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.



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

Drugs are no different.


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

Pharmaceutical quality is

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

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

Overview

- Processing of Controlled Correspondences (CCs) in OPQ
- Analysis of CCs quality questions
- Examples of frequently asked questions
- Issues with CCs submissions
- OPQ continual improvement process

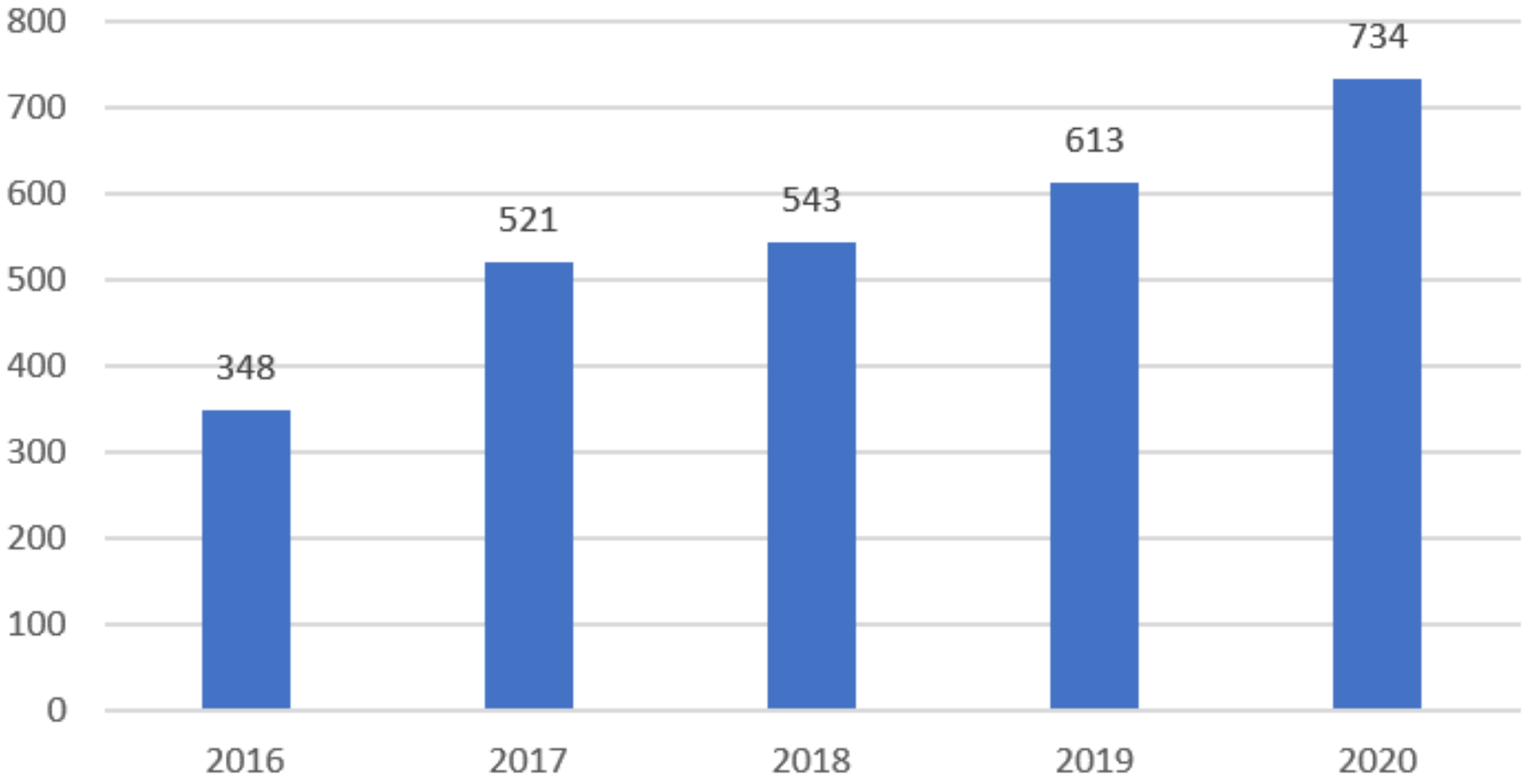
OPQ CC Process

- OGD triages incoming submissions and sends product quality questions to OPQ
- OPQ:
  - Assign review team, develop a written response, and send the response to the inquirer
  - Ensure that CCs and clarification requests are responded to by the goal date

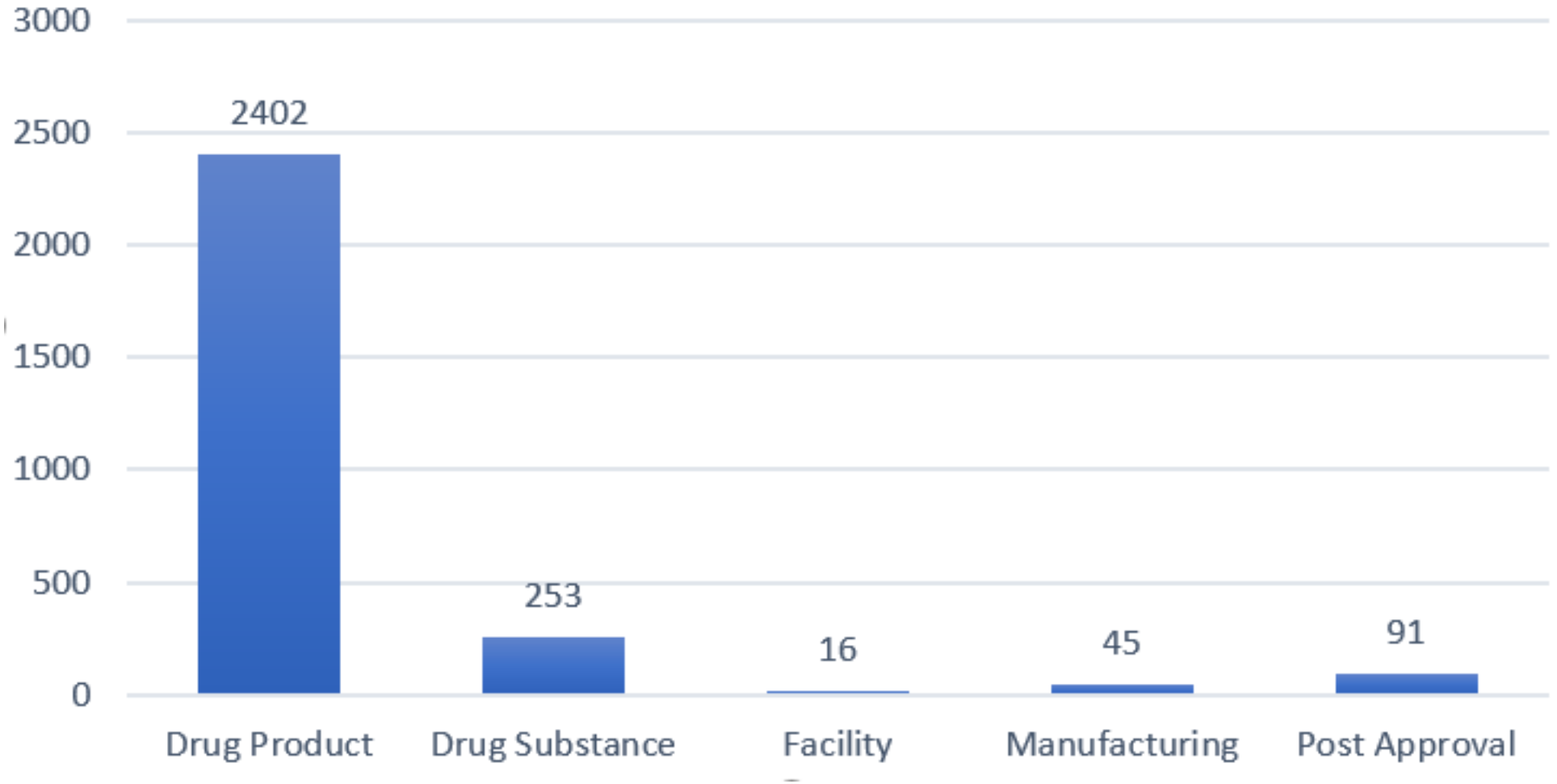
Analysis of CCs

- Actively collect metrics on CC questions
  - –Sort incoming CCs into topic–specific categories
  - –Analyze type(s) of question in each category
- Periodically analyze metrics in order to identify trends
- Implement continual improvements in OPQ's policies and policy documents

OPQ completed controls

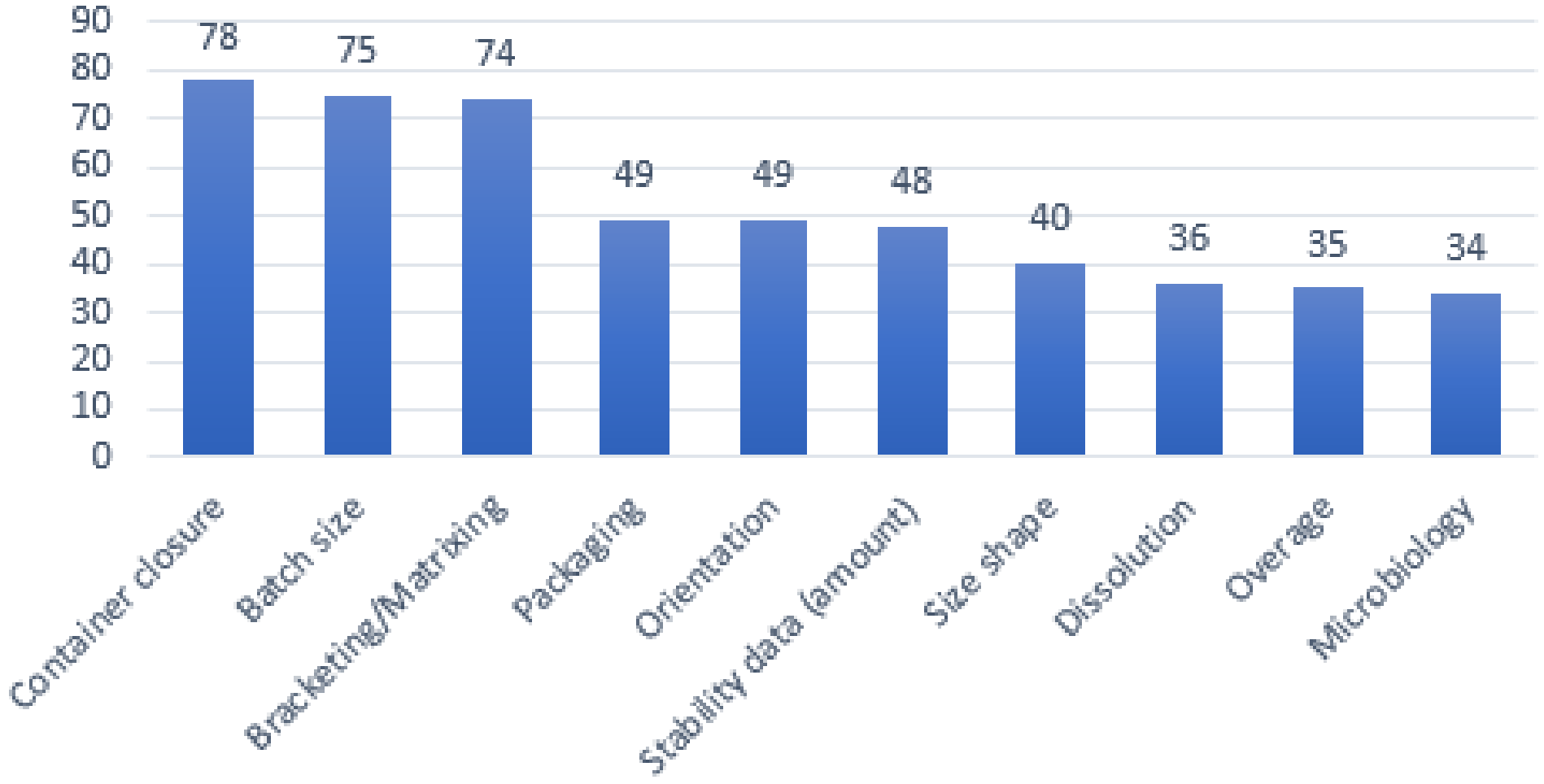


OPQ process for collecting metrics



2016 - 2020

Top 10 drug product subcategories in 2020



Example of CCs - batch size

CCs requesting confirmation on guidance[1] recommendations

- The reference listed drug product has an orphan drug designation
- The submission ANDA batches can have a smaller batch size 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

[1] ANDA Stability Testing of Drug Substances and Products Q&A guidance 2014

Example of CCs - container closure

- Ampoule ↔ vial, vial ↔ prefilled syringe, different vial size(s) from RLD
- Composition changes: Glass vial ↔ plastic vial, bottle ↔ sachet
- In general, container-closure changes are acceptable.
  - For a drug-device combination, analysis of user interface should be performed[1]

[1] 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

Example of CCs – bracketing/matrixing

- Dose similar formulation with comparable stability data from clinical (BE) or development batches
- Different strengths for solid oral dosage forms or different fill volumes for liquids manufactured from common blends is generally acceptable
- Follow the recommendations in ICH Q1D

Issues with CCs in OPQ

Not enough background information

- Not providing dimensions and volume for the RLD and test product for questions about size and shape of tablets/capsules
- Not including the commercial batch size for questions about reduced batch size
- Not providing information on the container/closure and whether the batch is manufactured using a common blend for bracketing different fill volumes

Issues with CCs in OPQ

Lack of clarity

- Question(s) phrased so that it is difficult to understand
- Not providing necessary product information which is needed to answer the question (e.g., Q1/Q2 with the RLD, etc.)

Too much information

- Lengthy and detailed information (complete study reports) not appropriate for a CC

Issues with CCs in OPQ

Too general

- Questions related to product development approach instead of a development specific issue
- Questions related to post approval changes without providing the dosage form

Examples of questions that cannot be answered in a CC

- Acceptability of a specification, in-process control, or study plan
- Acceptability of API overage in final product

General Recommendations

- Separate questions for multiple disciplines (BE and quality)
- Develop concise question(s) with appropriate supporting information
- Resolve Q1/Q2 formulation issues before sending a control to OPQ

General Recommendations

- Request clarification of the controlled correspondence response within 7 days
- Verify information submitted in a control (active RLD in Orange Book)
- Verify that a new guidance hasn’t been published

OPQ CCs Advancements

- Restructure response by indicating whether proposal is acceptable, not acceptable or provisional early in the FDA response
- OPQ responses are cleared by relevant suboffices to ensure response is clear and understandable

How OPQ policy use controls

- Evaluate policy effectiveness and relevance
  - –Actively track the types of CC questions submitted in each subcategory and address them through ongoing policy development
- Implement continual improvements in our policies and policy documents

Analysis

- Analyze the type and number of questions submitted and determine a strategy to address certain questions
    - 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

OPQ CC policy activities

- Revising the Guidance for Industry “ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers”
  - To clarify and update our policies since this guidance is frequently the subject of controls

OPQ CC policy activities

- Guidance Quality and Stability Testing of Drug Substances and Drug Products for NDAs, ANDAs, and BLAs and Associated Labeling Statements for Drug Products
- USP revisions: Due to the increase of CC questions related to endotoxins, OPQ is engaging with USP to discuss an FDA recommendation to remove endotoxin limits from individual USP monographs

OPPQ Activities and Goals

- Goal is to respond to CCs submitted to OPQ so our expectations are transparent
- Strive to ensure that OPQ's policies are clear, transparent, and intuitive to stakeholders.

Challenge Question #1

What type of question can be answered in a controlled correspondence?

1. Adequacy of an impurity clearance approach.
2. Adequacy of a product characterization study.
3. Specific question on generic drug development.
4. All of the above.

Challenge Question #2

What are characteristics of a good controlled correspondence submission?

1. Submitting a concise question(s) that can be answered by a single discipline.
2. Include appropriate supporting information.
3. Not verifying that there were no changes to the RLD in the Orange Book.
4. 1 and 2.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