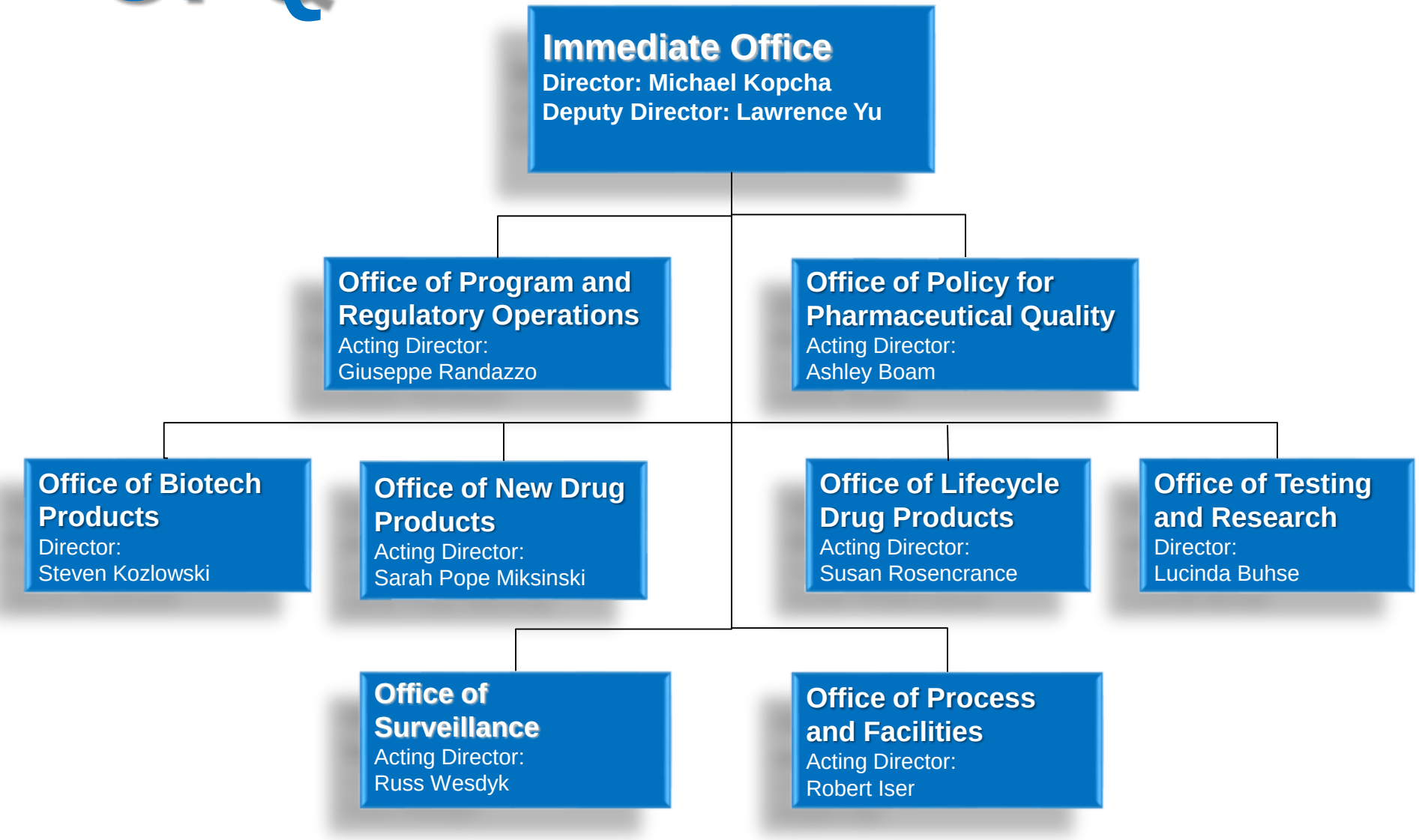
- **ANDA assigned to an RPM – introductory**
  - **Telephone**
- **ANDA reassigned to another RPM**
  - **Telephone**
- **Periodic Application status updates**
- **Easily Correctable Deficiency/Information Request**

Communications

- **Complete Responses (CR)**
- **Post CR meetings (clarification)**
- **CR Response Acknowledgements**
- **Inform application is in the clearance phase**
- **Issue Approvals and Tentative Approval Letters**

OPQ ANDA Review Process

OPQ


Immediate Office
Director: Michael Kopcha
Deputy Director: Lawrence Yu
Office of Program and Regulatory Operations
Acting Director:
Giuseppe Randazzo
Office of Policy for Pharmaceutical Quality
Acting Director:
Ashley Boam
Office of Biotech Products
Director:
Steven Kozlowski
Office of New Drug Products
Acting Director:
Sarah Pope Miksinski
Office of Lifecycle Drug Products
Acting Director:
Susan Rosencrance
Office of Testing and Research
Director:
Lucinda Buhse
Office of Surveillance
Acting Director:
Russ Wesdyk
Office of Process and Facilities
Acting Director:
Robert Iser

OPQ office structure

- OPQ Immediate Office (IO)
- Office of Program and Regulatory Operations (OPRO)
- Office of New Drug Products (ONDP)
- Office of Life Cycle Drug Products (OLDP)
- Office of Process and Facilities (OPF)
- Office of Testing and Research (OTR)
- Office of Surveillance (OS)
- Office of Policy for Pharmaceutical Quality (OPPQ)
- Office of Biotechnology Products (OBP)

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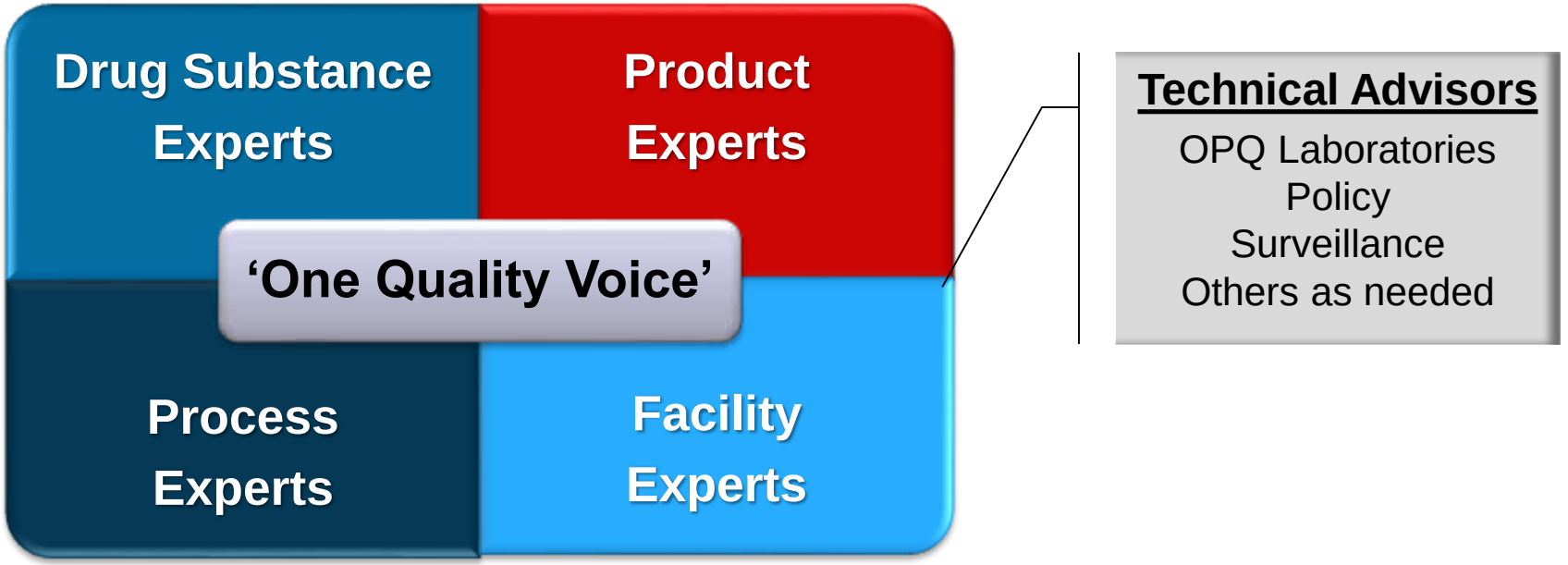
OPQ - Responsibilities

- Responsibilities include:
  - Review of Chemistry, Manufacturing, & Controls portion for:
    - New Drug Applications (NDA/ANDA/BLA)
    - Post-approval CMC changes
    - Annual Reports
  - Pre-Approval Inspection decisions
  - Evaluation of Compendia standards
  - Development of Guidance and Policy

Team Based Review

- **Integrated Quality Assessment (IQA)**
- **Team based review**
- **Kick off meetings begin each application**
- **Communication between disciplines throughout the review**

Seamless Integration of Review, Inspection, Surveillance, Policy, and Research



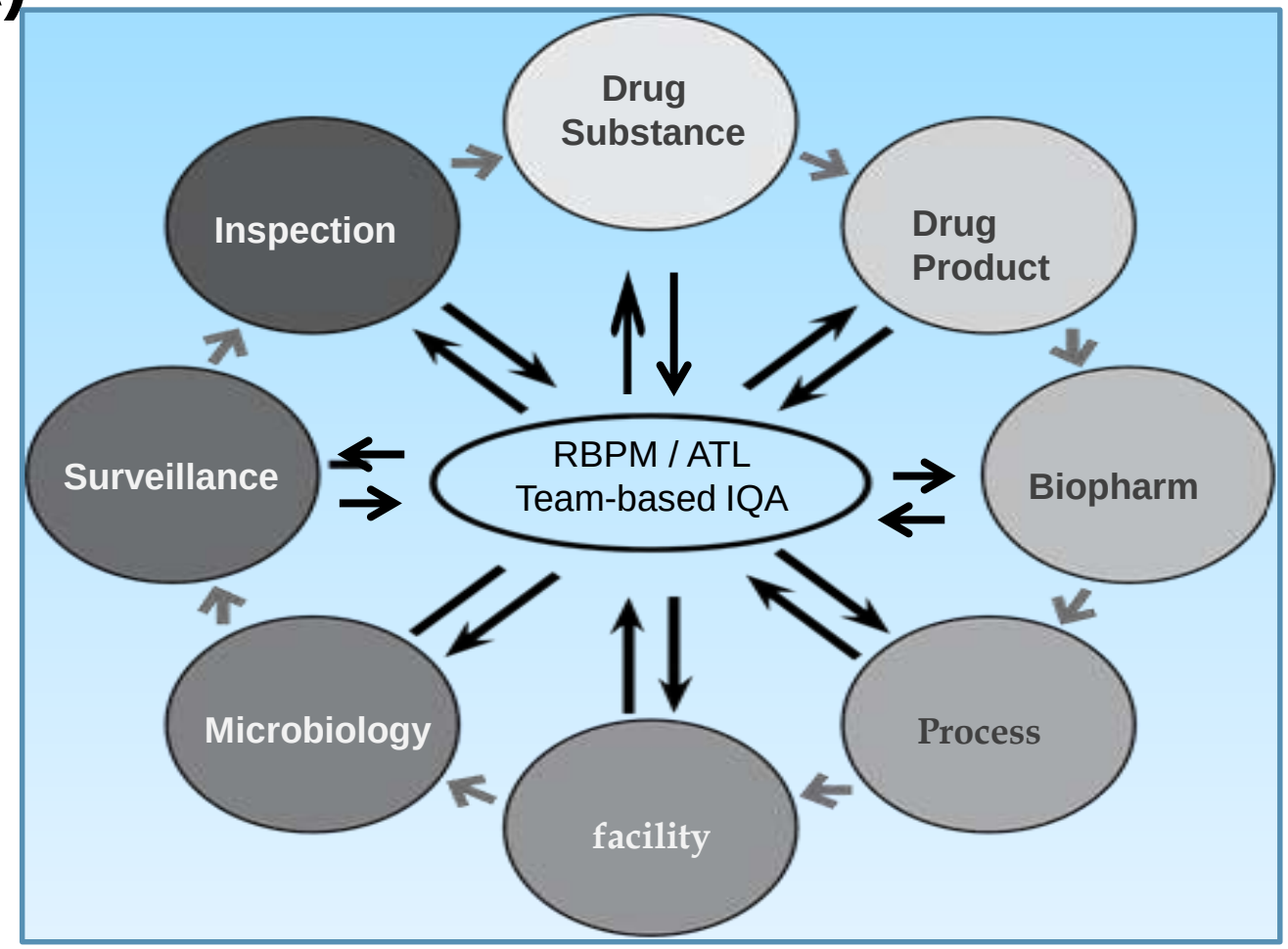
Application Technical Lead (ATL) – oversees the scientific content of the assessment

Regulatory Business Process Manager (RBPM) – manages the process, adhering to the established timelines

Integrated Quality Assessment Team

- **IQA team will provide an aligned, patient-focused and risk-based drug product quality recommendations for BLAs, NDAs, and ANDAs, inclusive of drug substance, drug product, manufacturing, and facilities.**
- **IQA Teams consist of:**
  - **Application technical lead (ATL)**
  - **Regulatory business process manager (RBPM)**
  - **Discipline reviewers**
  - **Advisors, if needed – lab (OTR), policy (OPPQ), surveillance (OS), etc.**

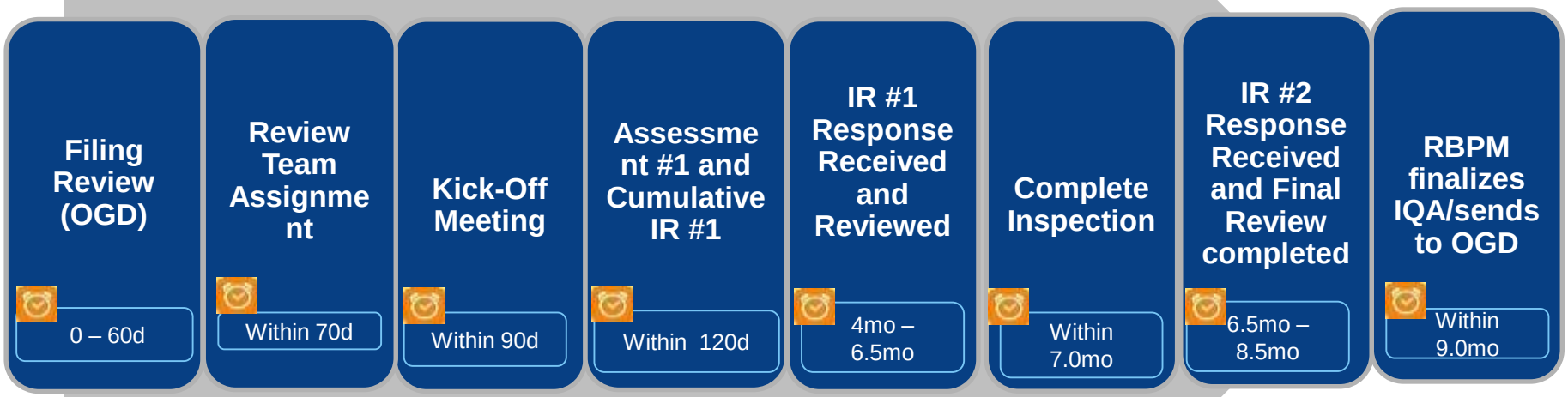
Team-based Integrated Quality Assessment (IQA)



ANDA Original Process

Current state: OPQ and OGD working to meet Cohort Year (CY) 3/4 15 mth GDUFA date.

Proposed example of 10 mth CY 5 timeline:



OPQ believes, in working with OGD and Industry, by CY5 the 1st cycle approvability rate for ANDAs can be improved. This goal is achievable provided the ANDA submissions we receive are of high quality and complete upon first submission.

Office of Program and Regulatory Operations (OPRO)

- **RBPMs**
  - **Co-leads along with the Application Technical Lead (ATLs) for ANDAs. Responsible for leading and managing all processes associated with drug quality review and facility inspections.**
  - **Coordinates with all OPQ offices to monitor and track all applications to ensure completion by goal dates**
  - **Serves as the internal and external liaison for quality related products**
  - **Triage all incoming submissions**

Office of New Drug Products (ONDP)

- **Division of Life Cycle API**
  - Drug Master File review
  - Primarily reviewing Type II DMFs for GDUFA applications
  - Only review DMFs which are referenced by an ANDA/NDA.
  - DMF communications include major deficiencies, IR's, deficiencies, ECD's and No Further Comment Letters.
  - The RBPM for quality responsible for issuing these letters
  - Drug Substance (in general)
    - Characterization (structure, physico-chemical properties, etc.)
    - Manufacturing Issues
    - Quality Control
    - Container-Closure System
    - Stability (shelf–life)

Division of Biopharmaceutics

Responsible for the Biopharmaceutics component of ANDA reviews. This entails release testing for quality control (e.g. dissolution) as well as biopharmaceutics related assessments to quality due to SUPAC related post approval changes

Office of Life Cycle Drug Product (OLDP)

- **Original application drug product review**
  - **Division of Immediate Release Products I**
  - **Division of Immediate Release Products II**
  - **Division of Modified Release Products**
  - **Division of Liquid Products**

- **Post approval drug product review**
  - **Division of Post Marketing Activities I**
  - **Division of Post Marketing Activities II**

OLDP Responsibilities

- **Manage the lifecycle of both brand and generic drugs**
- **Evaluate and assess product quality**
- **Make risk-informed recommendations**
- **Evaluate post-marketing activities for Approved brand and generic drugs**
- **Assists OGD on responding to consults related to product quality.**

Responsible for the following product quality components of applications:

- Formulation/product design
- Identifying potential failure modes
- Risk assessment
- Quality standards
- Clinically-relevant specifications
- Product characterization
- Method validation
- Control strategy related to product attributes
- Container/closure system
- stability

Office of Process and Facilities (OPF)

- **Division of Process 1,2 and 3**
  - Oversees the scientific review and quality evaluation of the manufacturing process
  - Participates PAIs as Subject Matter Experts when needed (based on risk)
- **Division of Microbiology Assessment**
  - Reviews the Sterility portion of the application
  - Responsible for the microbiological issues related to product quality and drug manufacturing
  - Participates PAIs as Subject Matter Experts for large molecules or when needed (based on risk) for other products

Office of Process and Facilities (cont.)

- **Division of Inspectional Assessment**
  - **Responsible for reviewing the Facility portion of the application and making decisions/recommendations for PAIs/facility status.**
  - **Works with Office of Regulatory Affairs (ORA) to prioritize inspection requests**
  - **Participates PAIs as Subject Matter Experts when needed (based on risk)**

Office of Testing and Research (OTR)

- **Method Validation Program (OPQ/OTR/DPA):**
  - **Perform method validation on applicant methods as requested by reviewers**
  - **Submit report detailing whether methods are acceptable, acceptable with modifications, or unacceptable for quality control and regulatory purposes**
  - **Common methods evaluated: Assay, Impurities, Degradants, Dissolution**
  - **DPA has averaged 30-40 completed method validations (NDA/ANDA) for the past 4 years**

OPQ disciplines complete

- **At this point, the RBPM will compile all of the OPQ discipline recommendations, and communicate that status to the OGD RPM. If it is adequate, OGD can move towards an approval or tentative approval if their disciplines are also adequate.**
- **If there are deficiencies which were not satisfied with the IR response, they will be communicated to industry via CR from OGD.**

Areas of Improvements

- **Missing/unclear facility information and responsibilities ensure that the 356H shows the most current and complete facilities for your application.**
- **Failure to link the development work to the proposed commercial process/product. This includes the scale up plan. Ensure you have the data to justify potential future scale ups.**
- **Missing in-process controls or inadequate justification for in-process criteria based on development studies.**

Areas of Improvements(cont.)

- Insufficient process/product knowledge.
- Address the issue of microbiological growth and controls during manufacturing of non-sterile oral dosage forms.
- Deficiencies related to facilities (OAI/POAI or data integrity issues.)
- Failure to make timely payments for facility user fees.

Areas of Improvements (cont.)

- Contact the RBPM for all questions related to Quality-only correspondences received (IR).
- Be aware of your information request response deadline.
- Only respond to IR with requested information. Additional unsolicited information may impact review time and goal dates.
- Continue to use the OGD/OND RPM as the point of contact for general inquiries.

Areas of Improvements (cont.)

- **Correctly code all submissions and amendments to ensure accurate triage and goal dates applied.**
- **Changes to facilities, either additions or withdrawals, at or near patent expiry dates or close to approval may cause delays in approval.**

Divisions of Bioequivalence

DB Responsibilities and Process

- **Review of bioequivalence data submitted in ANDAs**
- **Identify and request inspections for analytical and clinical BE sites requiring an Office of Study Integrity and Surveillance (OSIS) inspections**
- **Coordinate, draft, and inform ANDA applicants of BE IRs and ECDs**

DB Responsibilities and Process (cont'd)

- **Reviews may be two-tier (i.e., a primary and secondary review) or three-tier (i.e., a primary, secondary, and tertiary review) depending on the complexity of the submission**
- **Assist in product-specific recommendation development/revision**
- **Review of protocols**
- **Involved in projects pertaining to regulatory science**

Examples of Common Deficiencies

- **Incomplete bioanalytical report (e.g., missing validation studies, 100% raw analytical data not provided)**
- **Incomplete and/or inadequate justification of repeat analyses**
- **Standard operating procedures not provided**
- **Composition of colorant or flavor used in the test formulation not submitted**

Division of Clinical Review (DCR)

Division of Clinical Review (DCR)

- **Involved primarily in two types of reviews**
  - **Drug products that exert some or all of their activity directly at the site of application (such as topical dermatological products or nasal sprays)**
  - **Consults regarding clinical or safety concerns**

Division of Clinical Review (DCR)

- **Elements of topical drug product reviews**
  - **Review clinical endpoint studies and studies related to skin irritation and adhesion for transdermal films and patches**
  - **Contingent on satisfactory clinical site inspections when OSIS determines those inspections are necessary**

Suggestions to Improve Applications

- **Ensure novel excipients are not in the DMF**
  - **Not reviewed at filing**
  - **Typically requires preclinical and clinical safety data outside the scope of an ANDA submission**
- **Ensure that differences in proposed container closure system or drug-device product does not require clinical studies to establish safety or effectiveness or necessitate labeling differences from the RLD beyond those permitted in an ANDA**

Suggestions to Improve Applications

- **Consider the clinical aspects of the excipients**
  - **Some have biologic activity**
  - **May present safety issues**
    - **Examples:**
    - **Sugar in a product used to treat diabetes**
    - **Agents that cause osmotic diarrhea in a product to treat irritable bowel syndrome**
    - **Known migraine triggers in a product to treat migraines**
- **Failed studies**
  - **Avoid the temptation to do a post hoc analysis and submit it as a pivotal study in support of your product**

Risk Evaluation and Mitigation Strategy (REMS)

Risk Evaluation and Mitigation Strategy (REMS)

- **Does your ANDA require a REMS?**

- **Look up the RLD on FDA's REMS website at: http://www.fda.gov/rems**

Once an ANDA is Filled for Review:

- **You will receive a REMS notification letter (RNL) instructing you on:**
  - **Who to contact if there is a shared system REMS or if a shared system needs to be developed**
  - **The required elements of the REMS**

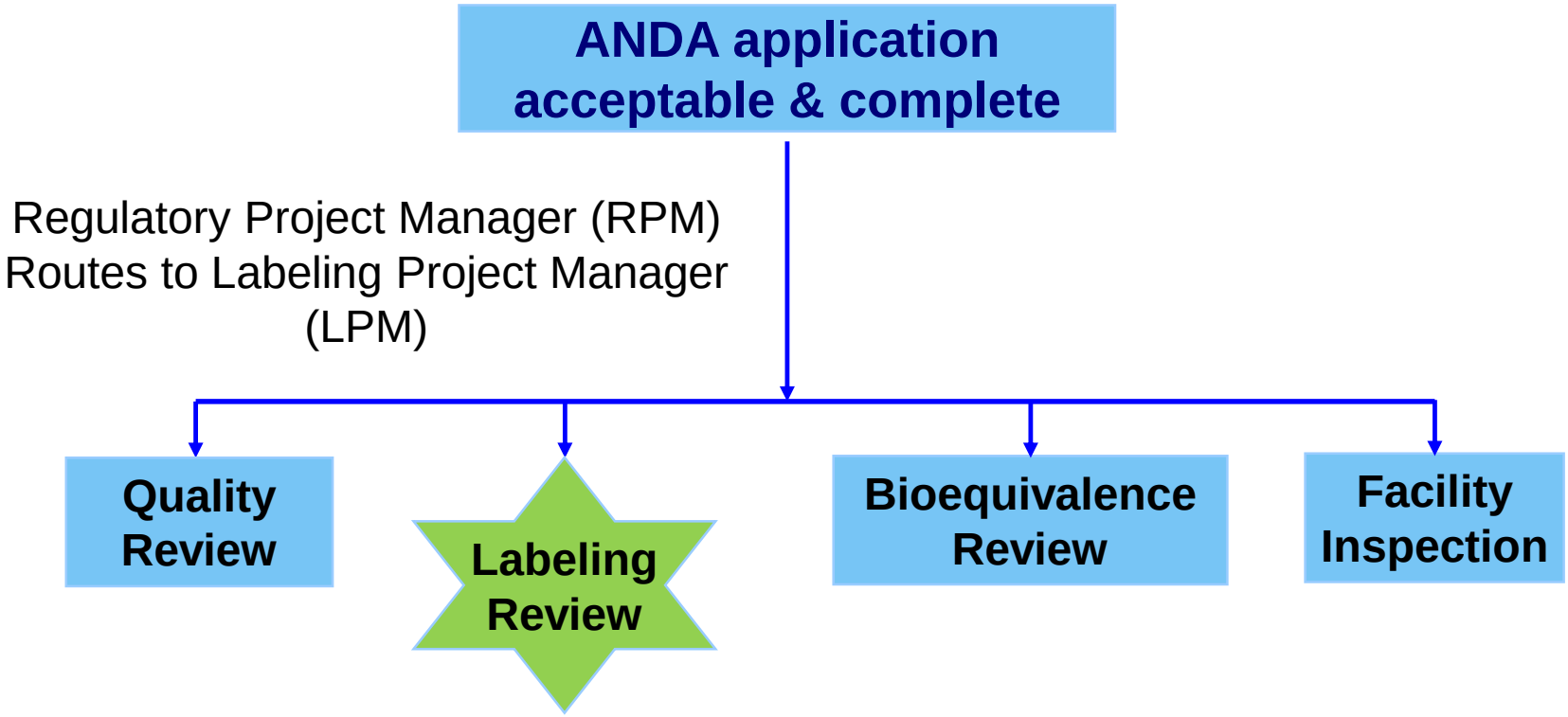
- **Follow the instructions on how the REMS should be submitted**
  - **Your REMS is NOT complete without a REMS supporting document**
  - **Title your cover letter as instructed and ensure your Form 356h Submission Type matches the cover letter title**
  - **You do NOT need to wait for RNL to submit your REMS**

Division of Labeling Review (DLR)

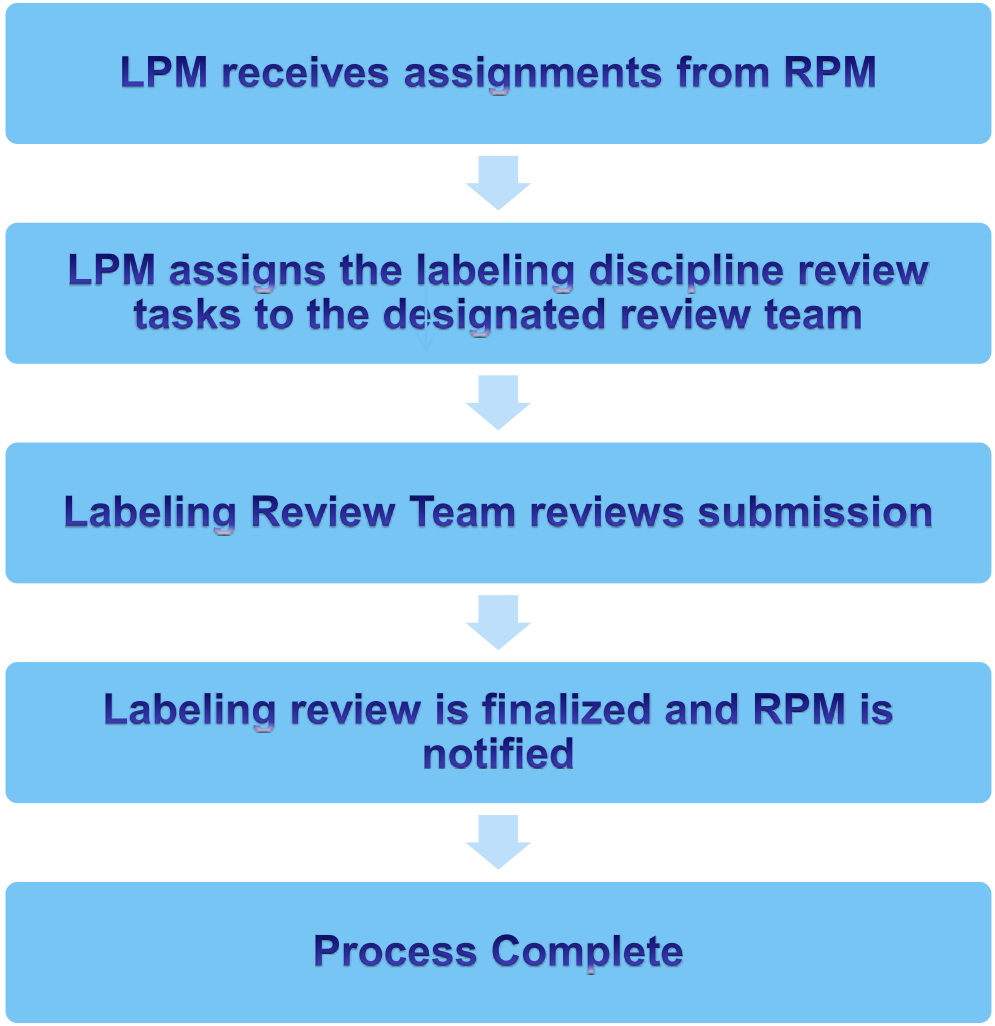
Labeling Review

- **Ensure generic labeling is the "same as" the reference listed drug**
- **Ensure labels and labeling are clear and accurate**
- **Verifies each listed patent and/or exclusivity has been addressed**
- **Labeling meets applicable guidelines**
  - **U.S. Pharmacopeial Convention (USP)**

Application Process



Labeling Review Process



Helpful Labeling Links

- **Drugs@FDA-for last approved labeling**
  - http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?CFID=16144758&CFTOKEN=efcc9740da7b781f-BE6C3C0A-F263-A15C-F9871BDEAE083C69
- **Orange Book-for patent, exclusivity information**
  - http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
- **Antibiotic Breakpoint Labeling Updates**
  - http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm275763.htm

Division of Legal and Regulatory Support

Review of Hatch Waxman related information by Patent/Exclusivity Team

- **Purpose:**
  - **OGD, in a ministerial role, ensures that ANDA applicants have addressed all listed patents and exclusivities prior to the issuance of TA or Full Approval**
  - **OGD ensures that all required documentation related to patents and exclusivities has been provided by applicants**
  - **OGD ensures consistent application of Hatch Waxman policy and precedents across applicants**

Review of Hatch Waxman related information by Patent/Exclusivity Team

- **Purpose: (Cont'd)**
  - **OGD ensures that all grants of 180 day exclusivity are consistently applied and compliant with the "Forfeiture Provisions" of 505(j)(5)(D)(I)-(VI) of the FD&C Act**
  - **Creates a record of ANDA status at the time the action was taken**
- **Conducted during endorsement phase of all actions for Tentative or Full Approval**

Frequent Problems/Omissions

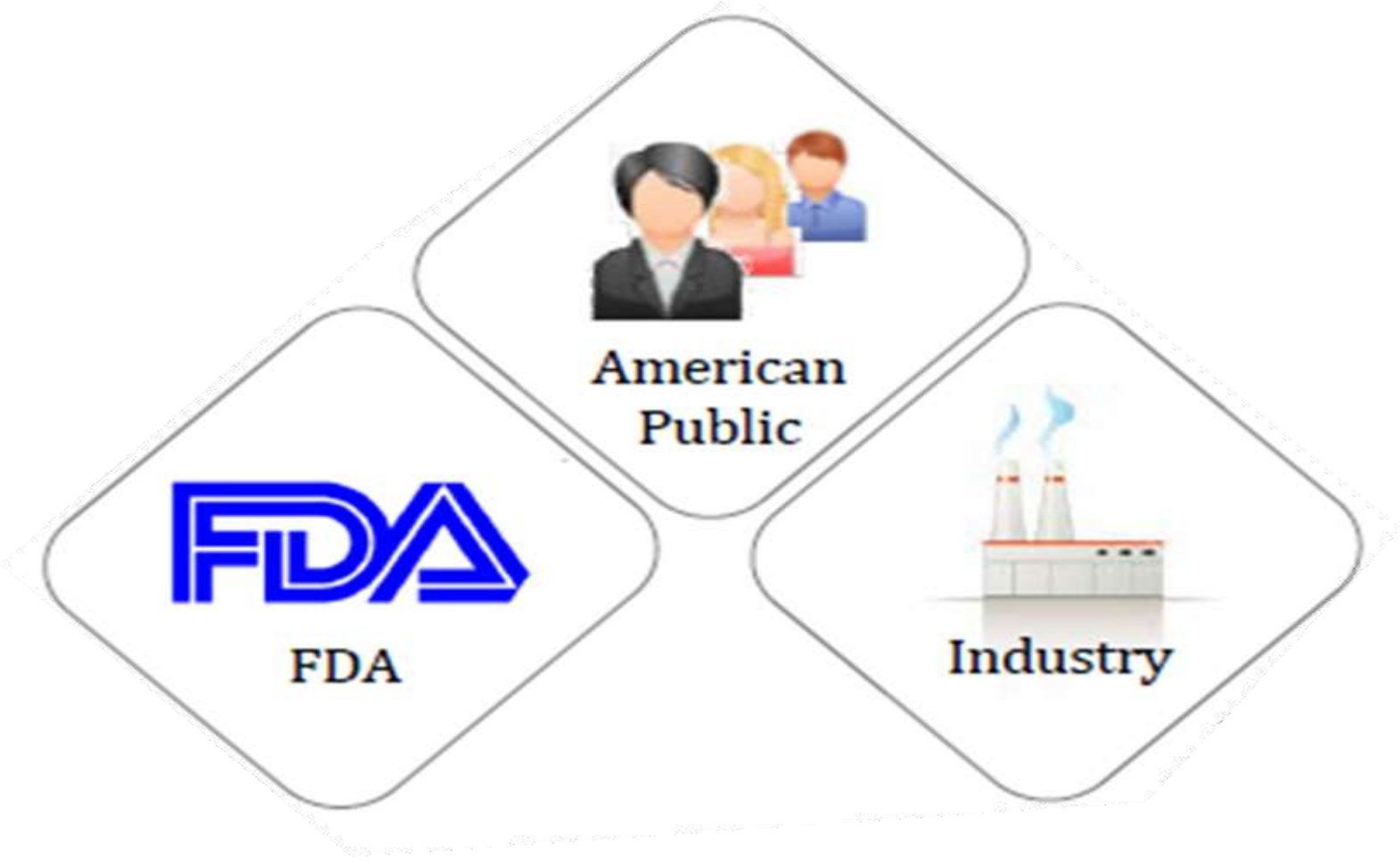
- **Sponsor has not addressed ALL patents and/or exclusivities**
- **PIV certifications to 'later-listed' patents**
  - **Sponsors must still submit documentation that notice was sent to NDA holder and patent assignees**
- **Inconsistencies between patent certifications or between patent certifications and labeling.**
  - **Labeling must match manner in which sponsor has addressed listed patents**
  - **Sponsor must generally address patent(s) which are associated with the same use code(s) in the same manner.**
  - **Sponsors may need to provide 'split-certifications' for patents to maintain consistency**

Frequent Problems/Omissions

- **Sponsors do not submit all information required by 21 CFR 314.107(e) and (f)(2)**
  - **All court decisions/orders MUST be submitted to the application**
  - **This includes dismissal orders and adverse court decisions**

- **Sponsors do not convert certifications from PIV to PIII**
  - **Required by 21 CFR 314.94(a)(12)(viii)(A) when a final judgment has been entered finding the patent infringed**

Working Together



Thank You!

Questions?

surveymonkey.com/r/GDF-D1S5