U.S. FOOD & DRUG ADMINISTRATION

Pre-ANDA Review Perspectives: Office of Pharmaceutical Quality (OPQ) Experience

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Immediate Office/OPQ

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Agenda

- Who we are and what we do
- OPQ Pre-ANDA process
- Metrics
- Lessons learned

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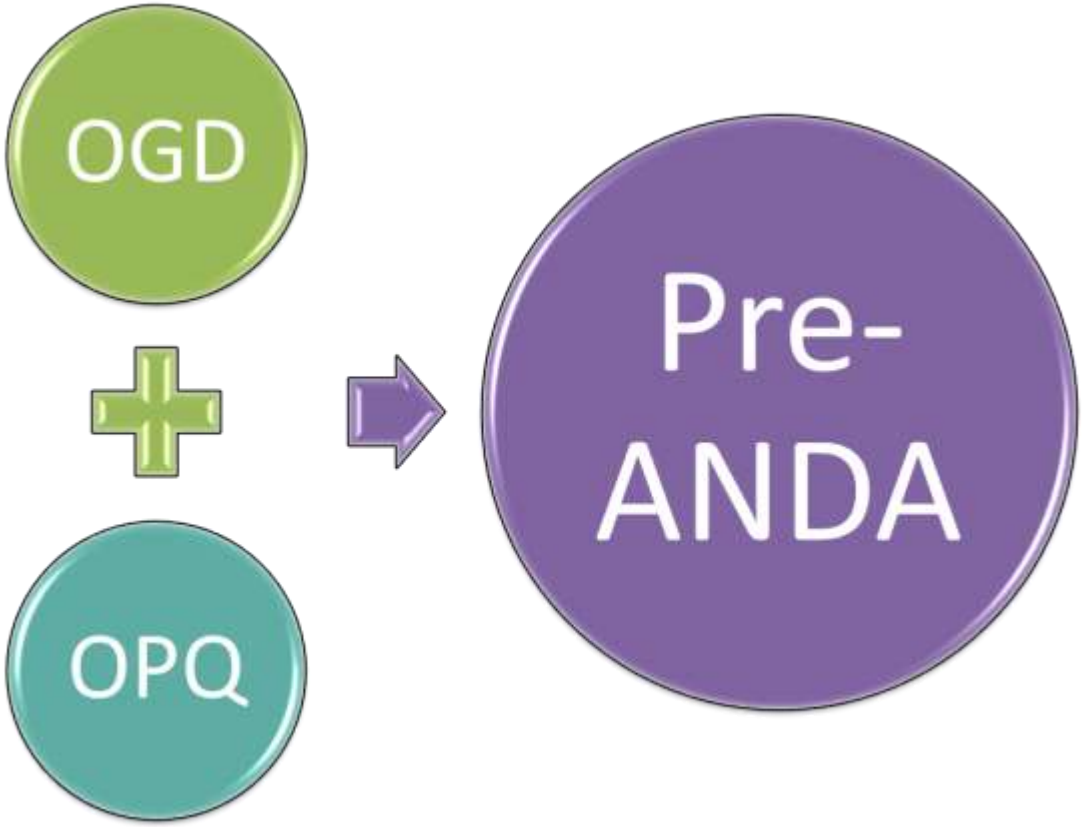
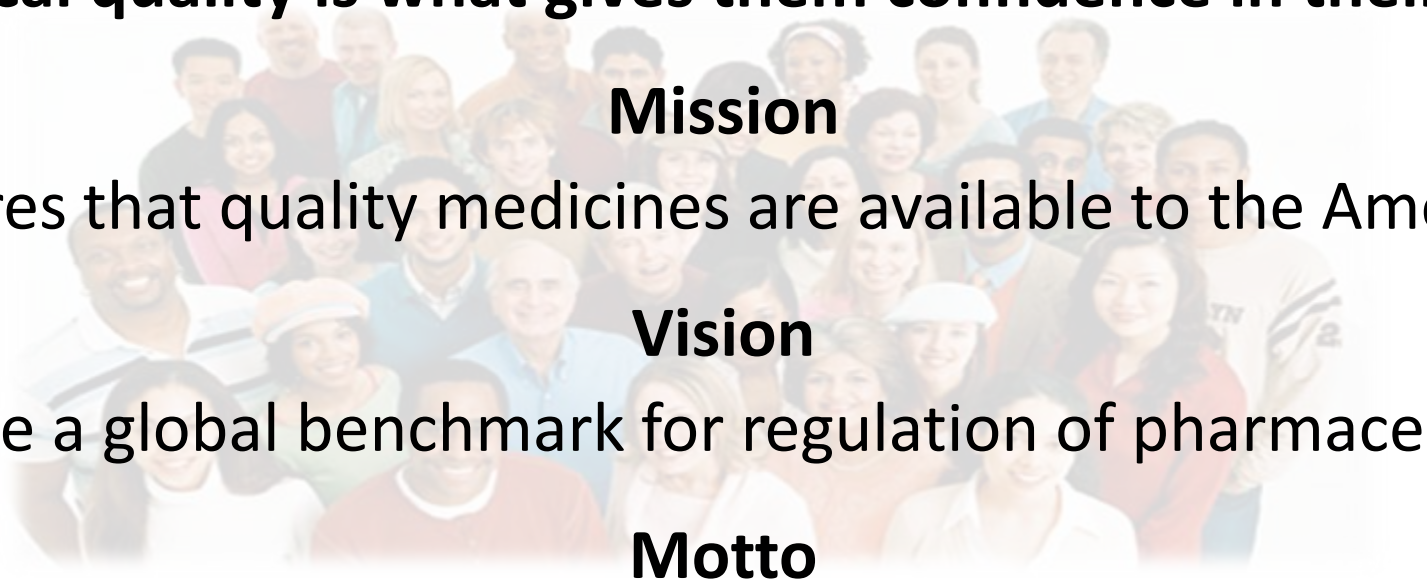
Pre-ANDA Program



Office of Pharmaceutical Quality (OPQ)

Pharmaceutical quality is our *shared* goal of assuring consistently safe and effective drugs are available to patients and consumers.

Pharmaceutical quality is what gives them confidence in their *next* dose.



Mission

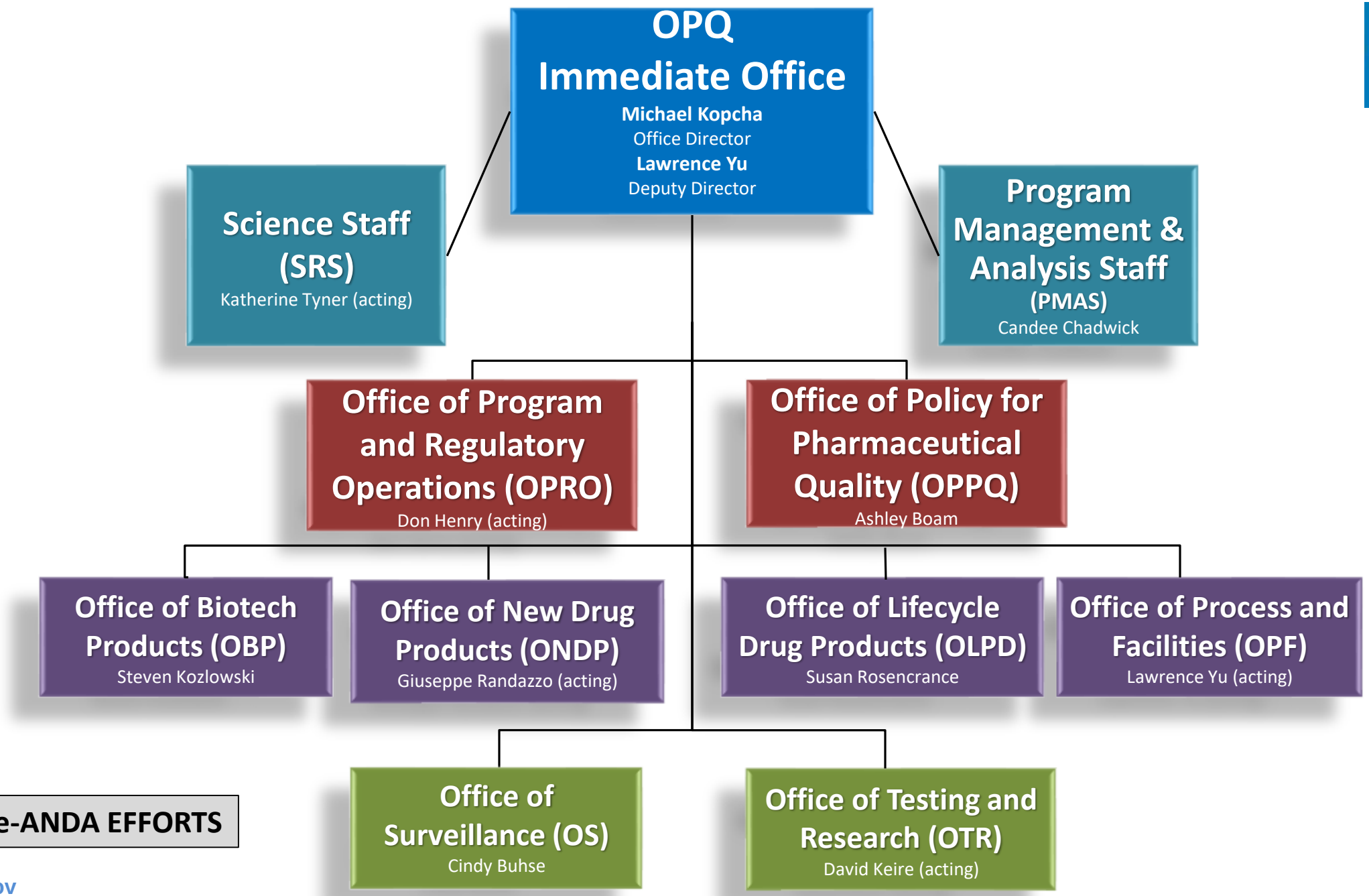
OPQ assures that quality medicines are available to the American public

Vision

OPQ will be a global benchmark for regulation of pharmaceutical quality

Motto

One Quality Voice



OPQ Pre-ANDA EFFORTS

OPQ Pre-ANDA Team

- **Triage Team** (IO/SRS)
  - OPQ Accept/decline the meeting request
  - Determines IQR team required
- **Regulatory Business Process Manager** (OPRO)
  - Facilitate the Pre-ANDA process
- **Integrated Quality Review Team** (OLDP, OPF, ONDP, OTR) – Reviews the meeting package
- **Meeting Chair** (OLDP or ONDP, if complex DS)
  - Coordinate technical matters
- **Technical Advisors**, as needed
  - Pre-ANDA Working Group
  - OTR/OPPQ/OBP
  - Research/Policy/Immunogenicity

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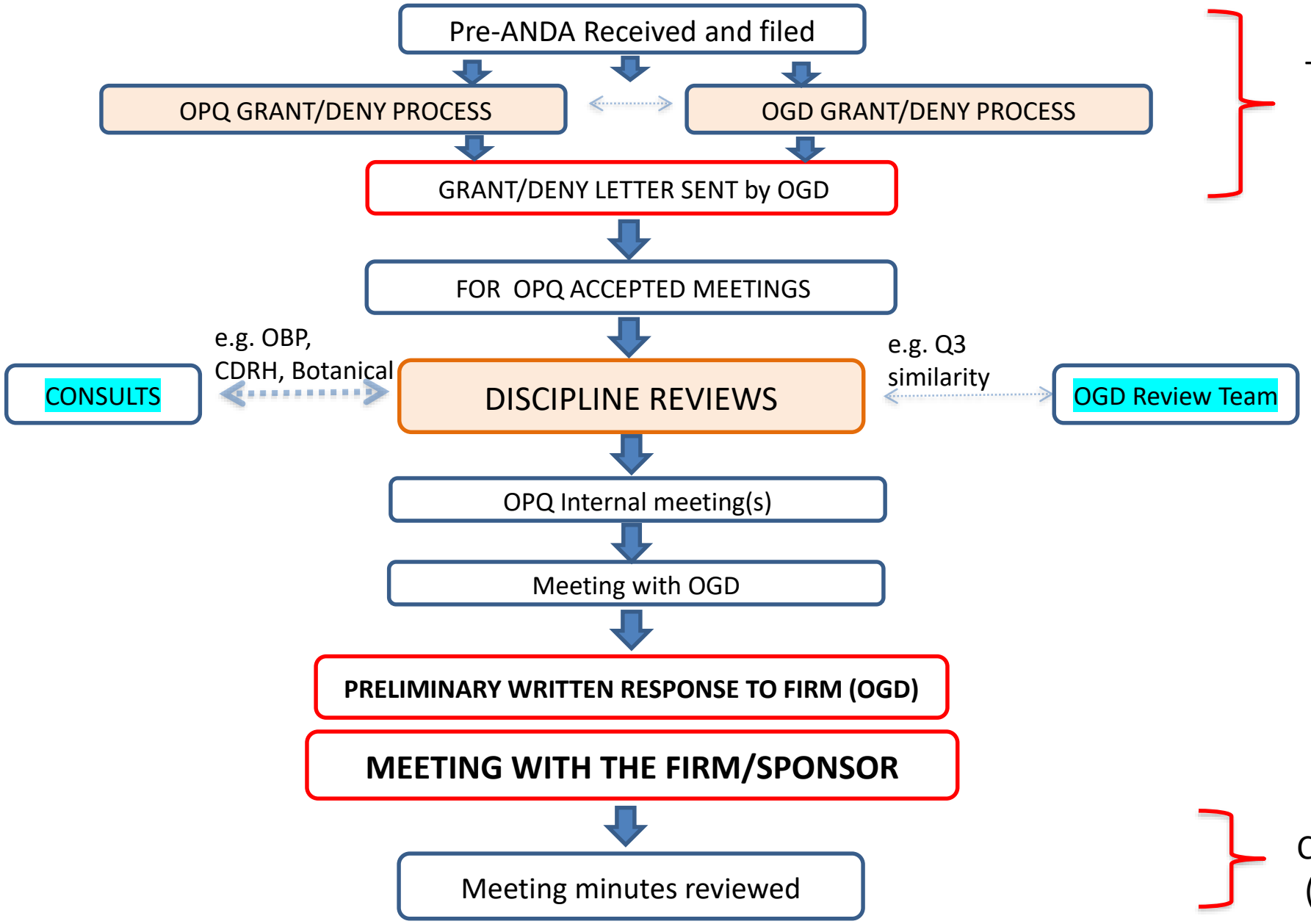
Pre-ANDA Number Facts

- Applicants must have a Pre-ANDA number prior to meeting package submission
- All Pre-ANDAs have a unique number system
  - ANDA-211208-PDEV-Meeting-00001 (Project)
    - Future ANDA #211208 (Program)
    - PDEV (Product Development) orPSUB (Pre Submission meeting)
    - Same ANDA number with different meeting # for resubmitted Pre-ANDA meetings (after previously denied)
  - All of the *Pre-ANDA* projects will be linked to the ANDA program

OPQ Pre-ANDA PROCESS



Triage Phase (30 days) (14 days)

Review Phase (120 days)

Closing phase (30 days)

Phase 1 OPQ Triage : Accept/Decline

- Triage team (within the OPQ Science Staff)
  - Reviews the product details and submitted questions in the meeting package
  - Determines to accept or decline OPQ's involvement (and extent) in the meeting
  - Presents the decision to OPQ's Pre-ANDA WG for concurrence

Decision Tree

- COMPLEX YES/NO (as defined by GDUFA II Commitment Letter)
- Meeting package complete YES/NO
- Complex equivalence issues YES/NO
- Will the CMC questions enhance the review efficiency ?
- Does the PSG/CMC guidance, if available, answer all of the questions raised?

Complex Products

COMPLEX…	Example	Example Products
Active ingredients	Peptides, complex mixtures, natural source products	Glatiramer acetate
Formulations	Liposomes, emulsions	Liposomal formulations
Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmological products	Acyclovir cream
Dosage Forms	Transdermal systems, extended release injectables	PLGA microspheres
Drug-Device Combinations	Dry powder inhalers, nasal sprays, transdermal systems	Mometasone nasal spray
Other products	Complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrence formulations

HOW DOES OPQ TRIAGE AFFECT MY Pre-ANDA ?

NO CMC QUESTIONS

OPQ DECLINE

If only Q3 sameness Questions

OPQ accept/decline depends on OGD's decision

If other CMC Questions

Triage based on GDUFA II criteria & SOP

Pre-ANDA Triage

FOR OPQ ACCEPTED MEETINGS:

Triage team

- Identifies OPQ discipline reviews needed for meeting package review
- Determines the need for OTR and OPPQ involvement
    - Based on past research within the office and the questions received
- Assigns the accepted meetings to specific OPQ discipline queues
- Monitors the Pre-ANDA program for metrics, process improvements, trends, and workload
- Coordinates with OGD

Integrated Quality Review (IQR)

- Team based Quality Review (similar to ANDAs- Integrated Quality Assessment)

- IQR Teams consist of Discipline Reviewers
  - ONDP/OLDP
    - Drug Substance
    - Drug Product
    - Biopharmaceutics
  - OPF
    - Manufacturing, process, controls
    - Facilities
    - Microbiology
  - OTR
    - Regulatory research

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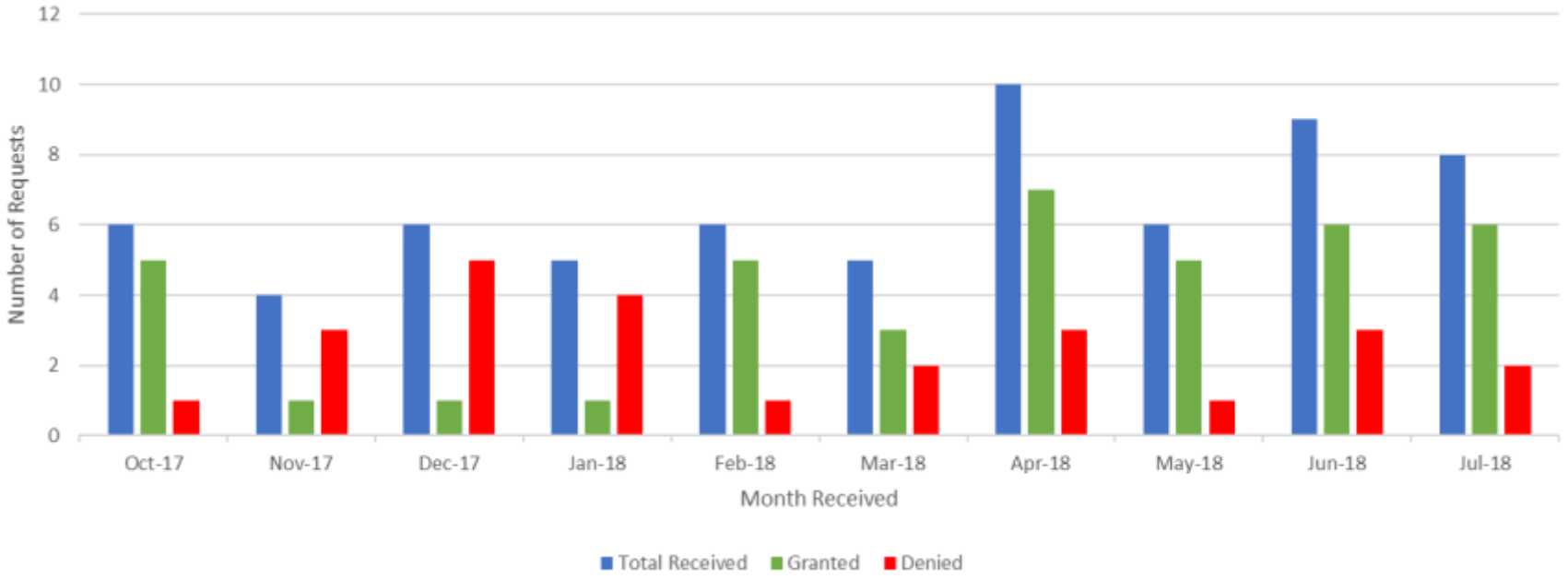
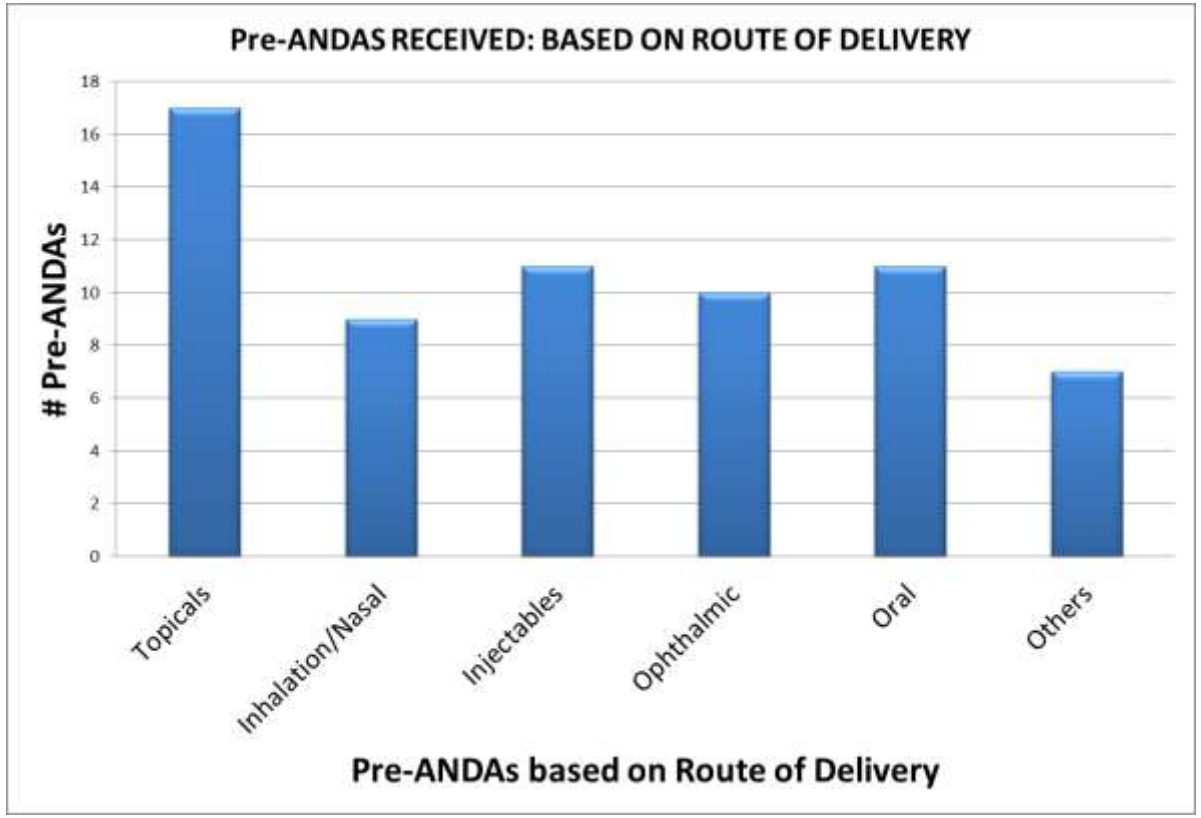
Pre-ANDA Metrics

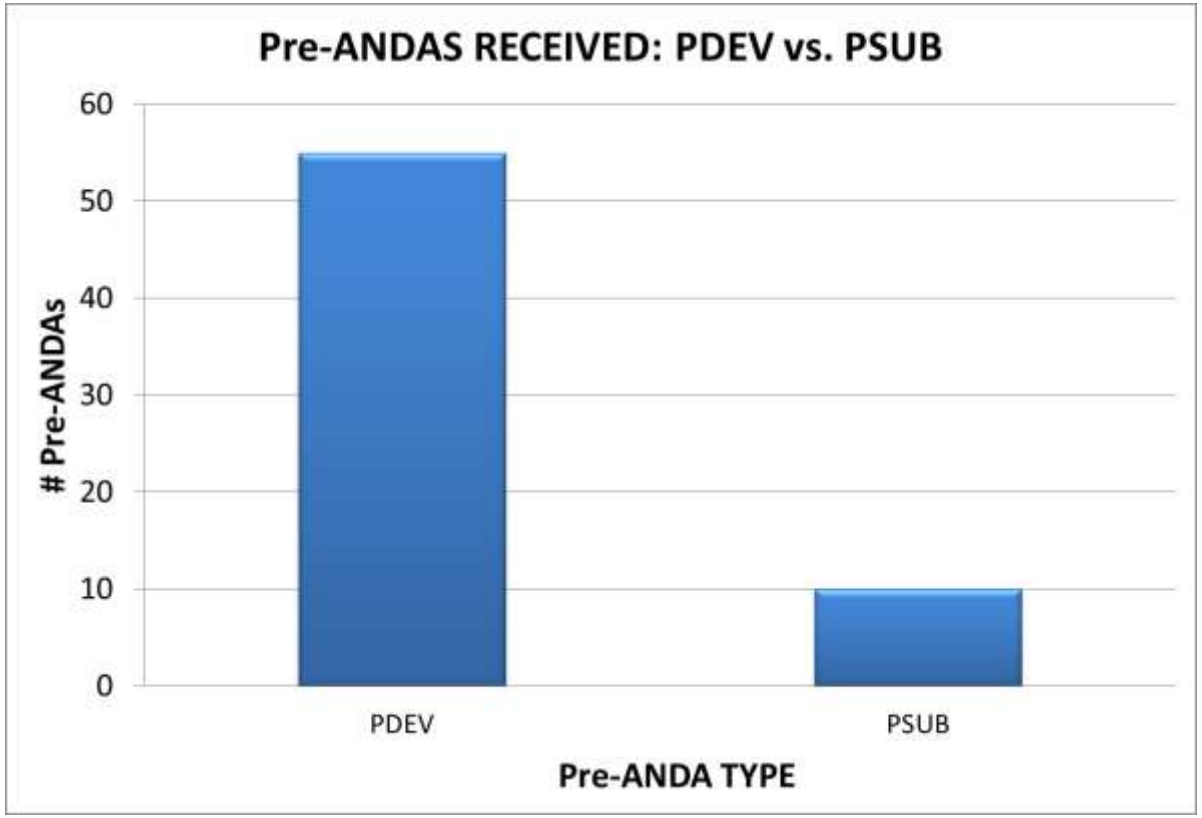


- **65 Total Pre-ANDAs** (as of 07/31/2018)
  - 40 FDA Granted
    - **<u>27 OPQ Grant</u>**

~40% Denied – **Incomplete meeting package > Not Complex > PSUB vs PDEV > CC route**

Pre-ANDA Metrics (As of Jul 31, 2018)





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Did You Know…

- **Discipline reviews** are performed based on meeting package questions
- Responses are **integrated** from different disciplines, as needed
- Responses are based upon the agencies **current thinking and knowledge**
  - May change with available data or research, etc.
  - Review issues are out of the scope of Pre-ANDA meetings

Example Pre-ANDA Questions (Reasonable)

- Are there additional critical material attributes or critical process parameters that FDA feels we should address?

- Does the Agency agree that, on the basis of the data presented, the proposed physicochemical tests are acceptable to support comparative physicochemical characterization?

- Does the Agency agree with the approach we designed to compare the overall particle size distribution of API particles in the test and RLD product by means of MDRS and SEM-EDS?

Example Pre-ANDA Questions

- Based on above mentioned observations, XXX believes that drug substance used by XXX to manufacture the submission batches either does not have amorphous material or could be present at an insignificant level which doesn't affect product performance. XXX believes that XRD Test at drug substance release test would be sufficient to show the crystalline purity. Is it acceptable to the agency?

- Does FDA agree with the proposed manufacturing process and controls including in-process tests?

- Does FDA agree with XXX's assessment that all the potential impurities listed in the table provided can be controlled in the drug substance consistent with the limits recommended in pharmacopeia and ICH Q3A(R2) guidance?

Review issues

The Pre-ANDA Program: Lessons Learned

- No run-on questions please!
- Group questions based on discipline (BE, CMC, Regulatory, Biopharmaceutics etc.)
- Provide adequate supporting information for each question
  - Prevents the Pre-ANDA from being denied
  - Allows FDA to provide the best response
  - Avoids information requests


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