

# Controlled Correspondences (CC) Office of Policy for Pharmaceutical Quality (OPPQ)

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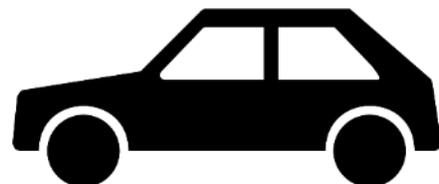
# Pharmaceutical Quality

**A quality product of any kind consistently meets the expectations of the user.**



## Pharmaceutical Quality

**A quality product of any kind consistently meets the expectations of the user.**



**Drugs are no different.**

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is softly blurred, showing a person's face and a blue garment.

**Patients expect safe and effective  
medicine with every dose they take.**

A close-up photograph of a person's hands. The left hand holds an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is softly blurred, showing a person's face in profile.

**Pharmaceutical quality is**  
assuring *every* dose is safe and  
effective, free of contamination  
and defects.

A close-up photograph showing a hand holding an orange pill bottle tilted to the left. Another hand is cupped underneath, holding three white, oval-shaped pills. The background is softly blurred, showing a person's face in profile.

**It is what gives patients confidence  
in their *next* dose of medicine.**

# Outline

- Processing of CCs in OPQ
- No. of CCs with quality questions
- Analysis of quality related CCs
- General recommendations for submitting CCs
- OPQ issues/problems with CCs
- Questions that cannot be answered in a CC

# OPQ CC Process

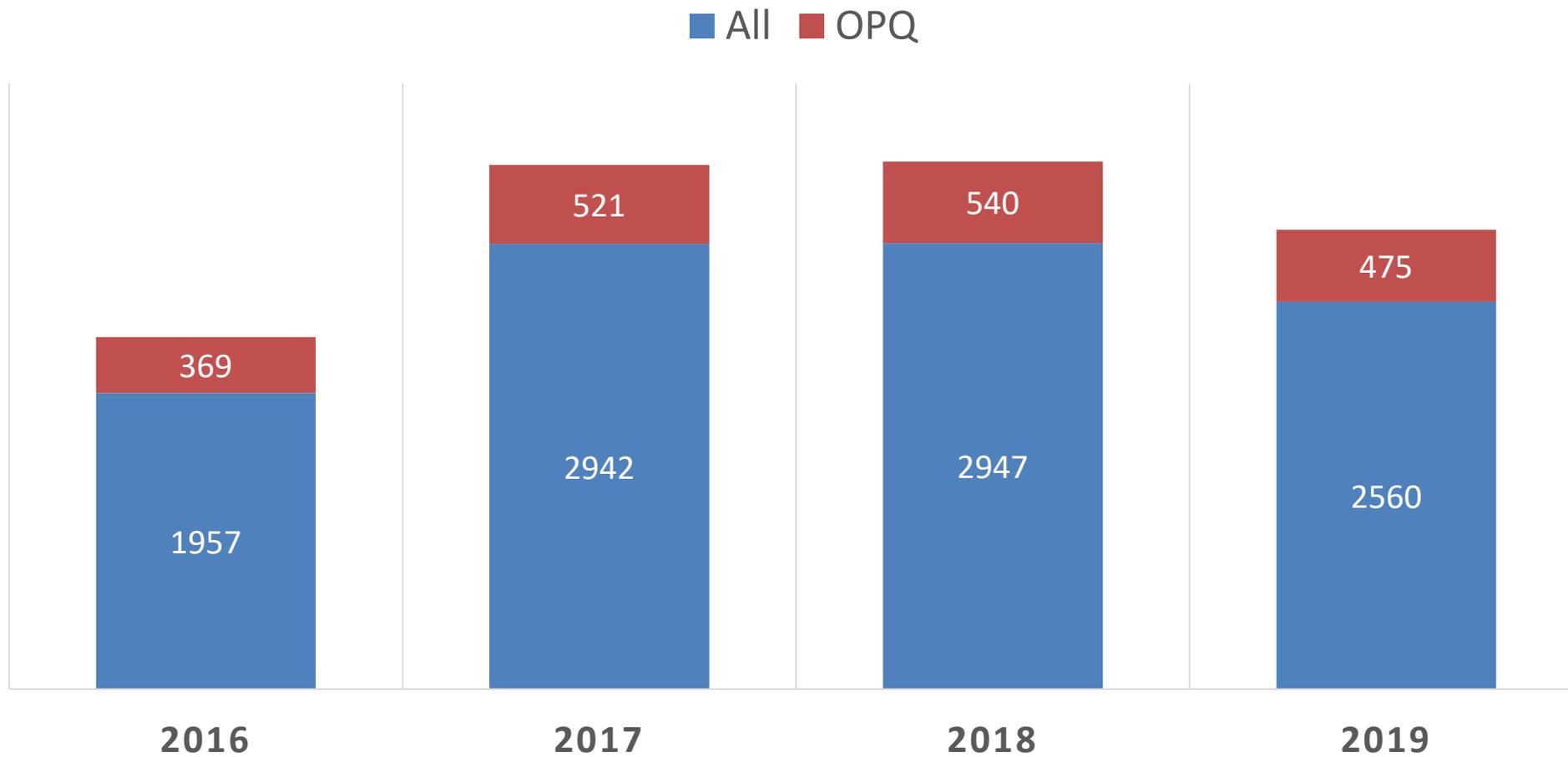
- OGD triages all incoming CC and clarification requests
- CC's with product quality questions are sent to OPQ
- OPQ issues the consults (if needed), develops a written response to the question, and sends the final letter to the inquirer
- To ensure consistency in the response, OPQ review divisions are part of the clearance process for CCs

U.S. Department of Health and Human Services  
Food and Drug Administration

# Process for Analysis of CCs

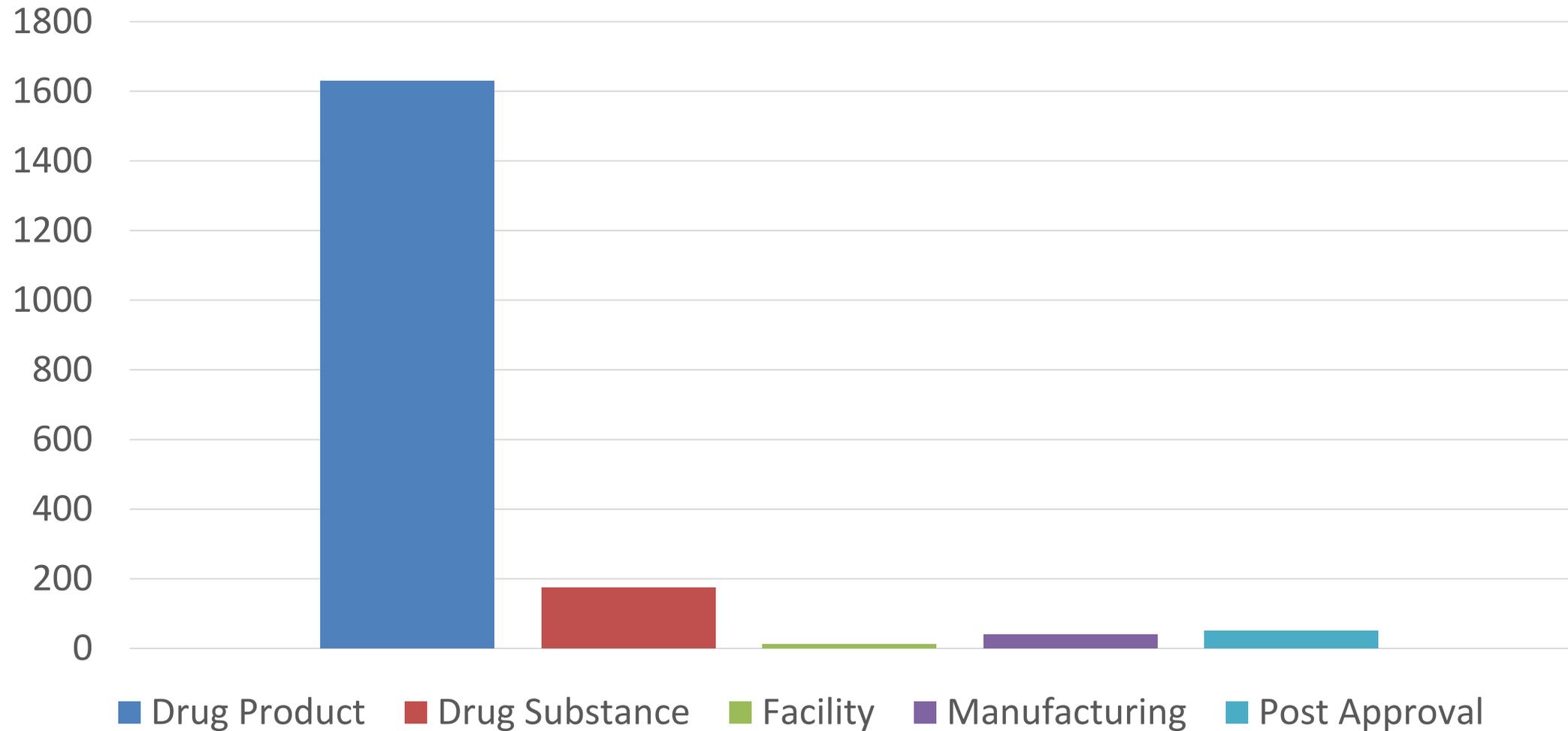
- Sort CCs into one or more categories based on the type of question
- Utilize 5 categories to identify general topics
- Sort into topic-specific subcategories to identify gaps and implement continual improvements in our policies

# OPQ CC Workload

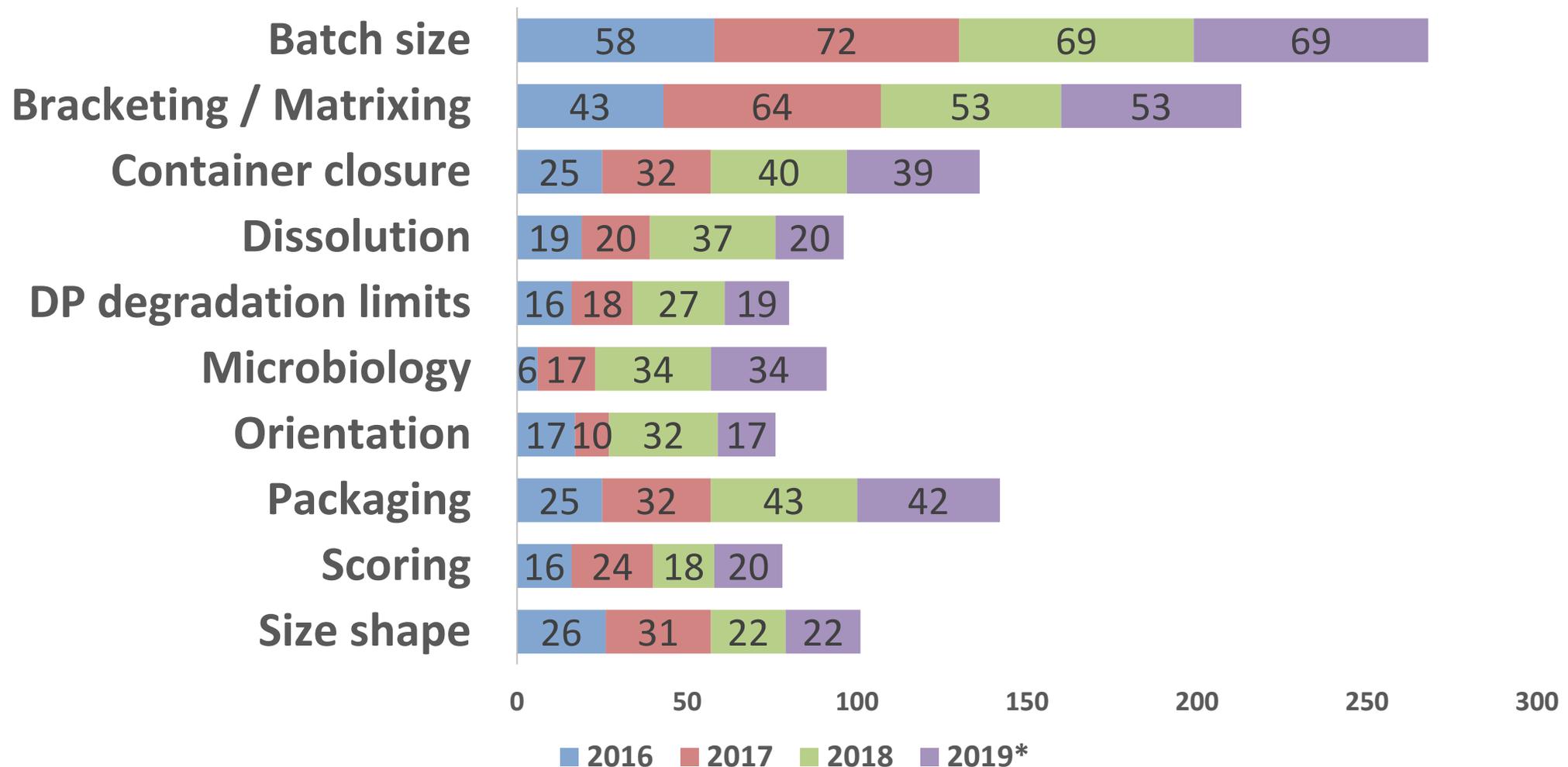


2016-2019: OPQ receives 18-19% of the CCs sent to CDER

# CC Categories 2016-present



# Top 10 CCs Subcategories



# CCs Analysis

- Goals are to address CCs submitted to OPQ so our expectations are transparent
- Analyze the type of questions submitted and determine a strategy to address certain questions  
For example:
  - Is there a lack of clarity in a guidance where a revision should be considered
  - Is there a policy gap where a new guidance on a specific topic is needed

# Example of CCs Analysis – Batch size

- CCs requesting confirmation on guidance<sup>1</sup> recommendations
  - The reference listed drug product has an orphan drug designation.
  - The submission ANDA batches can have a smaller size than the established pilot scale, when use of a controlled drug substance is based on a Drug Enforcement Administration (DEA) allocation
  - ANDA submission batches are the same as the commercial batch size
- OPPQ is actively looking for solutions to reduce the number of CCs for recurrent questions

<sup>1</sup> ANDA Stability Testing of Drug Substances and Products Q&A guidance 2014

# Examples of Issues with CCs in OPQ



- Not enough background information in the submission
  - Acceptability of starting material designation with no information on route of synthesis, how impurities are controlled, and proposed specification
  - API or excipient sameness with no comparative studies with the RLD or characterization data

# Examples of Issues with CCs in OPQ

- Lack of clarity
  - Question(s) phrased so that it is difficult to understand
  - Information provided not relevant to the question
  - Basic product information is not provided (dosage form, Q1/Q2 with the RLD, etc.)
- Too general
  - Questions related to the general approach for product development, instead of a development specific issue

# General Recommendations



- Resolve Q1/Q2 formulation issues before sending a CC to OPQ on a proposed Bracketing/Matrixing (B/M) approach for different strengths
- When an RLD is labeled as a salt and a potential ANDA applicant thinks it is a co-crystal, a pre-ANDA meeting may be needed
- Scored tablet should meet the recommendations in the tablet scoring guidance<sup>1</sup>. Comparative studies with the RLD are not recommended.

<sup>1</sup> Guidance for Industry: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (2013)



# General Recommendations

- For changes in a container closure (vial to prefilled syringe)
  - For a drug-device combination, analysis of user interface should be performed<sup>1</sup>
- Where a bracketing /matrixing approach allows for a reduced number of batches on stability, this should not be interpreted to mean that the number of batches to be manufactured can also be reduced
  - One exception in the ANDA Stability Testing of Drug Substances and Products Q&A guidance 2014, Q and A 19(i) for common blends

<sup>1</sup> Refer to Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry, 2017

# Examples of questions that cannot be answered in a CC



- Acceptability of a specification, in-process control, or study plan
  - Impurity clearance approach
  - Recommendations for the proposed manufacturing process
  - Adequacy of characterization studies

# OPPQ Activities and Goals

- Evaluate policy effectiveness and relevance
  - Actively track the types of CC questions submitted in each subcategory and address them through ongoing policy development
- Strive to ensure that OPQ's policies are clear, transparent, and intuitive to stakeholders.



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