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FDA Conduct of Clinical Investigators Inspections

Ruark Lanham, MSODL,
Supervisory Investigator
US Food & Drug Administration
San Jose Resident Post
San Francisco District

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Outline

- **FDA's Bioresearch Monitoring Program, what is it?**
- **Historical Perspective of Clinical Trails**
- **Clinical Investigator Program / Responsibilities**
- **How FDA Prepares for Clinical Investigator Inspection**
- **What to expect during and after an FDA Inspection.**
- **Top 10 Bioresearch Monitoring Observations Used in Turbo EIR and as seen during recent FDA Inspections at Clinical Sites.**

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Historical Perspective of FDA'S Bioresearch Monitoring (BIMO) Program

- First BIMO Inspections were done in the 1960s
- The Bioresearch Monitoring (BIMO) Program was formally established in 1977
- The agency has been performing Inspections of Institutional Review Boards (IRBs) since 1980
- First International BIMO inspections were done in 1980

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FDA's Bioresearch Monitoring (BIMO) Program

- FDA's Bioresearch Monitoring Program:
  - A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

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FDA's Bioresearch Monitoring (BIMO) Program Objectives

1. Protect the rights, safety, and welfare of subjects in FDA-regulated trials
2. Determine the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and
3. Assess compliance with FDA's regulations governing the conduct of clinical trials, including those for informed consent and ethical review

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FDA's Bioresearch Monitoring (BIMO) Program

- Good Clinical Practices (GCP)
  - Institutional Review Boards (IRBs)
  - Clinical Investigators (CIs)
  - Sponsor-Monitors, CROs
- Good Laboratory Practices (GLP)

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FDA's Authority to Inspect

- Where does FDA's authority to inspect comes from ?
- What Code of Federal Regulations (CFRs) are applicable to BIMO ?

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BIMO REGULATIONS
(Code of Federal Regulations)

- 21 CFR 314: New Drug Applications (NDA)
- 21 CFR 312: Investigational New Drug Exemption (IND)
- 21 CFR 814: Pre-Market Approval Applications (PMA)
- 21 CFR 812: Investigational Device Exemption (IDE)
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 56: Institutional Review Boards
- 21 CFR 58: Good Laboratory Practice for Non-Clinical Laboratory Studies

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Clinical Investigator Program / Responsibilities

- Clinical Investigation
- What is a Clinical Investigator
- Clinical Investigator Program / Responsibilities

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Clinical Investigation

- Any experiment in which a drug is administered to human subjects. An experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. (21 CFR 312.3)

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CLINICAL INVESTIGATOR PROGRAM

- Provides for study specific inspections and audits of physicians, veterinarians, and other investigators conducting clinical trials of new human and veterinary drugs, medical devices, biologics, etc.

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The Clinical Investigator

- An individual who actually conducts a study (i.e. under whose immediate direction the drug is dispensed to a subject.) In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team

  [21 CFR 312.3]

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Investigator Responsibilities

- General responsibilities (312.60)
- Control of investigational drug (312.61)
- Record keeping and retention (312.62)
  - An investigator is responsible for:
    - Maintaining adequate records of the disposition of the drug
    - Accurate case histories that record all observations, and
    - Other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation
  - An investigator is required to maintain investigation records for:
    - 2 years following the data a marketing application is approved for the drug for the indication for which it is being investigated
    - 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not approved for such indication

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Investigator Responsibilities (cont.)

- Investigator reports (312.64)
  - Progress reports
  - Safety reports
    - Promptly report any adverse event that may reasonably be regarded as caused by, or probably caused by, the drug (err on the side of reporting)
    - Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
  - Final report
  - Financial disclosure

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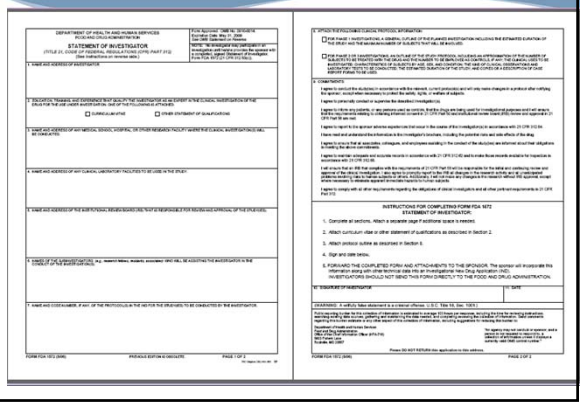
Form FDA 1572



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Commitments on Form 1572

- Personally conduct or supervise investigation
- Follow protocol
- Ensure all persons assisting in study are informed of obligations
- Inform subjects that drugs are being used for investigational purposes
- Ensure informed consent (21 CFR Part 50) and IRB review, approval and reporting (21 CFR Part 56)
- Report to sponsor adverse events (21 CFR 312.64)
- Maintain adequate and accurate records and make them available for inspection in accordance with 21 CFR 312.68
- Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards
- Comply with other requirements in 21 CFR 312

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Investigator Disqualification

- Disqualification of clinical investigators [21 CFR 312.70]
  - Repeated and deliberate failure to comply with the requirements
  - FDA provides notice of matter to investigator and provides opportunity to explain (informal hearing)
  - Opportunity for formal hearing
  - May result in ineligibility to receive investigational drugs

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HOW WE AT THE FDA PREPARE FOR AN INSPECTION

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Inspectional Assignments

- The assignment is sent to the District from the Center.
- Usually the FDA Investigator will call to pre-announce the inspection (no more than 5 days notice).
- PDUFA and MDUFMA mandate specific deadlines for agency reviews of NDAs and PMAs.

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Inspectional Assignments (cont'ed)

- CBER/Office of Compliance and Biologics Quality/Division of Inspections and Surveillance
- CDER/Division of Scientific Investigations
  - Good Clinical Practices Branches 1 and 2
  - Human Subject Protection Team
  - GLP/Bioequivalence Branch
- CDRH/Office of Compliance/Division of Bioresearch Monitoring
- CFSAN/Office of Food Additive Safety
- CVM/Bioresearch Monitoring Team

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GCP Inspection: Discrete Steps

- Planning and Preparation
- Conducting the Inspection
- Reporting and Documentation

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Preparing for the GCP Inspection- Manuals

- Compliance Program Guidance Manuals
  - 7348.811 (Clinical Investigator and Sponsor-Investigator)
  - 7348.810 (Sponsor, Contract Research Organizations, and Monitors)
  - 7348.809 (Institutional Review Boards)
  - 7348.001 (In vivo Bioequivalence)
- http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm

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Preparing for the GCP Inspection- Laws

- Code of Federal Regulations (CFR) Title 21
  - Part 50, Protection of Human Subjects
  - Part 56, Institutional Review Boards
  - Part 312, Investigational New Drug Application (IND)
  - Part 314, New Drug Application (NDA)
- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

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Preparing for the Inspection - continued

- Investigations Operations Manual (IOM)
  - Collection and development of evidence
  - Writing the establishment inspection reports (EIR)

  http://www.fda.gov/ICECI/Inspections/IOM/default.htm
- Review previous EIR(s)
  - What problems/issues were noted?
  - Was a Form FDA-483 issued?
  - Were corrections promised?
  - What was the final Classification?

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Preparing for the Inspection - continued

- Reads and becomes familiar with the entire study protocol and amendments
  - Identifies key elements of the study protocol
- Reviews background materials
- Develops audit plan

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Developing an Audit Plan

- Identifies specific concerns outlined in the Inspection Assignment
- Identifies specific records that will be examined to verify significant endpoint data and targeted issues
  - What will original source documents be audited against (compared to), e.g. CRFs, e-CRFs, data listings, summary reports?

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Site Records for Review

- Case report forms (CRFs) or electronic CRFs (e-CRFs)
- Informed consent forms (ICFs)
- Original patient medical records (i.e., hospital records, nursing notes, clinic notes, etc.
- Original laboratory reports (blood, urine, ECGs, x-rays, etc.) and consultation reports (radiology, cardiology, etc.)
- Original subjects' study diaries
- Correspondence records
- "Regulatory " file

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HOW TO PREPARE FOR AN FDA INSPECTION

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HOW TO PREPARE FOR AN FDA INSPECTION

When the FDA Investigator calls:

- Be sure you understand the specific study that will be inspected.
- The FDA Investigator will tell you what records will be needed.
- The FDA Investigator will tell you how much time will be needed with the PI and/or other study staff.

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HOW TO PREPARE FOR AN FDA INSPECTION

- Be sure the PI will be available.
- Reserve a place for the FDA Investigator to work.
- Get the name and phone number of the FDA Investigator.
- Provide specific and clear directions to your site.

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HOW TO PREPARE FOR AN FDA INSPECTION

- Have ALL records related to the study available, including:
  - Regulatory records – IRB approvals, protocols, investigator brochure, correspondence.
  - CRFs, monitoring reports.
  - Source records – clinic charts, hospital records, x-rays, lab reports, subjects diaries.
  - Test article accountability records.

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WHAT HAPPENS DURING AN FDA BIMO INSPECTION?

The FDA Investigator:

- Shows FDA credentials to the most responsible person;
- Issues a Form FDA 482 “Notice of Inspection” to the most responsible person;
  - Explains why FDA is there and what records and documents will be reviewed.

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WHAT HAPPENS DURING AN FDA BIMO INSPECTION?

- The FDA Investigator will ask some general questions of the study staff and the Principal Investigator.
- The bulk of the inspection will involve the FDA Investigator reviewing records.
- Photocopies of some records will be requested.
- Federal regulations allow the FDA to inspect and copy ALL records relating to a clinical investigation.

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WHAT HAPPENS DURING AN FDA BIMO INSPECTION?

- Any deficiencies or observations found during the inspection will be discussed during the inspection and at the close-out.
- The PI or Study Coordinator should be available to answer questions and to provide records during the inspection.

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WHAT HAPPENS DURING AN FDA BIMO INSPECTION?

- The FDA Investigator will schedule a close-out meeting with the most responsible person.
- The site inspected may receive a Form FDA-483, ”Inspectional Observations”.
- Observations may also be presented orally.
- The site may discuss all observations and issues with the FDA Investigator at the time of the close-out.

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Form FDA-483
"Inspectional Observations"

- Significant deviations from Regulations.
- Observations are based only on the FDA Investigator's review of available records and information.

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AFTER AN FDA BIMO INSPECTION

- The Principal Investigator should respond to the 483 observations in writing.
- The study site should take corrective actions for any deficiencies, if possible.
- Provide documentation of the corrective and preventive actions with the response.

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AFTER AN FDA BIMO INSPECTION

- The FDA Investigator will write an Establishment Inspection Report (EIR) that contains all the information collected during the inspection, including attachments and exhibits.
- This report is forwarded to the Center that issued the assignment for review and final classification.

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AFTER AN FDA BIMO INSPECTION

- The assigning Center will classify the inspection as:
  - NAI = no action indicated
  - VAI = voluntary action indicated
  - OAI = official action indicated

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AFTER AN FDA BIMO INSPECTION

- The inspected site will receive a copy of the EIR after the inspection is classified.
- The assigning Center will send a follow-up letter to the PI.

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AFTER AN FDA BIMO INSPECTION

- Possible consequences:
  - Untitled Letters
  - Warning Letters
  - Notice of Disqualification Proceeding and Opportunity to Explain (NIDPOE)
  - Rejection of the study
  - Prosecution

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HELPFUL HINTS:

- Keep files organized at all times.
- Keep ALL correspondence – sponsor, IRB, monitors, study subjects.
  - letters, faxes, e-mails, memos, phone contacts.
- Keep all test article accountability records:
  - Shipping receipts, enrollment logs, dispensing logs.

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HELPFUL HINTS:

- Know your IRB's requirements.
- Know the sponsor's Adverse Event reporting requirements.
- Know the protocol:
  - Inclusion/exclusion criteria, study windows, study procedures.
- Know each study staff member's roles and responsibilities – the PI is ultimately responsible.

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HELPFUL HINTS:

- Have written procedures:
  - SOPs, Quality Policy, training procedures, job descriptions.
- Have a Corrective and Preventive Action Plan.
- Memos to File????

- DOCUMENT!!!

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FOR MORE INFORMATION

- www.fda.gov
- www.fda.gov/cder/
- www.fda.gov/cber/
- www.fda.gov/cdrh/
- www.fda.gov/fdac/

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Bioresearch Monitoring (BIMO) Metrics – FY'11

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Bioresearch Monitoring (BIMO) Metrics – FY'11

BIMO Inspections Completed FY 2011

Center	CI	IRB	Spon/Mon	GLP	Total
CBER	62	22	12	3	99
CDER*	315	103	44	27	489
CDRH	173	62	78	8	321
CFSAN**	0	0	0	0	0
CVM	26	na	6	7	39
All Centers	576	187	140	45	948

* 3 **IRB = RDRC;** + 194 **BEQ** inspections (CDER specific)
⇨ total = **1142**
** **CFSAN's BIMO Program is under reorganization**

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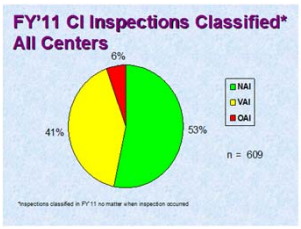
Bioresearch Monitoring (BIMO) Metrics – FY'11



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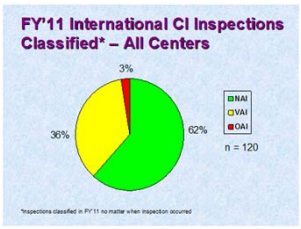
Bioresearch Monitoring (BIMO) Metrics – FY'11



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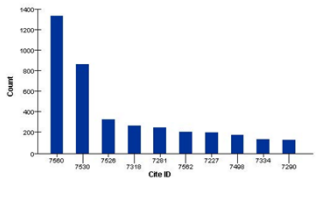
Top 10 Bioresearch monitoring Observations Used in Turbo EIR

As of 03/27/2012



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Top 10 Bioresearch monitoring Observations Used in Turbo EIR
As of 03/27/2012

Cite ID	Count	Reference No.	Citation Text
7560	1349	21 CFR 312.60	An investigation was not conducted in accordance with the [signed statement of investigator] [investigational plan]. Specifically***
7530	876	21 CFR 312.62(b)	Failure to prepare or maintain [adequate] [accurate] case histories with respect to [observations and data pertinent to the investigation] [informed consent]. Specifically, ***

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Top 10 Bioresearch monitoring Observations Used in Turbo EIR
As of 03/27/2012

Cite ID	Count	Reference No.	Citation Text
7526	335	21 CFR 312.62(a)	Investigational drug disposition records are not adequate with respect to [dates] [quantity] [use by subjects]. Specifically, ***
7318	272	21 CFR 56.115(a)(2)	Minutes of IRB meetings have not been [prepared] [maintained] in sufficient detail to show [attendance at the meetings] [actions taken by the IRB] [the vote on actions, including the number of members voting for, against and abstaining] [the basis for requiring changes in or disapproving research] [a written summary of the discussion of controverted issues and their resolution]. Specifically, ***

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Top 10 Bioresearch monitoring Observations Used in Turbo EIR
As of 03/27/2012

Cite ID	Count	Reference No.	Citation Text
7281	252	21 CFR 56.108(a)(1)	The IRB [has no] [did not follow its] written procedure for conducting its [initial] [continuing] review of research. Specifically, ***
7562	212	21 CFR 312.60	– Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to [drug administration] [conducting study - related tests] . Specifically***

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Top 10 Bioresearch monitoring Observations Used in Turbo EIR
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Cite ID	Count	Reference No.	Citation Text
7227	206	21 CFR 50.27(a)	Informed consent was not properly documented in that the written informed consent used in the study [was not approved by the IRB] [was not signed by the subject or the subject's legally authorized representative at the time of consent][was not dated by the subject or the subject's legally authorized representative at the time of consent]. Specifically, ***

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Top 10 Bioresearch monitoring Observations Used in Turbo EIR
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Cite ID	Count	Reference No.	Citation Text
7498	184	21 CFR 312.66	Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others. Specifically, ***
7334	142	21 CFR 56.115(a)(5)	A list of IRB members has not been [prepared] [maintained], identifying members by [name] [earned degrees] [representative capacity] [indications of experience sufficient to describe each member's chief anticipated contribution to IRB deliberations] [any employment or other relationship between each member and the institution]. Specifically, ***

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Top 10 Bioresearch monitoring Observations Used in Turbo EIR
As of 03/27/2012

Cite ID	Count	Reference No.	Citation Text
7290	131	21 CFR 56.108(c)	For other than expedited reviews, the IRB does not always review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. Specifically, ***

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COMMON BIMO OBSERVATIONS for CLINICAL INVESTIGATORS

- Protocol Deviations/Violations.
- Failure to report Adverse Events.
- Poor record-keeping.
- Informed Consent issues.
- IRB issues.
- Test Article Accountability.
- Failure of the PI to adequately supervise the study.

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Most Common CI Deficiencies

- Failure to follow the investigational plan
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate subject protection – including informed consent issues

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Common International Deficiencies

- Similar to domestic inspectional findings
- CI inspections
  - Protocol deviations
  - Inadequate investigational product accountability
  - Inadequate subject protections

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Final Thoughts

- Clinical investigators play a critical role in ensuring high quality studies
- Good care of patients is not the same as Good Clinical Practices (GCP) in research
  - It is important to have a clear understanding of responsibilities under FDA regulations
- At stake is public confidence and participation in the clinical trials and ultimately the availability of safe and effective products

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Thank You

Ruark Lanham, MSODL
Supervisory Investigator
US Food & Drug Administration
San Jose Residence Post
96 North Third Street, Suite 325
San Jose, CA. 95112
(408)291-7548 ext 115

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