U.S. FOOD & DRUG ADMINISTRATION

Breakout Session I: Biocompatibility (Day 1)

ASCA Public Workshop

May 22-23, 2018

Workshop: Biocompatibility Breakout Organizing Committee

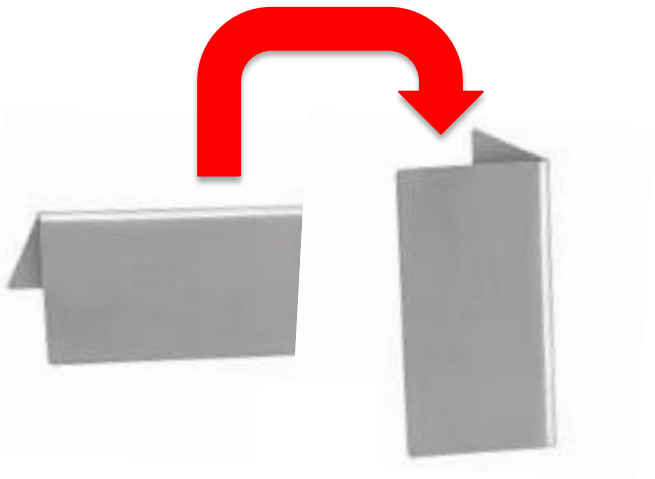
- Scott Colburn, Director, CDRH Standards Program
- Molly Ghosh, PhD, DABT, Deputy Director (Acting), Division of Biology, Chemistry and Material Science (DBCMS), OSEL/CDRH (molly.ghosh@fda.hhs.gov)*
- Jennifer Goode, BS, Biocompatibility Program Advisor, Office of Device Evaluation, CDRH (jennifer.goode@fda.hhs.gov)*
- Alan Hood, PhD, Toxicologist, DBCM/OSEL/CDRH
- Shuliang Li, PhD, Senior Standards Advisor, CDRH Standards and Conformity Assessment Program (standards@fda.hhs.gov)*
- Amy Phelps, PhD, Conformity Assessment, Standards Coordination Office, NIST
- Jianchao Zeng, PhD, Senior Standards Advisor, CDRH Standards and Conformity Assessment Program

*moderators

Breakout Session Logistics:

Ground Rules – Day 1:

- Moderated discussion
  - Audience participation encouraged
  - Strict time limits for discussions



Ground Rules – Day 2 Roundtable Discussion:

- Tent cards upright to comment
- State your name each time before you comment

Other:

- Box lunches, snacks and drinks are available for purchase in the lobby
- Visitors can only access Building 31 (workshop site)
- Webcast link: https://collaboration.fda.gov/ascabreakout/
  - Please use the "chat" function if you'd like to make a comment or ask a question during the breakout sessions; moderators will be monitoring these "chat" comments and will share them as time allows

Disclaimer

Information in these slides are intended for discussion purposes and to inform stakeholders of FDA's current thinking regarding biocompatibility testing under the ASCA Pilot. The purpose of this information is to generate input and discussion from all key stakeholders. Information in these slides does not represent FDA policy and should not be construed as such.

U.S. FOOD & DRUG ADMINISTRATION

Breakout Session I
Biocompatibility

Ed Margerrison PhD
Director, Office of Science and Engineering Labs
CDRH

Biocompatibility Breakout Session

- FDA Moderated ASCA Scheme Considerations
  - Dr Molly Ghosh, Acting Deputy Director, Division of Biology Chemistry and Materials Science
  - Jen Goode, Biocompatibility Program Advisor, Office of Device Evaluation
  - Dr Shuliang Li, Senior Standards Advisor, Standards and Conformity Assessment Program, Office of the Center Director

  - Topic 1: Proposed Biocompatibility Tests & Discussion
  - Topic 2: Proposed Roles/Responsibilities: Key Stakeholders & Discussion
  - Topic 3: Brainstorming Session - ASCA Scheme Discussion Points & Discussion
  - Topic 4: Proposed ASCA Test Report Summary & Discussion

Background for the Breakout Session

- Why are we doing this?
  - We all want to make the regulatory process more efficient, more transparent and more consistent
  - 21 Century Cures refreshed the concept of Least Burdensome
  - Efficiency can be compounded, but the answer is not only to throw more resources at problems

Background for the Breakout Session

- What do we want to achieve
  - We don't want to spend any more time than necessary on standard testing that is done well
- Instead we can focus on (and therefore accelerate):
  - Non standard methods
  - Data that suggests a deeper review is warranted
- This workshop helps us to define the operation of the pilot program so we all benefit…
  - Discuss why certain standard methods are being proposed
  - How the key stakeholders will all interact during the pilot to ensure success

And Devices

TOPIC 1: PROPOSED BIOCOMPATIBILITY TESTS

ASCA Biocompatibility

- 9 commonly conducted tests (related to 6 standards)

Cytotoxicity
MEM Elution
10993-5

Sensitization
GPMT, Closed Patch
10993-10

Irritation
Intracutaneous Reactivity, Dermal Irritation
10993-10

Required for all devices

+

Acute Systemic Toxicity
10993-11

Material Mediated Pyrogenicity
10993-11, USP 151

Hemolysis
10993-4, ASTM F756

Complement Activation
10993-4

Covers biocompatibility tests for all <24 hr tissue/bone and indirect blood contacting devices & any intact skin contacting devices

Why These Tests

- Apply to many devices.
- Commonly used and conducted in testing labs frequently.
- Test methods are well defined.
- Acceptance criteria built into some standards; commonly used approach to data assessment for others.

Q: Are there any other tests that you think could be included in the ASCA Biocompatibility Pilot?

Questions We Asked Biocompatibility Test Labs

- What are your qualification requirements (e.g., degrees, certifications, training) for a study director? Are they different for different types of tests?
- What qualification requirements (e.g., degrees, certifications, training) do you have for personnel who perform the tests? Are they different for different types of tests (e.g., *in vitro* tests, *in vivo* tests)?
- How do you train personnel to perform specific tests (e.g., cytotoxicity etc.)? Do you have specific requirements regarding retraining frequency or proficiency assessments, depending on the biocompatibility test?
- Which tests are relatively harder to train your testing personnel to perform or evaluate?

Questions We Asked Biocompatibility Test Labs (cont.)

- What selection criteria do you use if choosing a testing subcontractor?
- What is the scope of your accreditation?
- How many of each of these accredited tests do you perform in a year?
- Would you be willing to provide a tabular summary of the specific ISO, ASTM, USP standard biocompatibility test methods (by clause/annex, if appropriate) that you think would be helpful to include during the pilot phase of the ASCA program, and what methods would be helpful to exclude at the pilot phase?

What We've Learned

- Some tests are commonly conducted and well-defined (e.g., hemolysis).
- Some tests are more complicated to conduct (e.g., genotoxicity).
- For standards with multiple tests: different labs may focus on different test methods (e.g., MEM elution vs. Neutral Red Uptake).
- Some labs subcontract to other labs for particular tests.
- Each lab may have slight differences in test-specific SOPs:
  - Certain types of devices require non-traditional sample preparation methods.

What We've Learned (cont.)

- Some tests require more training than others:
  - Tests with subjective evaluations (e.g., MEM Elution Cytotoxicity).
  - Unique animal handling techniques (e.g., wrapping for GPMT).
- Labs may have different training, retraining and proficiency check practices, for example:
  - Use of control testing for training and proficiency.
  - Frequency of proficiency assessments.
- Accreditation Body Assessors:
  - May not have expertise in the technical aspects of biocompatibility testing.
- Goals:
  - Minimize the need for additional FDA inspections associated with ASCA program, if possible.
  - Reduce questions from FDA.

TOPIC 2: PROPOSED ROLES/RESPONSIBILITIES FOR KEY STAKEHOLDERS

Proposed Roles and Responsibilities

FDA ASCA Team	FDA Pre-market Reviewers	FDA GLP Info
TEST LAB INTERACTIONS: • Initial FDA SME review of ASCA test-related protocols and SOPs, data work sheets and training information for ASCA lab recognition. • FDA SME review of substantial changes to ASCA-related documentation. • FDA provided templates for ASCA biocompatibility test summary w/ test-specific data summary tables. ACCREDITATION BODY (AB) INTERACTIONS: • Selection of AB(s) • Training of technical assessors	• ASCA test report summary review in each submission. • No detailed test report review, if no flags in ASCA test report summary. SCOPE: • All pre-market submissions. GOALS: • Shorter review times for biocompatibility tests; fewer review rounds. • More consistent reviews.	• Confirmation that qualified lab site(s) have been inspected by FDA with most recent inspection classified as NAI/VAI(?) NOTES: • BIMO GLP inspection assess data integrity and compliance with GLP regulations. • FDA does not expect additional ASCA-related BIMO inspections.

Proposed Roles and Responsibilities (cont.)

Test Labs	Accreditation Bodies	Medical Device Manufacturers
• Submit a request to FDA to be an ASCA-recognized lab for specific biocompatibility tests. • Submit ASCA test related protocols and SOPs, data work sheets and training information. • Use FDA-provided template ASCA test summary w/ data table for each ASCA test. • Sign ASCA test summary w/data table (study director). • Maintain records of ASCA test summaries together with testing reports.	• Assess lab conformity to ISO/IEC 17025 and FDA scheme requirements. TO INCLUDE: • Participation in technical assessor training by FDA to ensure consistency across ABs. • Assessment of technical competency of labs. • Assessment of testing conformity and data documentation to specific standards, ASCA test protocols and SOPs.	SUBMISSION: • Explain how tested devices in the biocompatibility testing compares to the final device in the submission • Justify sample preparation (e.g., disassembly, components to be excluded, extraction condition). ASCA TEST SUMMARY: • Verify no transcription errors between test reports and ASCA test summary. • Sign to confirm accuracy of ASCA test summary.

TOPIC 3: BRAINSTORMING SESSION – ASCA SCHEME DISCUSSION POINTS

Biocomp Scheme Discussion

- Qualifications/experience of personnel (degrees/accreditations, number of animals/frequency of testing)
- Proficiency assessment and retraining for each test
  - Key steps for each selected test to demonstrate competency of the technician
  - Documentation of competence (practical vs. classroom training)
- ASCA Pilot: only GLP biocompatibility testing (21 CFR 58)
- Trending/analysis of control results and related decisions
- FDA ASCA program training and program update (how frequent)

Biocomp Scheme Discussion (cont.)

- BUCKET 1: Substantial changes to SOP/testing protocols and need (?) for FDA notification/review
- BUCKET 2: Study-specific amendments/deviations.
- Example modifications (either bucket):
  - Changes to sample for retesting to achieve a "passing" result
  - pH adjustments
  - Sample filtration
  - Documentation regarding particulates/fragments, color changes, turbidity in sample extractions
  - Frequency of non-concurrent control testing
  - Changes to acceptance criteria outside the validated/qualified laboratory-specific limits (e.g., for complement activation where the standard methods do not specify acceptable limits)
  - Changes to data calculations and presentation, if applicable (e.g., hemolytic index, irritation index, complement activation plots)

Q1: Other significant modifications FDA should consider?

Q2: Other insignificant modifications that FDA does not need to consider?

TOPIC 4: PROPOSED ASCA TEST REPORT SUMMARY

Possible ASCA Test Report Summary

Possible ASCA Pilot Test Report Summary (part 1) – ASCA Testing Laboratory

Biocompatibility Test: Cytotoxicity – MEM Elution (ISO 10993-5)

ASCA Test Article Prep SOP#: *[MAF######-ASCATAPrep(date/version)]*

☐ Test Article was prepared per the above protocol (no deviations/amendments); or

☐ Test was prepared per the above protocol, with the following deviations/amendments (e.g., filtering, extract manipulation, pH adjustment):

*Fillable text box**

Extraction Solvent: ☐ MEM with 5-10% animal serum ☐ Other*: *[DESCRIBE]*

Extraction Ratio:

☐ 6cm2/ml (<0.5mm thick) ☐ 3cm2/ml (0.5-1.0mm thick or molded items > 1.0mm)

☐ 1.25cm2/ml (elastomers > 1.0mm thick) ☐ Other*: *[DESCRIBE]*

Extraction Conditions:

☐ 37 °C, 72 h ☐ 50 °C, 72 h ☐ 72 °C, 24 h ☐ 121 °C, 1 h ☐ Other*: *[DESCRIBE]*

☐ The test article extract DID NOT change color, appear turbid or have particles.

☐ There were changes in color, turbidity or particles in the test extract or swelling/degradation of the test article.*

CYTOTOX: TEST LAB

Possible ASCA Test Report Summary (cont.)

ASCA Test Method SOP #: *[MAF######-ASCACytotox(date/version)]*

☐ Test was conducted per the above protocol (no deviations/amendments) and 21 CFR 58; or

☐ Test was conducted per the above protocol and 21 CFR 58, with the following deviations/amendments:

*Fillable text box**

Results:**

	24 hr Results (optional)	48 hr Results	72 hr Results (implants)	Conclusion
Vehicle Control	Grade 0/0/0	Grade 0/0/0	Grade 0/0/0	Performed as expected
Negative Control HDPE	Grade 0/0/0	Grade 0/0/0	Grade 0/0/0	Performed as expected
Positive Control Latex	Grade 4/4/4	Grade 4/4/4	Grade 4/4/4	Performed as expected
Test Article Extract (100% neat)	Grade 0/0/0	Grade 0/0/0	Grade 0/0/0	Non-cytotoxic
[INSERT ROWS FOR ANY ADDITIONAL TEST ARTICLE DILUTION/RETEST DATA]				

I confirm that:

☐ The above summary information includes all original and any retest data; and

☐ There are no transcription errors between the test report and this summary.

Name: [TYPED NAME], Study Director Date

CYTOTOX: TEST LAB

Page 1 – [TEST LAB/SPONSOR: Report number and Date]

Possible ASCA Test Report Summary (cont.)

*Include the full test report with ASCA Test Report Summary during the pilot (depending on the information provided, FDA may or may not need to review the full test report). Test Lab/Manufacturer may also need to provide a rationale to support a regulatory submission.
**Include the full test report with ASCA Test Report Summary during the pilot, if there were non-zero results for the test article, vehicle control or negative control, or if there were results less than 3 for the positive control at any timepoint.

CYTOTOX: TEST LAB

Possible ASCA Test Report Summary (cont.)

ASCA Pilot Test Report Summary (part 2) – Medical Device Manufacturer

CYTOTOX: MEDICAL DEVICE MANUFACTURER

I confirm that:

☐ There are no transcription errors between the test report and this summary;

☐ My device does not include: hydrogels, absorbable materials, nanomaterials, or in situ polymerizing materials; and

☐ Information on how the test article compares with the device provided in this FDA submission (including selection of "representative" devices/portions) can be found at the following location:

[INSERT SUBMISSION#/SUPPLEMENT#, page#]

Name: [TYPED NAME, POSITION] Date

Possible ASCA Test Report Summary (cont.)

Possible ASCA Pilot Test Report Summary (part 1) – ASCA Testing Laboratory

Biocompatibility Test: Irritation – Intracutaneous Reactivity (ISO 10993-10)

ASCA Test Article Prep SOP#: *[MAF######-ASCATAPrep(date/version)]*

☐ Test Article was prepared per the above protocol (no deviations/amendments); or

☐ Test was prepared per the above protocol, with the following deviations/amendments (e.g., filtering, extract manipulation, pH adjustment):

*Fillable text box**

Extraction Solvent:

☐ 0.9% Sodium Chloride (SC) ☐ Cotton Seed Oil (CSO)/Sesame Oil (SO) ☐ Other*: *[DESCRIBE]*

Extraction Ratio:

☐ 6cm2/ml (<0.5mm thick) ☐ 3cm2/ml (0.5-1.0mm thick or molded items > 1.0mm)

☐ 1.25cm2/ml (elastomers > 1.0mm thick) ☐ Other*: *[DESCRIBE]*

Extraction Conditions:

☐ 37 °C, 72 h ☐ 50 °C, 72 h ☐ 72 °C, 24 h ☐ 121 °C, 1 h ☐ Other*: *[DESCRIBE]*

☐ The test article extract DID NOT change color, appear turbid or have particles.

☐ There were changes in color, turbidity or particles in the test extract or swelling/degradation of the test article.*

INTRACUTANEOUS: TEST LAB

Possible ASCA Test Report Summary (cont.)

ASCA Test Method SOP #: *[MAF######-ASCAIntracut(date/version)]*

☐ Test was conducted per the above protocol (no deviations/amendments) and 21 CFR 58; or

☐ Test was conducted per the above protocol and 21 CFR 58, with the following deviations/amendments:

*Fillable text box**

Results**:

	Test Article	24 hr Results	48 hr Results	72 hr Results	Conclusions
Animal 1	SC Test	ER^: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	Performed as expected
	SC Control	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	Performed as expected
Animal 2	SC Test	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	Performed as expected
	SC Control	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	Performed as expected
Animal 3	SC Test	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	Performed as expected
	SC Control	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	ER: 0/0/0/0/0 ED: 0/0/0/0/0	Performed as expected
Animal 1	SQ Test	ER: 1/1/1/1/1 ED: 0/0/0/0/0	ER: 1/0/1/1/1 ED: 0/0/0/0/0	ER: 1/0/1/1/1 ED: 0/0/0/0/0	Performed as expected
	SQ Control	ER: 1/1/1/1/1 ED: 0/0/0/0/0	ER: 1/1/1/1/1 ED: 0/0/0/0/0	ER: 1/1/0/0/1 ED: 0/0/0/0/0	Performed as expected

INTRACUTANEOUS: TEST LAB

Page 1 – [TEST LAB/SPONSOR: Report number and Date]

Possible ASCA Test Report Summary (cont.)

	Test Article	24 hr Results	48 hr Results	72 hr Results	Conclusions
Animal 2	SO Test	ER: 1/1/1/1/1 ED: 0/0/1/0/0	ER: 1/1/1/1/0 ED: 0/0/1/0/0	ER: 1/1/1/1/0 ED: 0/0/0/0/0	Performed as expected
	SO Control	ER: 1/1/1/1/0 ED: 0/0/1/0/0	ER: 1/1/1/0/1 ED: 0/0/0/0/0	ER: 1/1/0/0/0 ED: 0/0/0/0/0	Performed as expected
Animal 3	SO Test	ER: 1/1/1/1/1 ED: 0/0/0/0/0	ER: 1/1/1/1/1 ED: 0/0/0/0/0	ER: 1/1/1/1/1 ED: 0/0/0/0/0	Performed as expected
	SO Control	ER: 1/1/1/1/1 ED: 0/0/0/0/0	ER: 1/1/1/1/1 ED: 0/0/0/0/0	ER: 1/1/1/1/1 ED: 0/0/0/0/0	Performed as expected
[INSERT ROWS FOR ANY ADDITIONAL REPEAT TEST DATA]					

^ER = erythema grade; ED = edema grade

Extract	Overall Test Group Mean	Overall Control Group Mean	Overall Mean Difference (Test – Control)	Conclusion
SC	0.0	0.0	0.0	Non-Irritant
SO	1.0	0.9	0.1	Non-Irritant

☐ There were no adverse clinical findings or animal deaths; or
☐ The following adverse clinical findings or animal deaths occurred:

*Fillable text box**

INTRACUTANEOUS: TEST LAB

Possible ASCA Test Report Summary (cont.)

I confirm that:

☐ The above summary information includes all original and any retest data; and

☐ There are no transcription errors between the test report and this summary.

Name: [TYPED NAME], Study Director Date

*Include the full test report with ASCA Test Report Summary during the pilot (depending on the information provided, FDA may or may not need to review the full test report). Test Lab/Manufacturer may also need to provide a rationale to support a regulatory submission.

**Include the full test report with ASCA Test Report Summary during the pilot, if the overall score differences between the test and control are greater than one (i.e., per ISO 10993-10:2010, Clause 6.4.7), or if there were non-zero results for the sodium chloride control, or results greater than 2 for the oil control at any timepoint.

INTRACUTANEOUS: TEST LAB

Possible ASCA Test Report Summary (cont.)

ASCA Pilot Test Report Summary (part 2) – Medical Device Manufacturer

I confirm that:

☐ There are no transcription errors between the test report and this summary;

☐ My device does not include: hydrogels, absorbable materials, nanomaterials, or in situ polymerizing materials; and

☐ Information on how the test article compares with the device provided in this FDA submission (including selection of "representative" devices/portions) can be found at the following location:

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Name: [TYPED NAME, POSITION] Date

BREAKOUT I: BIOCOMPATIBILITY WRAP-UP (D1)

Breakout I: Biocompatibility Wrap-Up

- D1 Notes:
  - T1:
  - T2:

Breakout I: Biocompatibility Wrap-Up

- D1 Notes:
  - T3:
  - T4:

Thank You

TOMORROW'S SESSION:

- Day 2 Biocompatibility Breakout Session (9:00 am-11:00 am) in Great Room A
  - Test-Specific Biocompatibility Roundtable
  - Webcast link:

https://collaboration.fda.gov/ascabreakout/


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