Common Errors and Opportunities to improve FDA Submissions and Communications.

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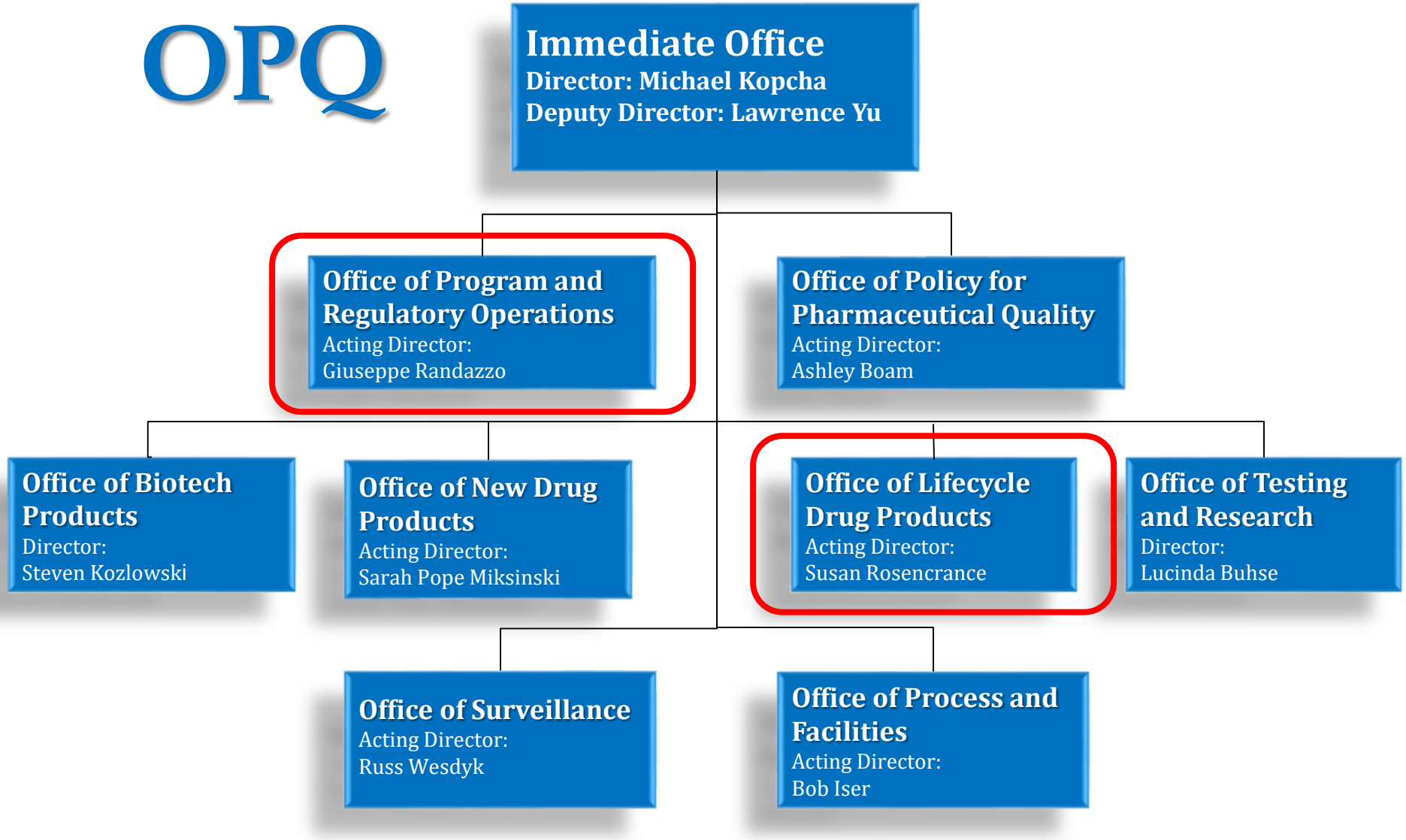
OFFICE OF PHARMACEUTICAL QUALITY

Outline

- OPQ and OPRO Structure
- OPRO contacts
- Information Requests (IR) and Complete Responses (CR)
- Examples of common errors
- Best practices to improve submissions
  - (e.g. 356h, cover letter and facility info)

OPQ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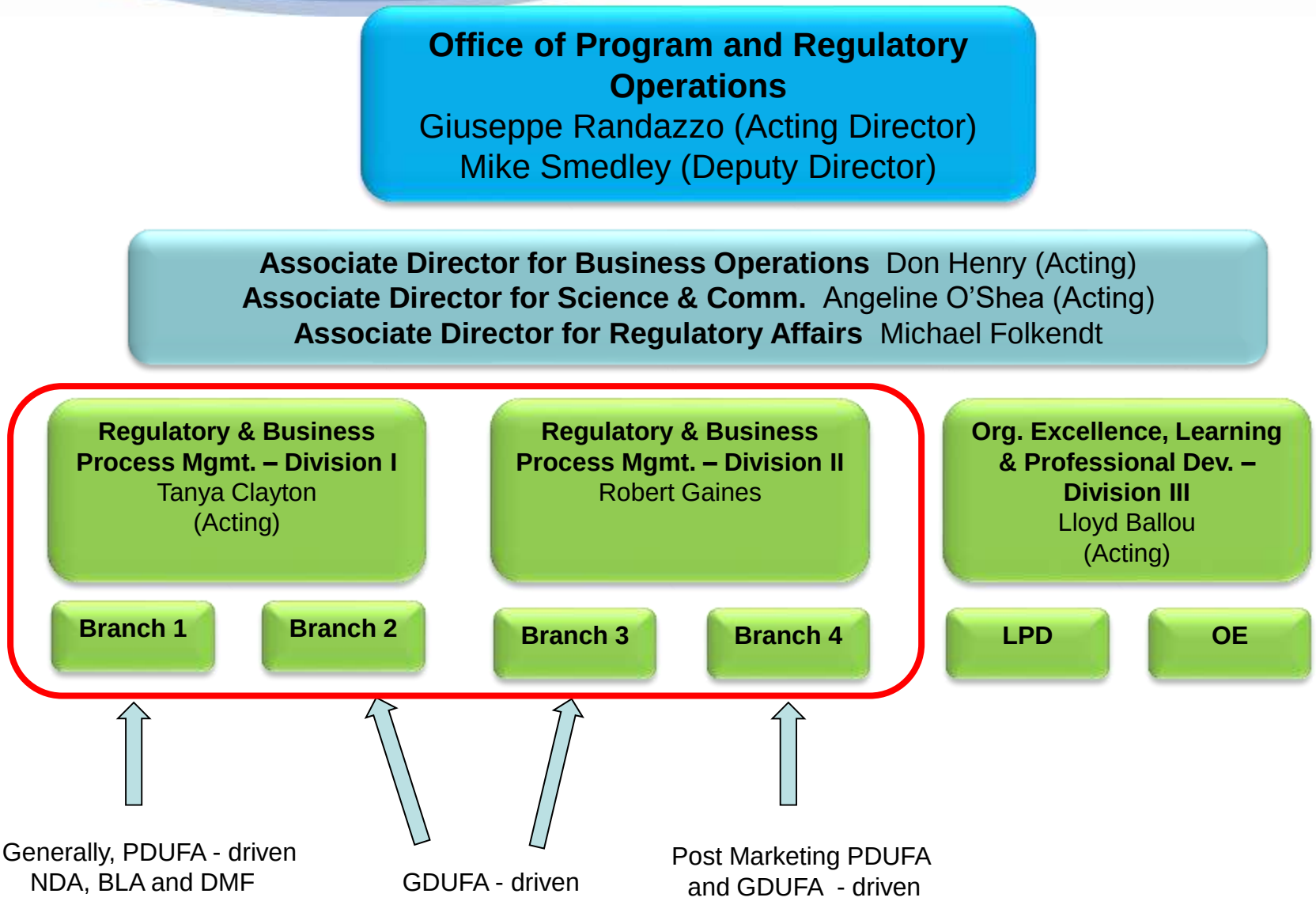
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Branch 4
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OE
Generally, PDUFA - driven NDA, BLA and DMF
GDUFA - driven
Post Marketing PDUFA and GDUFA - driven

Regulatory Business Process Manager (RBPM)

- Centralized POC in OPQ for information regarding the quality portion of ANDAs
- Provides a focal point for communication external to the review team
- Provides expert regulatory knowledge to the OPQ review team
- Facilitates teams to ensure the timely completion of work products
- Works with SMEs to identify and facilitate process improvement opportunities

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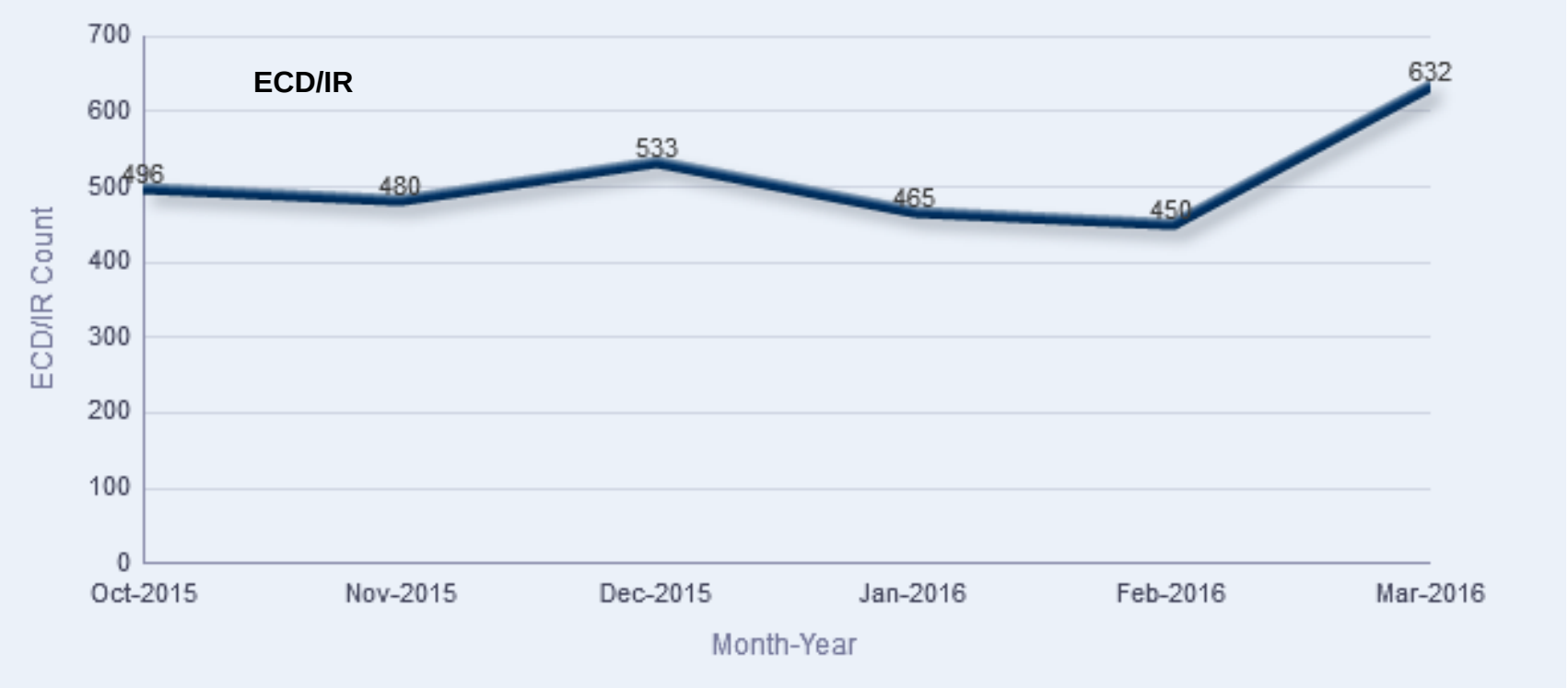
FY16 Trends (ANDA Originals) – ECD/IRs Issued by Month

*excludes filing



	Oct-2015	Nov-2015	Dec-2015	Jan-2016	Feb-2016	Mar-2016
ECD/IR Count	496	480	533	465	450	632

Best practices to facilitate IRs

- Contact the RBPM for all questions related to Quality-only correspondences received (IR).
  - If clarification is needed contact your RBPM.
- Continue to use the OGD/OND RPM as the point of contact for general inquiries.
- Be aware of your required information request response deadline.
- Only respond to IR with requested information.
  - Additional unsolicited information may impact review time and goal dates.
- Respond to the IR requests completely and wholly.
  - If 15 IRs listed, please respond to all 15.

ANDA complete responses (CR) – recent activity

- Complete responses will generally contain all discipline deficiencies

Best practices to facilitate CR responses

- Respond to each deficiency listed in the CR letter
- If clarification is needed for a listed deficiency reach out to your appropriate PM
  - (quality – OPQ RBPM, general questions OGD RPM)
- Like original applications, when responding to the CR, for facilities section (box 29), follow appropriate instructions as described in INSTRUCTIONS FOR FILLING OUT FORM FDA 356h
  - http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf

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Best practices upon submitting submissions to FDA

- Once you submit electronically, continue doing so – do not go back to paper submissions.
- Complete Form FDA 356h accurately and with appropriate details
- Examples of errors:
  - Applicants listed the wrong NDA/ANDA number (box 7)
  - List accurate Supplement number (box 8)
    - Some firms are very thorough in clearly identifying their submission types and tracking their number of tiered amendments.
  - Establishment Information (box 29) – more on this later
- Add appropriate and helpful detail on the cover letter – more on this later

FDA Form 356h reminders

- #6 Provide authorized U.S. agent contact info (if applicable)
- #13 List all strengths, not just the affected strength(s)
- #20 Provide the RLD number
- #29 Include current address and contact info of all establishments
  - For GDUFA Cohort year 3 and moving forward, facilities listed could be subject to a PAI (pre-Approval Inspection) as described in CPGM 7346.832 within the 15 month or appropriate GDUFA goal date for that cohort year
  - Use continuation page as needed
- Correctly code all submissions and amendments to ensure accurate triage and goal dates applied.

Best practices to improve your cover letter

- Give the history of your application
  - Ex: some older applications may have had several amendments and a historical background or timeline of submissions and FDA communications facilitates process
- Helpful supplement best practices:
  - Describe/List all proposed changes within the first 2 paragraphs
  - State the regulatory basis for each change: risk level and filing category – proper risk assessment is critical!
  - Identify potential disciplines to be affected by the change(s)
  - List any other ANDAs that the same or similar change(s) was made to (even not grouped)

Supplement Best Practices adapted from Andrew Langowski's slides @ 2014 GPhA CMC Workshop

Helpful supplement best practices continued

- Rational for proposed change(s) (e.g., OOS, equipment change, unavailable CCS materials, compendial update)
- For change(s) in specifications, provide the current and the proposed specifications for comparison
- Relevant supporting data in the CTD quality module(s): Do not include changes that are not listed in the cover letter!
- A summary pertinent to the proposed change(s) is helpful!
- Assess the risk of each proposed change → highest level decides the filing category (AR, CBE 0/30, PAS)
- Grouping: if the same change is made to several ANDAs AND using the same supporting data package
- Make reference to other ANDAs to which same/similar change(s) was made, if submitted separately

Important points to consider – facilities

- Establishment Information (box 29)
- Provide the name and address of all facilities involved in the manufacturing process (e.g., drug substance and drug product, control and testing labs, primary packaging and labeling)
- Register all manufacturing sites intended for production of the to-be marketed drug product
- If a facility is listed and referenced in the application be prepared for inspection upon submission of a new marketing application.
- Provide the responsibilities of each facility, including activities to support application approval
- If your DMFs cross reference a DS or DP, then the facilities need to be listed on 356h.

Tips for Industry

- Respond completely and timely to IRs and CRs
- If extension is needed for IR responses contact the discipline PM
- Upon submission of IR response, send a courtesy email to discipline PM (OPQ/OPRO = RBPM)
- When in doubt contact the OPQ/OPRO DD and/or BC
- General questions to OPQ = CDER-OPQ-Inquiries CDER-OPQ-Inquiries@fda.hhs.gov

Common Errors and Opportunities to Improve FDA Submissions and Communications (Part II)

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Scope

The discussion is limited to the findings and observations during the **quality assessment** of two main types of submissions throughout the lifecycle of generic drug products:

- Controlled Correspondence
- Original ANDAs

Details related to supplemental ANDAs are discussed in Part I.

Three Types of Submissions

R&D:
Controlled Correspondence

Pre-Marketing:
Abbreviated New Drug Application

Post-Marketing:
Supplemental ANDA

High Quality Submissions are critical to both the Agency and the applicants!

Lifecycle of a generic product: R&D → Discontinuation

SM Rosencrance & GK Wu. Advancing pharmaceutical quality oversight during the lifecycle of generic drug products. J Generic Medicine, 2015, 12(1): 26-33

Controlled Correspondence

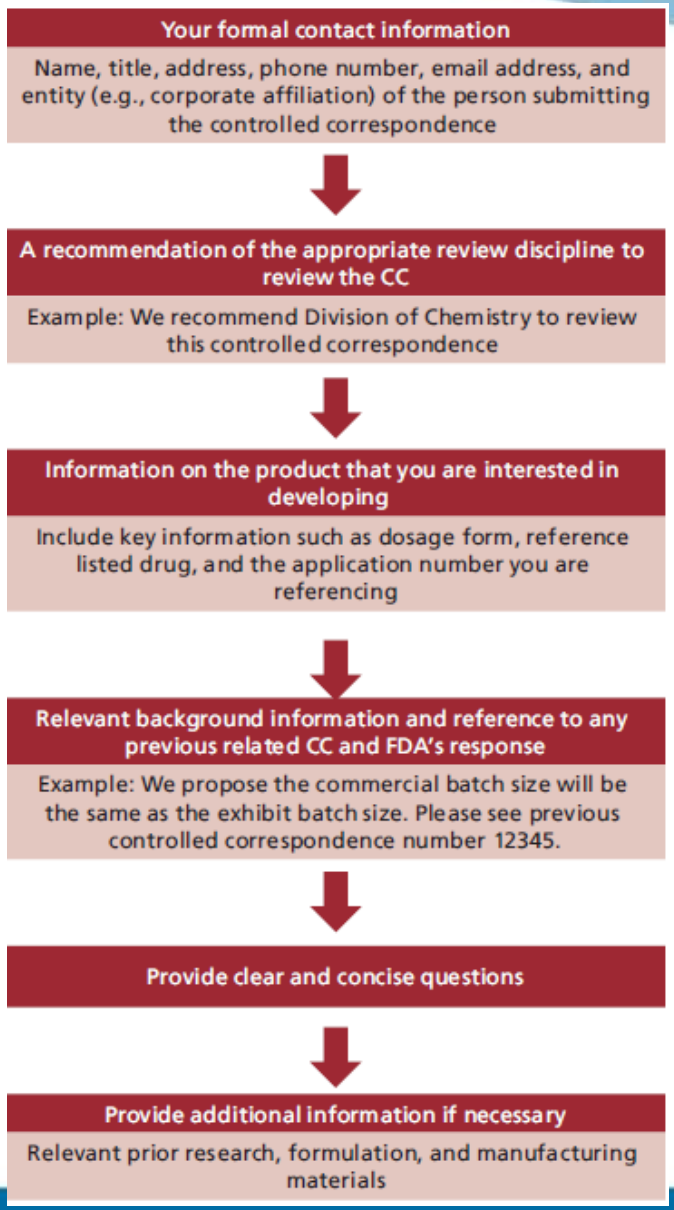
Controlled Correspondence –
Commonly seen chemistry related inquiries

Table I: Common questions and answers in controlled correspondences. PAS is prior approval supplement; CBE is changes being effected; ANDA is abbreviated new drug application; RLD is reference listed drug.

Category	Question	Answer
Stability	We fit the criteria; can we submit a reduced batch size?	Yes, please provide sufficient justification for the batch size in your submission.
Formulation	What if there are two sources for the API?	Equivalency between the sources should be demonstrated in the application. For instance, comparative stability and release data from one batch of the drug product manufactured using the API from alternate source(s) against the primary source are recommended.
Post-approval Changes	Should a (major) change be reported as a PAS, CBE-30, CBE-0, or in the annual report?	Guidance was given on a case-by-case basis.
Overage	Is it acceptable to have an overage of the API?	In general, overage is discouraged and a review issue. In most cases, the firms were directed to include sufficient justification (if overage is used) in their ANDA submission for review. In rare cases, the agency might concur based on the information available.
Formulation	Is it acceptable to submit a tablet or capsule size larger than that of the RLD?	This is not recommended; if it is deemed necessary, sufficient justification should be provided in the ANDA submission for review.

GK Wu et al. Regulatory considerations for controlled correspondence related to generic drug chemistry. Pharm Tech, 2015, s27-32

Controlled Correspondence – Submission |recommendations



Abbreviated New Drug Application (ANDA)

ANDAs –

A Retrospective study for future reference

- Evaluate communications with the industry to identify topic areas and specific review findings
- Goal: To inform the Agency and the Industry for continual improvements
- Scope: 1st cycle CR letters issued in FY2013 & FY2014 (291 CRs)
- Reference: ANDA Submissions: Amendments and ECDs under GDUFA (Appendix A-C)

ANDAs –
Major Deficiencies (9) Defined

Legend	Description
1-Tox	Unqualified impurity level(s) if tox studies are required
1-API source	New source of API
1-Mfg site	New site of FDF manufacture
1-CQA	CQA failure or is not identified/controlled
1-Failed acc/intemed	Stability failure under both accelerated & intermediate conditions → need full-term stability to establish expiration
1-New packaging	New packaging system needed
1-Excipient IIG/Clinical	Unacceptable excipient due to exceeding IIG limit or clinical concerns
1-New analytical	New analytical method(s) needed →not stability indicating or suitable
1-Biobatch	Biobatch is not representative of the commercial product

ANDA –
Minor Deficiencies (14) Defined

Legend	Description
2-Overage	Need to identify/justify overage
2-API impurity	Unidentified/unacceptable spec for API-related impurities/chiral molecules
2-API polymorphism	API polymorphism is inadequately justified/controlled
2-API residual solvent	Unacceptable spec for residual solvents in the DS
2-API particle size	Uncontrolled/unacceptable spec for particle size
2-API other CQA	Any other uncontrolled aspect related to potential DP CQA failure
2-Excipient control	Lack of excipient control affecting DP CQA

ANDAs –
Minor Deficiencies (14) Defined (cont'd)

Legend	Description
2-DP impurity	Unidentified/unacceptable spec for impurities/residual solvents
2-DP attribute	Unacceptable range for CQA or other relevant QA in DP release/stability spec
2-Method validation	Inadequate method validation and request revalidation
2-In-process control	Insufficient in-process control for CQA or related process parameters
2-Tablet score	Improper tablet score testing
2-Stability protocol	Unacceptable stability testing
2-Questionable trends	Unexpected trends observed during stability studies

ANDAs –
Information Requests (23) Defined

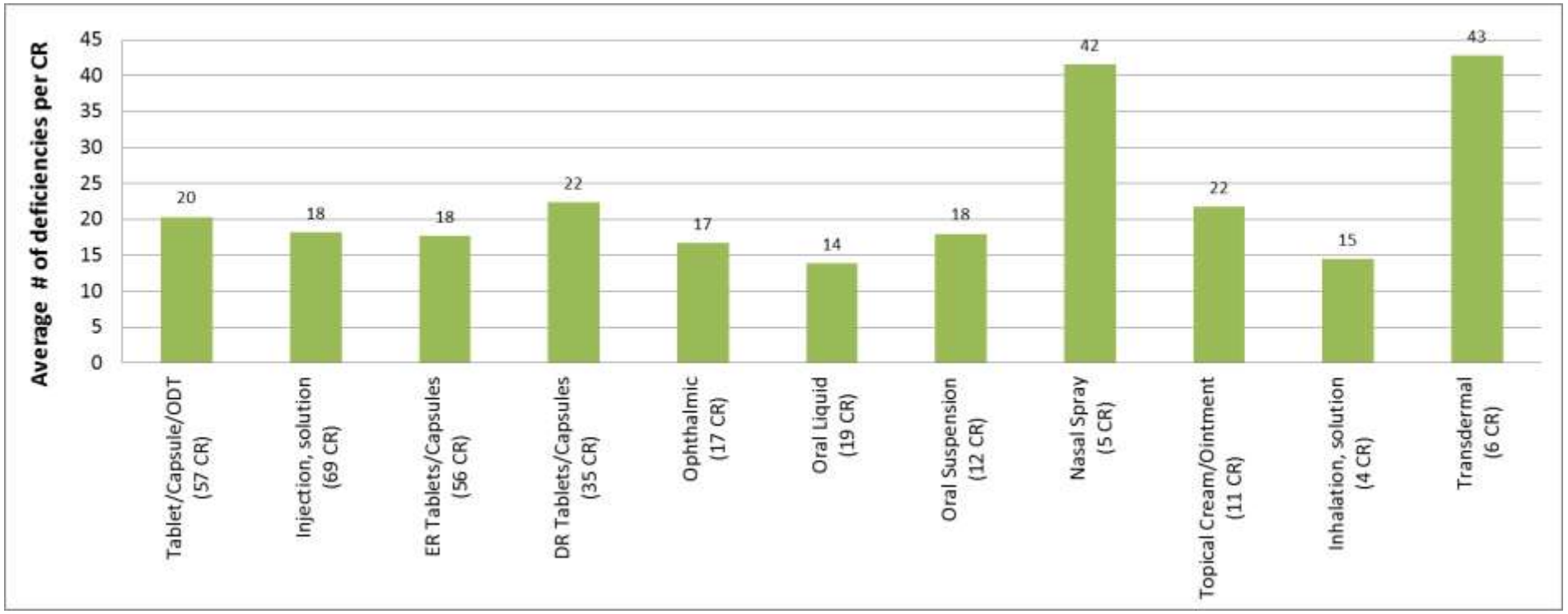
Legend	Description
3-QC of application	QC issues in application (e.g., wrong DS, batch records)
3-inconsistencies	Inconsistencies between different sections of the application
3-Missing documentation	Missing easily retrievable docs (e.g., CoA, cGMP, etc.)
3-QOS	QOS is inconsistent with data in Module 3, or presents data not found in Module 3
3-DMF	Notice of DMF inadequacy or note to update DS spec based on DMF holder's spec
3-API IR	IR for API physicochemical properties (e.g., pH, solubility)related to PD
3-Retest date	Insufficient/missing retest date information
3-Composition info	DP Composition including function of excipients, grade, standard
3-PD IR	Additional info requested regarding PD related to potential CQA failure
3-Excipient IR	Additional info requested, including impurities and residual solvent
3-Reference Std	Missing info for reference standards
3-Mfg process	Manufacturing process related to potential CQA failure

ANDAs –
Information Requests (23) Defined (cont'd)

Legend	Description
3-Reconciliation	Insufficient or missing justification of low reconciliation
3-Hold time	Missing or IR regarding hold time
3-CC test	Inadequate CCS testing per USP 661/671, USP 660/1660, leachable/extractable
3-CC IR	Additional info regarding CCS (e.g., shipping study)
3-Method validation	Addition info or clarification regarding method validation
3-Method verification	Missing or inadequate method verification
3-Identity test request	Request for further identity testing
3-Update to DBE recommendations	Note to update spec based on recommendations from DBE
3-Compendial updates	Updates to compendia needed
3-PAC	Request for post-approval commitment
3-Data request	Miscellaneous: missing data that the applicant is like to have (e.g., batch records, stability data updates)

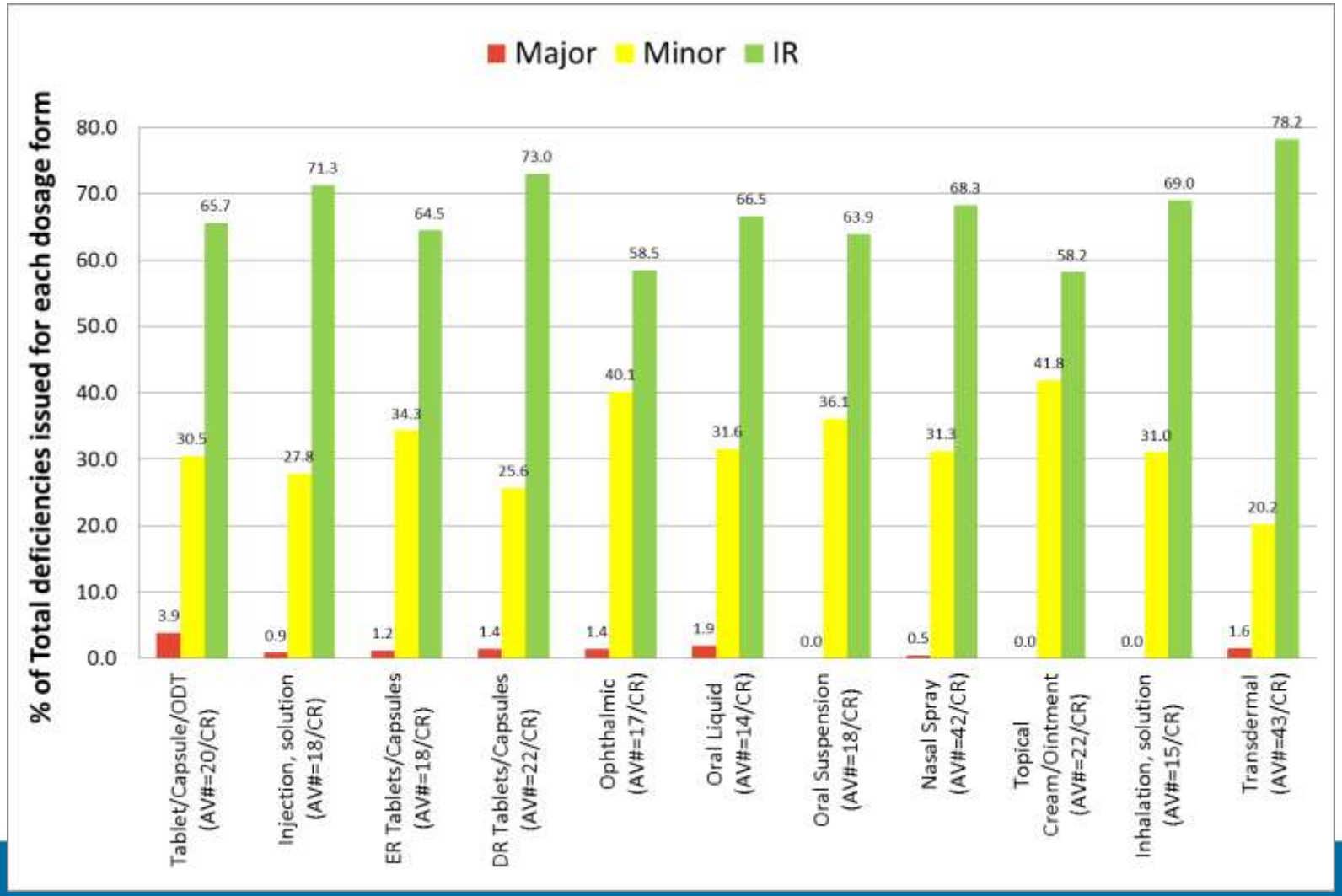
ANDAs

Up to 40 Chemistry Deficiencies/IRs per CR!

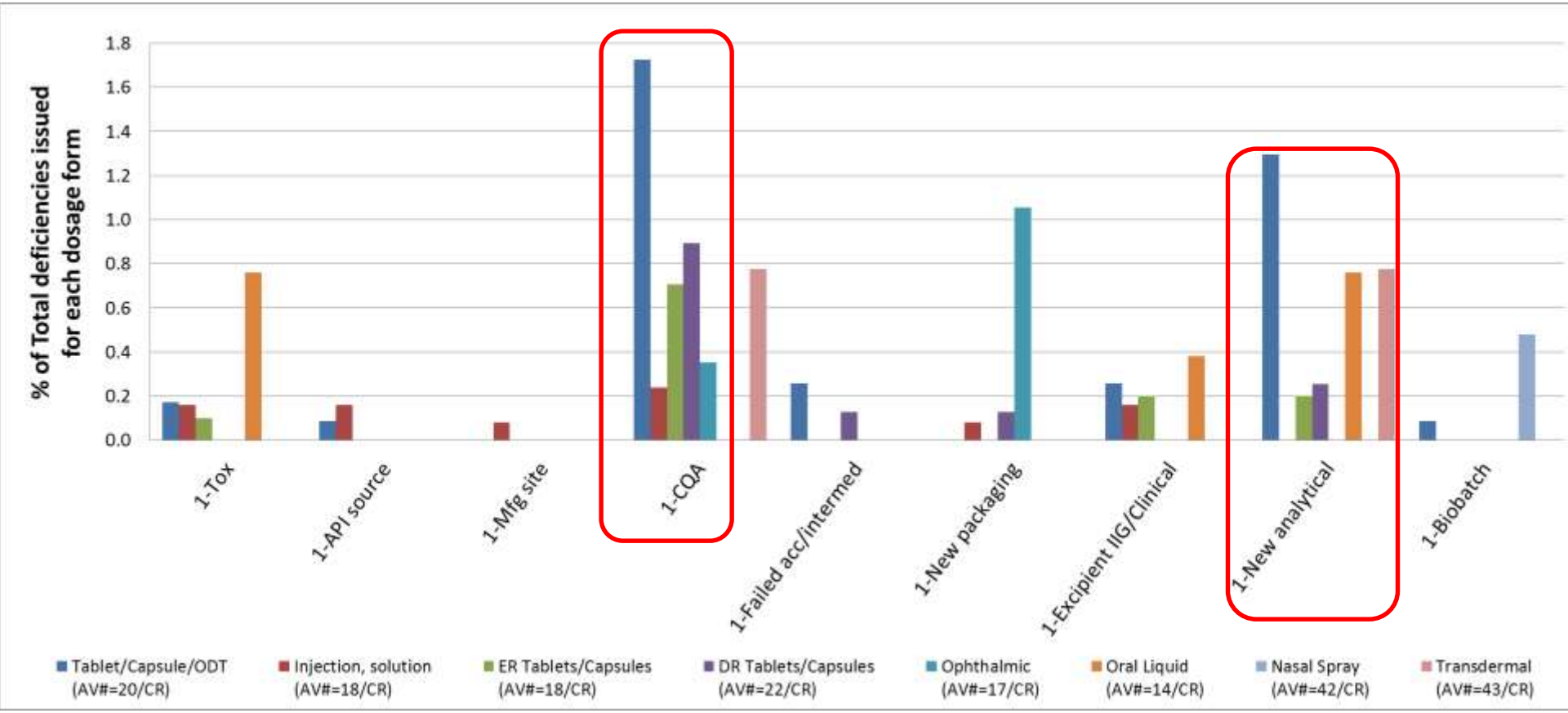


ANDAs

~70% Information Requests → Poor submission quality

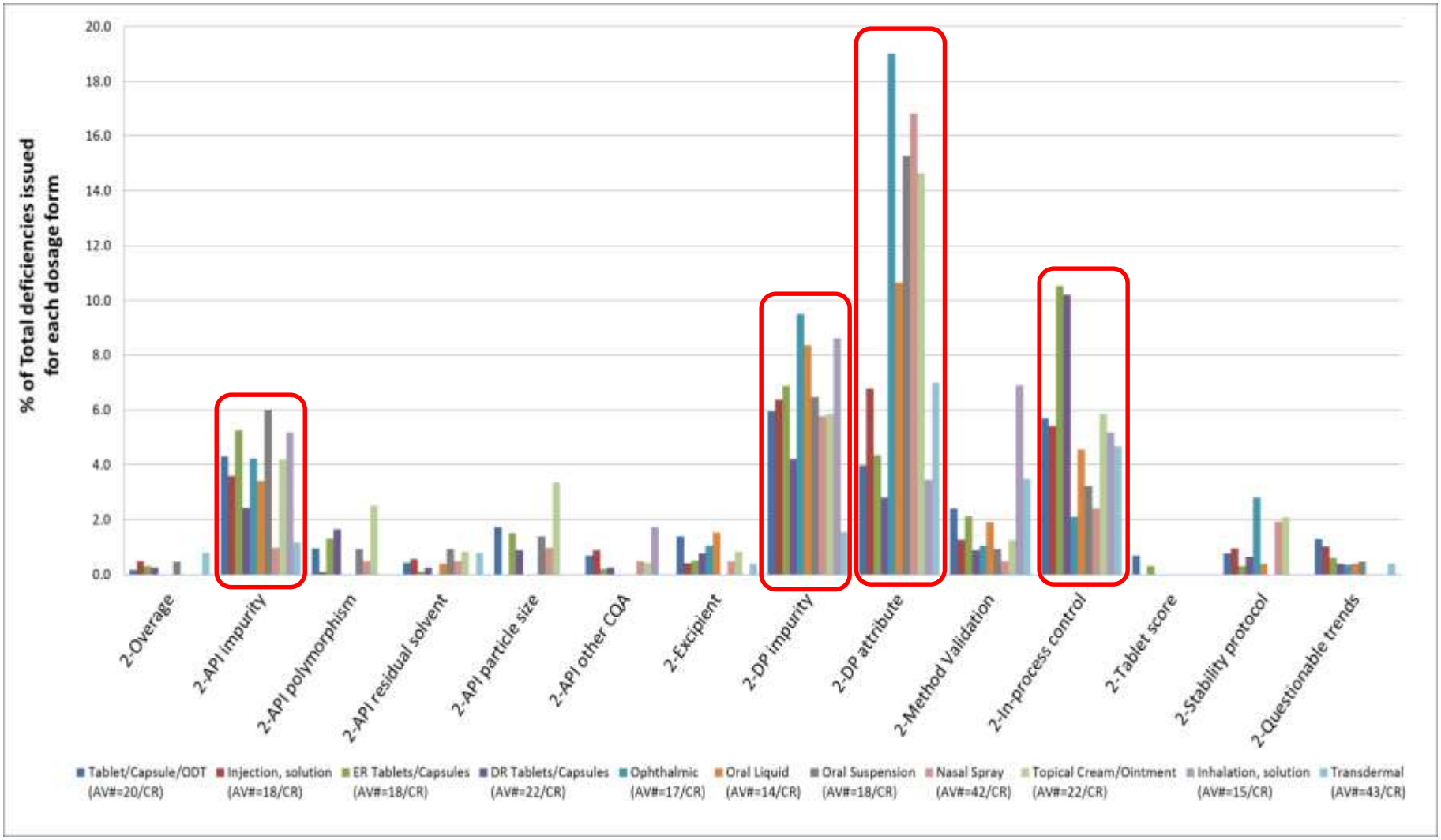


ANDAs–
Distribution of Major Deficiencies

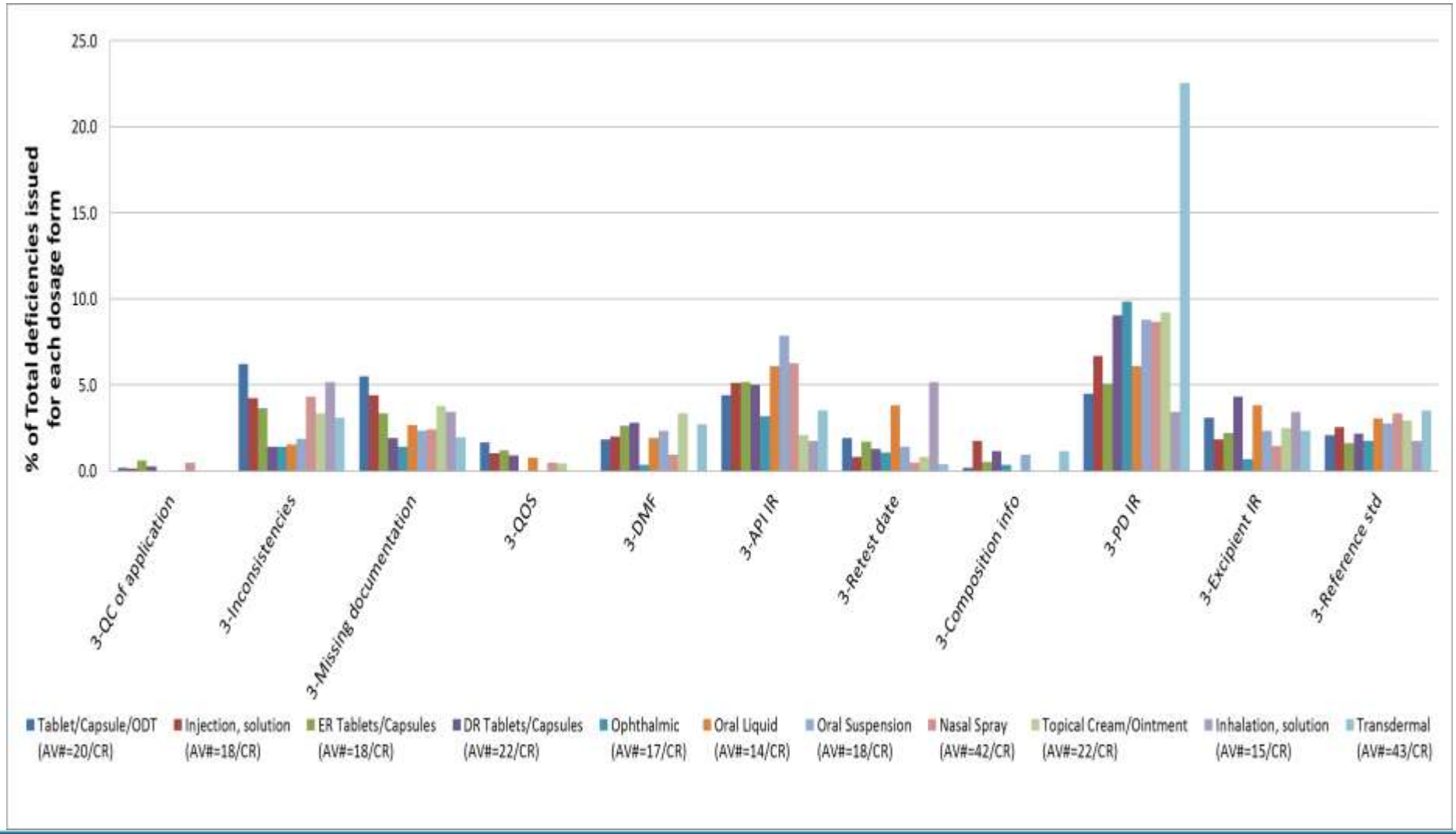


ANDA –

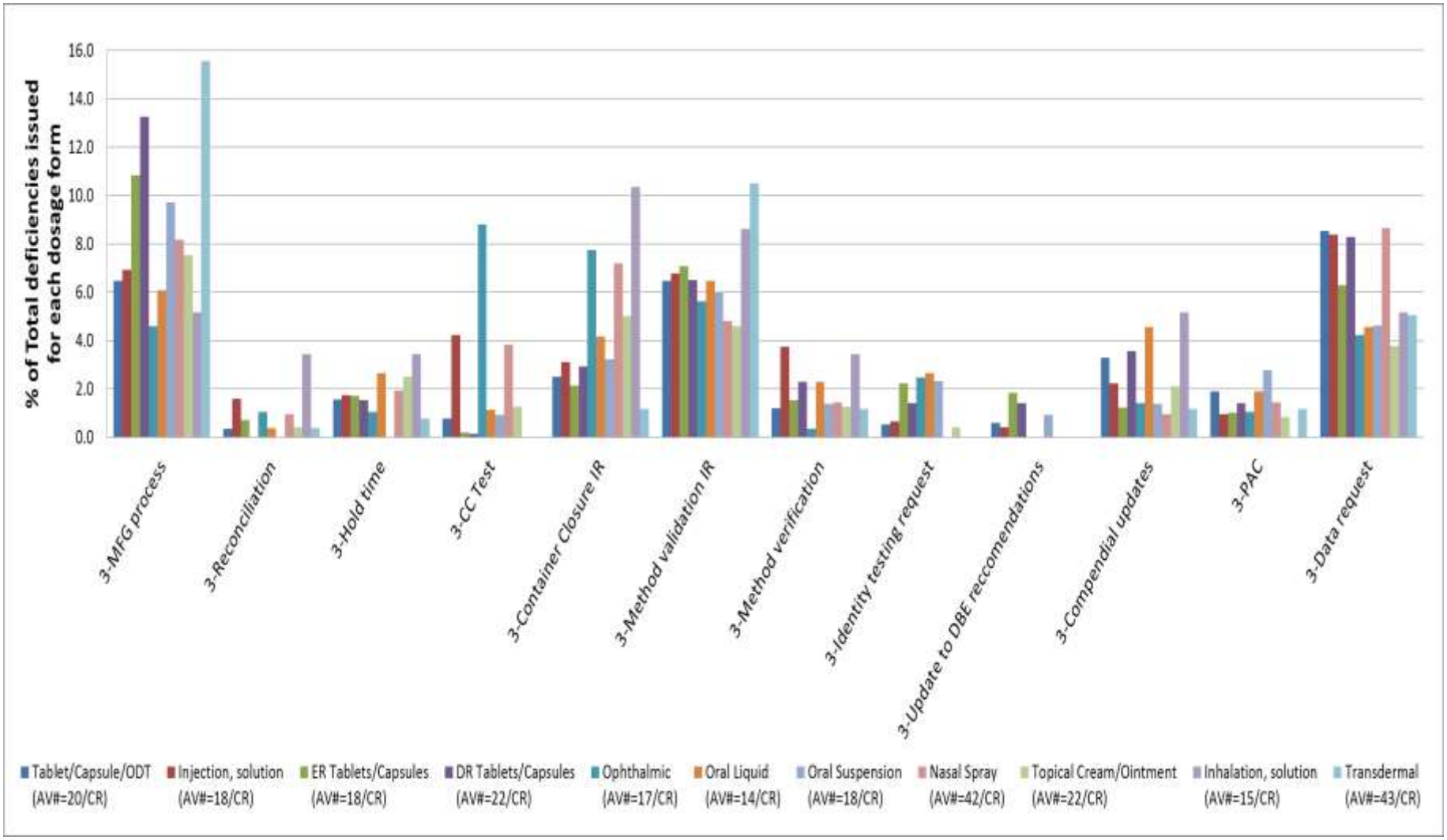
Distribution of Minor Deficiencies



ANDA –
Distribution of Information Requests



ANDAs –
Distribution of Information Requests (cont'd)



ANDA –
Summary

- Certain dosage forms are more challenging.
- Major/Minor deficiencies: CQA, analytical methods, DP impurity, PD, and process control.
- Opportunity: Mainly IR → Improving submission quality can eliminate all!
- Continuous improvements needed for both to strive for the common goal: safe, quality and affordable generics for the public.

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genericdrugs@fda.hhs.gov; CDER-OPQ-Inquiries@fda.hhs.gov

Thank you!

Questions?

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surveymonkey.com/r/GDF-D2S6