IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MEDA PHARMACEUTICALS INC. and **CIPLA LTD.**,	)	
Plaintiffs,	)	
v.	)	
	)	C.A. No. 14-1453-LPS
APOTEX INC. and **APOTEX CORP. ,**	)	
Defendants.	)	

REPORT OF MATTHEW J. HERPIN, PH.D.

I. Introduction and Qualifications

1. I have been retained by Meda Pharmaceuticals Inc. ("Meda") and Cipla Ltd. ("Cipla") (collectively, "Plaintiffs") to formulate and test the composition described in EP 0780127 (Cramer) Example III.

2. I attach my *curriculum vitae* to this report as Appendix A. I am currently a Postdoctoral Research Fellow at the University of Texas, Austin, College of Pharmacy. I obtained my Ph.D in Pharmaceutics from the University of Texas, Austin.

3. I have never testified as an expert witness or prepared an expert report in connection with any litigation. A list of my publications is included in my CV.

4. My rate is $300 per hour, and my compensation does not depend upon the ultimate outcome of this case. I will also be compensated for any reasonable expenses, including travel costs incurred in conducting activities at counsel's request.

5. If called to testify, I am prepared to testify regarding the results of my experiments as reported here and the attached documents.

II. Summary of Work and Results

6. Plaintiffs retained me to formulate Cramer Example III using three different processes: (1) the process Cramer describes in Example I ("Cramer Example I Method"); (2) the process Geena Malhotra describes in her August 12, 2011 declaration ("Malhotra Method"); and (3) the first process Dr. Govindarajan used in his June 30, 20016 report ("Govindarajan Method"). I was instructed to document and photograph the formulation process. I attach the protocols for the Cramer Example I Method and the Malhotra Method as Appendix B.

7. Plaintiffs also retained me to perform the following tests on the formulations prepared using the three different processes: (1) visually describe the final preparation; (2) measure the pH; (3) test the sprayability; (4) measure the pH 7 days after preparation; (5) visually describe the preparation after 7 days with and without mixing; (6) test the Delivered Dose Uniformity; (7) test the Bulk Blend Uniformity Assay for Triamcinolone Acetonide for freshly prepared samples, samples after 3 hours, and samples after 7 days; and (8) visually describe the preparation after 14 days with and without mixing. I did not conduct the Delivered Dose Uniformity tests and Bulk Blend Uniformity Assay for Trimacinolone Acetonide on formulations that failed the sprayability test (i.e., produced a jet spray). Additionally, the preparation made using the Govindarajan Method did not result in a large enough volume for me to perform the Delivered Dose Uniformity Testing and Bulk Blend Uniformity Assay for Trimacinolone Acetonide.

8. The Cramer Reference is silent as to the grade of HPMC to use and whether the triamcinolone acetonide is micronized or unmicronized. Therefore, I used two different grades of HPMC, a low-viscosity grade (HPMC-E3-LV) and a medium-viscosity grade (HPMC-E4M), and I used both micronized and unmicronized triamcinolone acetonide.

9. Exhibit A shows the following formulation matrix:

Formulation Matrix			
Formulation	Polymer	Method	API
HS-D	HPMC-E4M (4000 cps)	Cramer Example I	Micronized TAA
Mal-A	HPMC-E3-LV (3cps)	Malhotra	Raw TAA
Mal-B	HPMC-E4M (4000 cps)	Malhotra	Raw TAA
Mal-C	HPMC-E3-LV (3cps)	Malhotra	Micronized TAA
Mal-D	HPMC-E4M (4000 cps)	Malhotra	Micronized TAA
X-Form	HPMC-E3-LV (3cps)	Govindarajan	Micronized TAA

10. The legend for the formulation matrix is:

a. TAA – Triamcinolone Acetonide;
b. Mal-A, Mal-B, Mal-C, and Mal-D were preparations using the Malhotra Method;
c. HS-D is a preparation using Cramer Example I Method;
d. X-Form recreated the Govindarajan Method.

11. Exhibit B reports the process steps, visual results, and pH testing for the Mal-A, Mal-B, Mal-C, and Mal-D preparations made using the Malhotra Method.

12. Exhibit C reports the process steps, visual results, and pH testing for HS-D. The exhibit also shows the preparation made using the Cramer Example I Method.

13. Exhibit R reports the Pump Delivery Shot Weight Raw Data and the Sprayability results for Mal-A, Mal-B, Mal-C, Mal-D, and HS-D formulations.

14. Exhibit D reports the visual results and pH testing results for X-form. I annotated a copy of Dr. Govindarajan's lab notebook.

15. Exhibit E reports the results of pH testing of each formulation (Mal-A, Mal-B, Mal-C, Mal-D, HS-D, and X-Form) 7 days after initial preparation.

16. Exhibit F reports the visual appearance of each formulation (Mal-A, Mal-B, Mal-C, Mal-D, HS-D, and X-Form) 7 days after initial preparation. It also reports the visual appearance of each formulation after attempting to re-disperse settled particles. Re-dispersion was done by swirling and shaking the vessel in a moderate action to minimize foaming.

17. Exhibit G reports the sprayability of formulations Mal-A and Mal-C after 7 days. Because formulations Mal-B, Mal-D, and HS-D only produced a jet during the initial test, I did not conduct another sprayability test 7 days after preparation of those formulations.

18. Exhibit H reports the Delivered Dose Uniformity analysis and assay of formulation Mal-A.

19. Exhibit I reports the Delivered Dose Uniformity analysis and assay of formulation Mal-C.

20. Exhibit J reports the Delivered Dose Uniformity summary for Mal-A and Mal-C preparations.

21. Pictures from Mal-A preparation showing the formulation after step 11 and after 7 days are attached as Exhibit K.

22. Pictures from Mal-B preparation showing the formulation after step 11 and after 7 days are attached as Exhibit L.

23. Pictures from Mal-C preparation showing the formulation after step 11 and after 7 days are attached as Exhibit M.

24. Pictures from Mal-D preparation showing the formulation after step 11 and after 7 days are attached as Exhibit N.

25. Exhibit O contains pictures from the HS-D preparation that show the formulation after step 11, 7 days after preparation, and pictures of the undissolved EDTA taken during the initial preparation.

26. Pictures from the X-Form preparation show the formulation after the addition of azelastine hydrochloride, after the addition of HPMC, and 7 days after initial preparation are attached as Exhibit P.

27. I also took videos of the sprays from Mal-A and Mal-B preparations, which were representative of the spay patterns of the low-viscosity HMPC and medium-viscosity HPMC formulations, respectively, which I attach as Exhibit Q.

28. Pictures for Mal-A, Mal-B, Mal-C, HS-D, and X-Form formulations 14 days after the initial preparation are attached as Exhibit S.

29. Exhibit T contains pictures of the visual appearance of each formulation (Mal-A, Mal-B, Mal-C, HS-D, and X-Form) 14 days after the initial preparation and after attempting to re-disperse any settled particles of the formulation. Re-dispersion was done by swirling and shaking the vessel in a moderate action to minimize foaming.

III. Declaration

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct to the best of my knowledge.

Date: 7/28/2016

Matthew J. Herpin, Ph.D

Appendix A

MATTHEW J. HERPIN, Ph.D

601 Hearn Street #202 • Austin, Texas 78703 • 512.947.8626
matt.herpin@.utexas.edu

I. Personal

Born October 31st 1981 in Corpus Christi, Texas. United States Citizen.

II. Education

Ph.D., Pharmaceutics, December 2015
Advisor: Dr. Hugh D.C. Smyth
The University of Texas, Austin, TX

Bachelor of Science, Biochemistry, May 2005
The University of Texas, Austin, TX

III. Positions Held

January 2016 to Current
Postdoctoral Research Fellow- University of Texas at Austin, College of Pharmacy

May 2015 to January 2016
Graduate Research Assistant- University of Texas at Austin, College of Pharmacy

January 2012 to January 2014
PhRMA Foundation Pre-Doctoral Fellow- University of Texas at Austin, College of Pharmacy

January 2011 to May 2015
Teaching Assistant- University of Texas at Austin, College of Pharmacy
Courses:

- Physical and Chemical Principles of Drugs & Laboratory, Fall: 2011
- Pharmaceutical Compounding Laboratory, Spring: 2011, 2014, 2015

2008 to July 2010
Research Associate
Appian Labs, LLC, Austin, TX
Aeonclad Biomedical, LLC, Austin, TX
Enavail, LLC, Austin, TX

- Responsible for leading a product development group with the overall responsibility of developing solid dosage forms. The development group is comprised of formulation development and analytical team members. Reports directly to the Director of Research and Development and company President.

- Responsible for the development of solid dosage forms with a strong emphasis on products utilizing diffusion based hydrogel controlled release systems, plasma enhanced chemical vapor deposition/polymer based controlled release coatings and particle engineering technologies to drug absorption profiles and improve bioavailability.
- Provide strategic, scientific and managerial leadership to the formulation and analytical teams to solve complex drug development issues
- Develop experimental plans based on client needs and overall project goals
- Coordinate the production and analytical testing of pharmaceutical formulations
- Interpret experimental observations according to sound scientific principles
- Interact with clients and consultants to provide project updates verbally and in the form of technical reports
- Work closely with the Operations group to coordinate the transfer of technology from R&D to cGMP manufacturing
- Prepare and review batch records and standard operating procedures
- Provide and submit intellectual property ideas relating to novel pharmaceutical formulations, processing techniques or analytical methods.

2006 to October 2008
Analytical Chemist, Quality Control
Inhalation Chemist, Platform Development, and Quality Control
Pharmaform, LLC, Austin, TX

- Responsible for the USP testing of pharmaceutical dosage forms in Research and Development and in Phase I to III clinical trials. Reported to the Vice President of Quality Control
  - Interacted with clients to determine project goals and to provide project updates
  - Planned, designed, and performed experiments relating to the development of as standard method of analysis for solid dosage forms and dry powder inhalers.
  - Conducted testing on physical and chemical properties pertaining to product purity potency and performance. Including: High Performance Liquid Chromatography, USP Dissolution Testing,
  - Worked closely with method development chemists and manufacturing to solve problems associated with production.
  - Provide manufacturing analytical support.
  - Coordinated product analytical testing
  - Wrote and reviewed technical reports submitted to clients

August 2003 to 2006
Compounding Pharmacy Technician (CPhT)
Peoples Pharmacy, Austin, TX

- Responsible for compounding preparation of various pharmaceutical dosage forms including: capsules, gels, lotions, creams, suppositories, rapid-disintegrating tablets, medicated lollipops and others.
    - Assists pharmacist in the dispensing of medication to patients
    - Managing inventory and ordering supplies

IV. Relevant Training Completed

- Inhalation Aerosol Technology Workshop: University of Maryland, Baltimore.
- Waters HPLC Operation and Utilization Course
- cGMP Certification Training: Compliance LLC

V. Relevant Coursework Completed

Biopolymers: Drug and Gene Delivery
Biopharmaceutics and Pharmacokinetics
Physical and Chemical Principles of Drugs
Pharmaceutics
Pharmaceutical Compounding
Modern Advances in Pharmaceutics
Advanced Manufacturing Pharmacy
Product Development
Statistics for Translational Scientists

VI. Professional Memberships

American Association of Pharmaceutical Scientists	2011 – present
American Chemical Society	2011 – present
American Association of Advancing Science	2012 – present

VII. Current Research Interests

- Precision ophthalmic drug delivery via tunable aerosol dynamics
- Drug particle engineering by way of super-heated processing and high pressure homogenization
- Ophthalmic and pulmonary drug delivery device design and development
- Enhanced aerodynamics and performance of inhalation powders
- Preformulation, formulation, and characterization of novel delivery systems.

VIII. Formulation Development Proficiencies

- Inhalation Aerosol Based Systems- Including various nebulizers, pMDI and evaporation/condensation aerosols
- Topical Ophthalmic drug delivery systems/vehicles-
- Diffusion Based Controlled Release Tablets (direct compression)
- Various Particle Engineering Technologies: High Pressure Homogenization, Solvent Precipitation/Evaporation, Spray Drying, Super-Heated Aqueous Particle Engineering
- Solubilization/Complexation with Cyclodextrins
- Dry Powder Inhalation formulations
- Powder Encapsulation

- Preparation of Emulsions, Creams, Lotions, Gels, Suspensions
- Excipient Uses and Functionality

IX . Technical Proficiencies and Research Experience

Analytical Instrumentation and Methodology:

- UV-Vis/Fluorescence Spectrophotometers
- Fourier Transform Infrared Spectroscopy
- Laser Diffraction Particle Sizing (Sympatec-Helos)
- High Performance Liquid Chromatography-Method Development/Qualification
- Inverse Gas Chromatography
- Dynamic Light Scattering
- Atomic Absorption
- Differential Scanning Calorimetry
- Faraday Cage for Electrostatic Analysis
- Powder X-Ray Diffraction

Physical Testing

- United States Pharmacopoeia (USP) Dissolution Tests
- Angle of Repose
- Moisture Analyzer
- Next Generation Impactor (aerodynamic assessment of fine particles)
- Anderson Cascade Impactor/ Twin Stage Impactor
- Instron Compression and Elongation Analysis
- Tablet Hardness
- Tablet Friability

Biochemical Techniques

- Polymerase Chain Reaction(PCR)
- Western Blotting
- PAGE/Agarose Gel Electrophoresis
- Various enzyme activity assays

Microscopy

- Atomic Force Microscopy (AFM)
- High Performance Liquid Chromatography-Method Development/Qualification
- Two Photon Microscopy
- Scanning Electron Microscopy
- Raman Microscopy

X. Awards and Honors

- PhRMA Foundation Pre-Doctoral Fellowship (2012 - 2014)
- Teaching Excellence Award- Outstanding Teaching Assistant- 2014
- Student Entrepreneur Acceleration and Launch, Program Graduate- 2015
- Texas Venture Labs- Founding Company Participant

XI. Publications and Presentations

Herpin MJ, Raffa-Carvhalo S, Smyth HDC, McConville JT, Variable Flow Pattern Effects on Fine Particle Generation from a Dry Powder Inhaler, Littlefield Excellence in Research Poster Presentation, 2010

Bosselmann S, Owens III DE, Kennedy RL, **Herpin MJ**, Williams III RO. Plasma deposited stability enhancement coating for amorphous ketoprofen. European Journal of Pharmaceutics and Biopharmaceutics. 2011;78(1):67-74.

Donovan MJ, Gibbons A, **Herpin MJ**, Marek S, Mcgill S, Smyth HDC. Novel Dry Powder Inhaler Particle Dispersion Systems-A Review. Future Medicine. 2011

Herpin M.J, Smyth HDC, A Novel Ocular Soft Mist Aerosol Device for Tunable Drug Delivery, American Association of Pharmaceutical Scientists Conference, Poster Presentation, Oct. 2012

Herpin M.J, Smyth HDC, Non-Aqueous Aerosol Deposition for Ocular Drug Delivery, American Association of Pharmaceutical Scientists Conference, Poster Presentation, Oct. 2013

Moraga, D., Bahamondez, T., **Herpin, M.,** Maloney, A. Yazdi, A., Du, P., Du, J., Smyth, H., Hydrofluoroalkane Propellant Driven Metered Dose Inhaler Formulations. In Textbook of Aerosol Medicine.

Herpin M.J, Smyth HDC, Aqueous Based Aerosol Vehicles for Enhanced Ocular Drug Delivery, American Association of Pharmaceutical Scientists Conference, Poster Presentation, Oct. 2014

Herpin M.J., Ebi, Dominik, Clemens, N., Smyth H.D.C. Characterization of Toroidal Vortices Generated by a Novel Ocular Drug Delivery Device. *International Journal of Pharmaceutics*. 2016 (In Preparation)

Herpin M.J., Xinfei, X. Smyth, H.D.C., Super Heated Aqueous Particle Engineering for Poorly Water Soluble Drugs. International Journal of Pharmaceutics. 2016 (In Preparation)

Herpin M.J., Smyth, H.D.C. Precision Ocular Drug Delivery Via Aerosol Ring Vortices. *Drug Delivery in Translational Medicine*. 2016. (In Preparation)

Bandara, H. M. H. N., **Herpin M.J**, Kolaccny D., Harb A., Romanovicz D., Smyth H.D.C., . "Incorporation of farnesol significantly increases the efficacy of liposomal ciprofloxacin against Pseudomonas aeruginosa biofilms in vitro." *Molecular Pharmaceutics* (2016).

XI. Intellectual Property

1. Smyth, H.D.C., **Herpin M.J**., Toroidal Pharmaceutical Formulations, U.S. Patent No. 61/501,671
2. Smyth, H.D.C., **Herpin M.J.,** Method for Fine Particle Manufacture, U.S. Patent No. 14/458,818
3. Cannon C., Parth, S., Smolen, J., Smyth H., Yazdi A., **Herpin M.J**., Antimicrobial and Anti-Inflammatory Compositions. Provisional U.S. Patent Application. # 62/168,561

Appendix B

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing using E4MP HMPC and micronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the mixing techniques described in Cramer Example I.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	E4MP (4000 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E4MP will be tested
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			This drug will be in suspension and will therefore need to be procured in micronized form.
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Preparation according to Example I

Example III will be prepared by combining the following components utilizing "conventional mixing techniques similar to that described in Example 1":

> In an appropriately sized vessel, the dextrose, polysorbate 80 and benzalkonium chloride are added one at a time to water with mixing, allowing each to dissolve or completely disperse before adding the next. To this is added, with mixing, a premixed slurry of the avicel and water. Upon forming a uniform solution, the beclomethasone, loratadine and phenylethyl alcohol are added. After all the ingredients are added, purified water is used to bring the batch to the appropriate weight.

Accordingly 500 mL of Example III will be made using the procedure outlined below:

1. In an appropriately sized vessel to manufacture 500 mL of product,
    a. To 100 mL of distilled water
    b. Add polysorbate 80
    c. Mix step – Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
    d. Add benzalkonium chloride
    e. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
    f. Add glycerin

g. Mix- Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
h. Add EDTA
i. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
j. Add NaCl
k. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed

2. In a separate vessel the hydroxyl methylcellulose is prepared"
    a. As per the Handbook of Pharmaceutical Excipients (2^{nd} Edition, 1994) 20% of the required water is used to hydrate the HPMC (100 mL distilled water)
    b. The water is vigorously stirred at RPMs adequate to disperse the powder and heated to approximately 90 deg C
    c. While stirring, the HPMC is added, and mixing continues until all particles are thoroughly wetted
    d. Then to the dispersed HPMC, 200 mL of cold distilled water is added while mixing
    e. The mixture is then cooled to between 20 to 25°C (68 to 77°F) or below as according to the Methocel™ product guide ("How to Prepare Aqueous Solutions of METHOCEL™").
3. This premixed HPMC mixture is then added to the ingredients of step 1 to form a uniform solution.
    a. Note: Since Example III does not list the grade of HPMC used, this experiment will be replicated using grades AAA, BBB, and CCC. The manufacturer has stated that each grade is suitable for nasal administration.
4. To this solution Triamcinolone and Azelastine are added and mixed at 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed.
    a. Perform bulk product testing (top, middle, and bottom) to ensure stability over a period (2-3 or more hours) sufficient to demonstrate uniformity of the bulk following production.
5. The samples are then mixed using a high-speed homogenizer.
6. The formulations are then filled into nasal spray bottles (approximately 16.5 g per bottle) and spray pumps fitted to the bottles.
7. Filled bottles will be stored at room temperature and optionally additional bottles not stored at room temperature will be stored at accelerated stability conditions (40 deg C and 75% RH).
8. Bottles will be tested at time points indicated below using various performance assays.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual Inspection of spray quality	a. Visual observation of emission of formulation during actuation of pump	Observation of spray/jet/ failure to emit	Qualitatively assesses acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			

Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing Following Malhotra Method using E3 Prem HMPC and micronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	Low viscosity: E3 PREM LV (3 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E3 Prem will be tested
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			This drug will be in suspension and will therefore need to be procured in micronized form.
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Preparation by Method Detailed in Geena Malhotra's 2011 Declaration

The technique will use the ingredients and process described below:

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.

10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.

11) Volume was made-up with purified water.

12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual	a. Visual observation of emission of formulation	Observation	Qualitatively assesses

Inspection of spray quality	during actuation of pump	of spray/jet/ failure to emit	acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing Following Malhotra Method using E3 Prem HMPC and Unmicronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	Low viscosity: E3 PREM LV (3 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E3 Prem will be tested
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

A. Preparation by Method Detailed in Geena Malhotra's 2011 Declaration

The technique will use the ingredients and process described below:

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.

10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.

11) Volume was made-up with purified water.

12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual	a. Visual observation of emission of formulation	Observation	Qualitatively assesses

Inspection of spray quality	during actuation of pump	of spray/jet/ failure to emit	acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing Following Malhotra's Method using E4MP HMPC and micronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	E4MP (4000 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E4MP will be tested.
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			This drug will be in suspension and will therefore need to be procured in micronized form.
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Preparation by Method Detailed in Geena Malhotra's 2011 Declaration

The technique will use the ingredients and process described below:

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.

10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.

11) Volume was made-up with purified water.

12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual	a. Visual observation of emission of formulation	Observation	Qualitatively assesses

Inspection of spray quality	during actuation of pump	of spray/jet/ failure to emit	acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/716

Nasal Spray Manufacturing and Characterization Testing Following Malhotra's Method using E4MP HMPC and Unmicronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	E4MP (4000 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E4MP will be tested.
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.
10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.
11) Volume was made-up with purified water.
12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual Inspection of spray quality	a. Visual observation of emission of formulation during actuation of pump	Observation of spray/jet/ failure to emit	Qualitatively assesses acceptability of spray
Spray	a. Dose collection tubes	SMA-001-00	Quantitative assessment of

Content Uniformity	b. HPLC drug assay c. Actuation Station d. Analytical Balance		the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Exhibit A – Formulation Matrix

Formulation Matrix			
Formulation	Polymer	Method	API
HS-D	HPMC-E4M (4000 cps)	Cramer Example I	Micronized TAA
Mal-A	HPMC-E3-LV (3cps)	Malhotra	Raw TAA
Mal-B	HPMC-E4M (4000 cps)	Malhotra	Raw TAA
Mal-C	HPMC-E3-LV (3cps)	Malhotra	Micronized TAA
Mal-D	HPMC-E4M (4000 cps)	Malhotra	Micronized TAA
X-Form	HPMC-E3-LV (3cps)	Govindarajan	Micronized TAA

Exhibit B - Malhotra Preparations

Project No. _____

Book No. _____ TITLE Formulation Prep.

From Page No. N/A

Formulation: MAL-A MSH

~~HS-A~~ July 12 2016

Mal-A

Molhatra - Cramer Preparation

☑ 1.) 300 mLs, part quantity of water taken into a vessel. (300mL)

☑ 2.) 4,5060 grams of NaCl (4.5grams) and 250,0 milligrams of EDTA (250mg) was added and dissolved under stirring and heating the bulk.

☑ 3.) 5.0081 grams Hydroxy propyl methylcellulose (5 gr), grade: E3-Prem^{LV} was added and dispersed under stirring.

☑ 4.) Stirring and was done and bulk was held at 2-8 deg.C overnight

☑ 5. 10.1 grams of Glycerin was added and mixed into above bulk under stirring (10 gr.)

☑ 6. 50 mLs of waters, part quantity (50 mL) and Azelelastine HCl was dissolved in it to form drug slurry (350mg) 350.2 mg

☑ 7. Drug Slurry from step #6 was added to the main bulk in step #5 under stirring

☑ 8.) 50 mLs of water (50 mL) was taken into a vessel and 244.1 milligrams of Polysorbate 80 (250mg) was added under stirring until dissolved, then 250.0 mg of Triamcinolone Acetanide (250mg) was added to the solution and dispersed under stirring. (Raw)

☑ 9.) Drug Slurry from step #8 was added to the bulk of step #7 under stirring

☑ 10. 50 mLs of water water was taken into a vessel and 110.7 mgs of Benzalkonium chloride (100mg) was added under stirring.

☑ 11.) Volume was made up with purified water

☑ 11a.) & High speed Homogenization was done for 5 minutes @ 10,000rpms

☑ 12.) Stirring was done and pH was measured and recorded. pH: 2.66

note: — Formulation resulted in a uniform white suspension with foam that dissapated in about 10 minutes. Settling of particulates was observed over this time period.

To Page No

Witnessed & Understood by me,	Date	Invented by:	Date
MSH	7/12/2016	Recorded by:	

Project No. _____

E Formulation Prep Book No. _____

Page No. N/A

Formulation: MAL-B MSH

Mal-B July 12 2016

Molhatra - Cramer Preparation

☑ 1.) 300 mLs, part quantity of water taken into a vessel. (300mL)

☑ 2.) 4,5084 grams of NaCl (4.5grams) and 250,8 milligrams of EDTA (250mg) was added and dissolved under stirring and heating the bulk.

☑ 3.) 5.0116 grams Hydroxy propyl methylcellulose (5 gr), grade: E4M was added and dispersed under stirring.

☑ 4.) Stirring and was done and bulk was held at 2-8 deg.C overnight

☑ 5. 10.0 grams of Glycerin was added and mixed into above bulk under stirring (10 gr.)

☑ 6. 50 mLs of waters, part quantity (50 mL) and Azelelastine HCl was dissolved in it to form drug slurry (350 mg) 350.1 mg

☑ 7. Drug Slurry from step #6 was added to the main bulk in step #5 under stirring

8.) 50 mLs of water (50 mL) was taken into a vessel and 247.8 milligrams of Polysorbate 80 (250mg) was added under stirring until dissolved, then 250.0 mg of Triamcinolone Acetanide (250mg) was added to the solution and dispersed under stirring. (Raw)

9.) Drug Slurry from step #8 was added to the bulk of step #7 under stirring

10. 50 mLs of water water was taken into a vessel and 96.3 mgs of Benzalkonium chloride was added under stirring. (100mg)

11.) Volume was made up with purified water
High speed homogenization was done for 5 minutes @ 10,000rpms

12.) Stirring was done and pH was measured and recorded. pH: 2.67

- Formulation resulted in a uniform white suspension with a high viscosity
- Large air bubbles slowly rose to the top over a ~30 minute period

To Page No. ____

sed & Understood by me,	Date	Invented by:	Date
MSH	7/12/2016	Recorded by:	

Project No. _____

Book No. _____ TITLE Formulation Prep

From Page No. ____

Formulation: MAL-C MSH

Mal-C July 12 2016

E3-LV

Molhatra - Cramer Preparation

☑ 1.) 300 mLs, part quantity of water taken into a vessel. (300mL)

☑ 2.) 4.5048 grams of NaCl (4.5grams) and 250.5 milligrams of EDTA (250mg) was added and dissolved under stirring and heating the bulk.

☑ 3.) 5.0108 grams Hydroxy propyl methylcellulose (5 gr), grade: E3-PREM-LV was added and dispersed under stirring.

☑ 4.) Stirring and was done and bulk was held at 2-8 deg.C overnight

☑ 5. 10.0 grams of Glycerin was added and mixed into above bulk under stirring (10 gr.)

☑ 6. 50 mLs of waters, part quantity (50 mL) and Azelelastine HCl was dissolved in it to form drug slurry (350mg) 350.6 mg

☑ 7. Drug Slurry from step #6 was added to the main bulk in step #5 under stirring

☑ 8.) 50 mLs of water (50 mL) was taken into a vessel and 246.1 milligrams of Polysorbate 80 (250mg) was added under stirring until dissolved, then 250.0 mg of Triamcinolone Acetanide (250mg) was added to the solution and dispersed under stirring. (micronized)

☑ 9.) Drug Slurry from step #8 was added to the bulk of step #7 under stirring

☑ 10. 50 mLs of water water was taken into a vessel and 94.8 mgs of Benzalkonium chloride was added under stirring. (100 mg)

☑ 11.) Volume was made up with purified water
high speed Homogenization for 5 min. @ 10,000 rpm.

☑ 12.) Stirring was done and pH was measured and recorded. pH: 2.66

note: - Formulation resulted in a uniform white suspension with foam that quickly dissapated dissapates. Settling of particulates was observed over a 10-15min period

To Page No

Witnessed & Understood by me,	Date	Invented by:	Date
MSH	7/12/2016	Recorded by:	

Project No. _____

: Formulation Prep Book No. _____

Page No. N/A

Formulation: MAL-D MSH

Mal-d July 12 2016

E4M

Molhatra - Cramer Preparation

1.) 300 mLs, part quantity of water taken into a vessel. (300mL)

2.) 4.5031 grams of NaCl (4.5grams) and 250.6 milligrams of EDTA (250mg) was added and dissolved under stirring and heating the bulk.

3.) 5.0287 grams Hydroxy propyl methylcellulose (5 gr), grade: E4M was added and dispersed under stirring.

4.) Stirring and was done and bulk was held at 2-8 deg.C overnight

5. 10.0 grams of Glycerin was added and mixed into above bulk under stirring (10 gr.)

6. 50 mLs of waters, part quantity (50 mL) and Azelelastine HCl was dissolved in it to form drug slurry (350mg) 350.1 mg

7. Drug Slurry from step #6 was added to the main bulk in step #5 under stirring

8.) 50 mLs of water (50 mL) was taken into a vessel and 247.9 milligrams of Polysorbate 80 (250mg) was added under stirring until dissolved, then 250.3 mg of Triamcinolone Acetanide (250mg) was added to the solution and dispersed under stirring. (micronized)

9.) Drug Slurry from step #8 was added to the bulk of step #7 under stirring

10. 50 mLs of water water was taken into a vessel and 91.9 mgs of Benzalkonium chloride was added under stirring. (100mg)

11.) Volume was made up with purified water

High speed homogenization for 5 min. @ 10,000 rpms

12.) Stirring was done and pH was measured and recorded. pH: 2.66

de:

- Formulation resulted in a uniform white suspension that contained bubbles that rose to the top over a 30 minute period.

To Page No. ____

sed & Understood by me,	Date	Invented by:	Date
MSH	7/12/2016	Recorded by:	

Exhibit C – Cramer Example I

Project No. _____

Book No. _____ TITLE Formulation Prep

From Page No. N/A

Formulations: ~~HS-A~~ → N/A HS-D

1. In an appropriately sized vessel, to manufacture 500 mL of product,

   ☑ a. To 100mL mL of distilled water (100 mL)

   ☑ b. Add 258.9 mgs polysorbate 80 (250 mg)

   ☑ c. Mix step – Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed

   ☑ d. Add 96.4 mgs benzalkonium chloride (100 mg)

   ☑ e. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed

   ☑ f. Add 10.0 grams of glycerin (10 grams)

   ☑ g. Mix- Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed

   ☑ h. Add 249.8 mgs of EDTA (250 mg)

   ☑ i. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed note: did not visually dissolve (EDTA

   ☑ j. Add 4.5131 grams of NaCl (4.5 grams)

   k. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed → did not fully dissolve @ this stage either note: (EDTA)

2. In a separate vessel the hydroxyl methylcellulose is prepared"

   a. As per the Handbook of Pharmaceutical Excipients (2nd Edition, 1994) 20% of the required water is used to hydrate the HPMC

   ☑ b. 100 mLs of water is vigorously stirred at RPMs adequate to disperse the powder and heated to approximately 90 deg C. (100 mLs)

   ☑ c. While stirring, 5.0122 grams HPMC (Grade: E4M) is added, and mixing continues until all particles are thoroughly wetted.

   ☑ d. Then to the dispersed HPMC, 200mL mL of cold distilled water is added while mixing (200 mL)

   ☑ e. The mixture is then cooled to between 20 to 25°C (68 to 77°F) or below as according to the Methocel™ product guide ("How to Prepare Aqúeous Solutions of METHOCEL™").

To Page No

Witnessed & Understood by me,	Date	Invented by:	Date
MJH	7/12/2016	Recorded by:	

Formulation Prep

Project No. _____

Book No. _____

Page No. 10

Formulation HS-D

~~HS-A~~ - Continued

~~MA HS-A - Cont'd~~

MSH 7/13/2016

3. This premixed HPMC mixture is then added to the ingredients of step 1 to form a uniform solution.

   a. Note: Since Example III does not list the grade of HPMC used, this experiment will be replicated using grades E3 Prem LV and E4M. The manufacturer has stated that each grade is suitable for nasal administration.

☑ 4. To this solution, 253.9 (Micronized) mgs of Triamcinolone Acetonide (250 mg) and 350.8 mgs of Azelastine (350 mg) are added and mixed at 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed.

☑ 5. High Speed Homogenization was done until a visually homogenous mixture was acheived (5 min @ 10,000 rpms)

Note: Since Example III does not indicate whether the triamcinolone is micronized or not, this experiment will be replicated using triamcinolone acetonide that is non-micronized and micronized [ADD any specification here].

☑ 6. The formulations are then filled into nasal spray bottles (approximately 16.5 g per bottle) and spray pumps fitted to the bottles.

☑ 7. Filled bottles will be stored at room temperature and optionally additional bottles not stored at room temperature will be stored at accelerated stability conditions (40 deg C and 75% RH).

8. Bottles will be tested at time points indicated below using various performance assays.

9. pH was immediatly tested after completion

pH: 3.00

note: Formulation resulted in a uniform white suspension with a large amount of foam. Foam subsided in about 10-15 minutes and small particulates appeared in about 30 minutes at the bottom of the flask

To Page No. ____

sed & Understood by me,	Date	Invented by:	Date
MSH	7/12/2016	Recorded by:	

Exhibit D - Dr. Govindarajan Process

4

formulation: X-form
ED

Product: Triamcinolone Acetonide and Azelastine HCl nasal spray Book No:

Lot No: 1345-004 Company:

Time Point:

Analysis Performed: Trial suspension preparation Initials/Date: SP 10 Jun 2016

Purpose: Preparation of a trial batch of triamcinolone acetonide (0.05%) and azelastine HCl (0.07%) nasal spray. Expt. Ref. 1345-004

Composition for a 100mL batch (ingredient details - pg 3)

MSH 7/14/16

Ingredient	Target qty	Actual quantity	Quantity
① Triamcinolone Acetonide	0.05g	0.05011g	50.3 mg
② Azelastine HCl	0.07g	0.07023g	69.7mg
③ Polysorbate 80	0.05g	0.05040g	57.8 mg
④ Glycerin	2.00g	1.994g	1,991.2mg
⑤ Hypromellose *	1.00g	0.9989g	1.0094g
⑥ Sodium chloride	0.90g	0.9012g	0.8998g
⑦ Edetic Acid	0.05g	0.05072g	52.9mg
⑧ Benzalkonium chloride	0.02g	0.01981g	21.6mg
⑨ Purified water	qs 100mL	qs 100mL	✓QS'd to 100mL

*HPMC E3-LV was used

Procedure: In this attempt to prepare a nasal spray with the composition listed above ingredients ②, ⑥ and ⑧ will be weighed out and transferred to approximately ~~500~~ SP 10 Jun 2016 50mL of deionized water under stirring till all of them dissolve. ⑤ will be added under vigorous stirring to generate a vortex. ⑤ will be slowly sprinkled into the solution. After addition is complete stirring will continue till a clear dispersion is obtained. ③, ④, ① and ⑦ will be added sequentially into a vial and the contents will be mixed well on a vortex mixer followed by sonication. A small portion of the purified water will be added under stirring to obtain a pourable dispersion. This dispersion will be added to the aqueous phase containing ②, ⑤, ⑥ ⑧ and a portion of the water, while being mixed with a homogenizer.

Analysis by: S. Rapalli Reviewed by:

Date: 10 Jun 2016 Date:

To Page No. 5

Product: See page 4. Book No:

Lot No: Company:

Time Point:

Analysis Performed: Initials/Date: SRp 10 Jun 2016

when homogenization is complete, sufficient water will be used to rinse the container originally used to prepare a mixture of ① ③ ④ & ⑦ and transferred to the bulk container. Homogenization will be continued till a uniform dispersion is visually confirmed. Additional water may be added to adjust the final volume to 100 mL and appropriate additional mixing will be carried out. The final preparation will be filled into a suitable container for observation.

11-Jun-2016 - This procedure will incorporate edetic acid as a slurry in glycerin and poly-sorbate 80 and upon addition to the aqueous phase with homogenization is expected to dissolve to the extent of its solubility in the vehicle.

13-Jun-2016

☑ Benzalkonium chloride was transferred (weighed out) in a 20 mL vial and approximately 10 mL of water was added. ☑ The contents were mixed manually to obtain a solution.

☑ In a 100 mL beaker, approximately 30 mL of water was transferred ☑ and the weighed quantity of Sodium chloride was added to it under stirring using a magnetic stir-bar. When the Sodium chloride had dissolved, ☑ the benzalkonium chloride solution was transferred to the beaker ☑ and additional 10 mL of water was used to rinse out the vial and transferred to the beaker. ☑ Azlantine HCl was then weighed out and transferred to the aqueous solution. Under stirring. ☑ After about a minute of stirring

Analysis by: S. Rajput Reviewed by:

Date: 13 Jun 2016 Date:

To Page No. 6

Product: See page 4 Book No.:

Lot No: Company:

Time Point:

Analysis Performed: Initials/Date: SP 13 Jun 2016

the beaker was placed in an ultra sonic bath for 1 min to break up the few remaining undissolved aggregates of azelaic HA to facilitate dissolution. An additional 1 minute of stirring yielded a clear solution. While stirring to create a vortex the hypromellose was weighed out and sprinkled into the solution. The solution was continued to stir to hydrate and disperse the hypromellose to yield a clear solution. This aqueous solution was stirred using a magnetic stir bar while the second pre-mix of ingredients was prepared. Glycerin, Polysorbate 80, triamcinolone acetonide and edetic acid were weighed out and transferred into a 20mL vial. The contents were mixed on a vortex mixer for 30 seconds to yield a uniform slurry. Approximately 8mL of water was added to this slurry while being mixed with a magnetic stir-bar. This yielded a hazy dispersion of the solids in the water + glycerin + polysorbate 80 vehicle. The magnetic stir-bars were removed from both containers. The beaker containing the aqueous solution was placed on the homogenizer stand and the contents were mixed at 2800 rpm. The dispersion containing the undissolved solids was added to the beaker while being mixed. Additional water was added to the vial, and the rinse water was added to the beaker in two portions of 10mL each. Homogenization was continued for 5 min at 6000 rpm. The homogenization tool was raised on the beaker cover. The contents were allowed to stand for

Did not dissolve see 2 photos ↓ proceeded anyway

The HPMC mixture did not form a clear soln.

Glycerin, Polysorbate 80 were weighed directly into the vial after taring the balance

IKA T25 Ultra Turrax was used @ same RR RPMs

Analysis by: S. Lopez Reviewed by:

Date: 13-Jun-2016 Date:

To Page No. 7

Product: See page 4 Book No.:

Lot No.: Company:

Time Point:

Analysis Performed: Initials/Date: S Rp 13 Jun 2016

the foam to subside. ① The final volume was made up to 100 mL and homogenized at 6000 rpm | 5 min. The preparation was stored overnight to be observed the next day in a stoppered vial.

→ pH = 3.04

14-Jun-2016

The preparation was a cloudy dispersion. It exhibited presence of fine settled solid upon shaking. The solid was easily redispersed upon gentle agitation by overturning the vial 3-4 times.

The contents were transferred to a 250 mL beaker and homogenized at 1000 rpm for 10 min. The final preparation was transferred back to a stoppered 100 mL capacity Serum vial and stored at room temperature.

① On 13-Jun-2016, the final volume was made up by transferring the contents to a 250 mL beaker marked for 100 mL volume and making up volume by adding water used to rinse out the original container ~~and~~ S. Rp 14-Jun-2016

Conclusion - A uniform suspension product was prepared. Although settling of the suspended solid was observed, the sediment was readily and uniformly resuspended with gentle agitation.

S. Rp 14 Jun 2016

- formulation was uniformly dispersed
- Formulation was able to be sprayed

Analysis by: S. Rampal Reviewed by:

Date: 14-Jun-2016 Date:

To Page No.: END

Exhibit E - 7 Day pH results

pH Testing

Project No. _____

Book No. _____

Page No. ____

7 day pH of Bulk Testing

MaL-A : 2.73

MaL-B : 2.71

MaL-C : 2.71

MaL-D : 2.71

HS-D in : ~~2.97~~ 2.97

pen error MJH 7/22/2016

X-A : 2.75

To Page No. ____

ed & Understood by me, MJH

Date 7/22/2016

Invented by:

Date

Received by:

Exhibit F - 7 Day Appearance

Project No. _____

Book No. _____ TITLE _____

From Page No. ____

7 day Appearance

Mal-A: Clearly ~~v~~visible settling w/ ~~cloudly~~ Cloudy faint Aqueous phase

Mal-B: Slight settling of particulates w/a more cloudy aqueous phase

Mal-C: Clearly visible settling w/ cloudy faint Aqueous phase

Mal-D: Very small amount of settled material at bottom of flask. Cloudy white aqueous phase.

Redispersability observations

Mal-A: upon swirling settled particles were redispersed but within a few minutes they would begin to set

Mal-B: upon swirling the increase thickness didn't not allow for complete resuspension of particulates

Mal-C: Upon swirling settle particles were redispersed but beg to settle back within only a few minutes.

Mal-D: upon swirling the was obvious difficulty in redispe-ing the particles. Some particulates remained @ the bottom

To Page No. ____

Witnessed & Understood by me,	Date	Invented by:	Date
MSR	7/22/2016	Recorded by:	

Project No. _____

Book No. _____

age No. ____

Redispersability Cont.:

HSD: upon swirling, there's difficulty resuspending the particulates however, most of the material eventually was redispersed.

X-form: Particles were very easily dispersed but settled very rapidly

To Page No. ____

ed & Understood by me,	Date	Invented by:	Date
MSD	7/22/2016	Recorded by:	

Exhibit G - Sprayability after 7 days

Project No. _____

Book No. _____

Page No. ____

7-day Sprayability

Sp

Mal-A: Formulation produced a uniform spray

Mal-C: Formulation produced a uniform spray

To Page No. ____

ed & Understood by me,

MSH

Date

7/22/2016

Invented by:

Date

Recorded by:

Exhibit H - Mal A Delivered Dose Uniformity and Assay

Bulk Blend Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-A

Product Attribute Bulk Blend Uniformity
Analyte Triamcinolone Acetonide
Method HPLC- Isocratic 40% CAN

Testing Type Bulk Uniformity Assay
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 5.1 mL
Theoretical Conc. 500 ug per sample

HPMC Grade: E3 LV
Triamcinolone Raw/Unprocessed

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
	53.2667	2141220.091

		Sample Lot No.	Sample No.	Sample Volume	Peak Area	Concentration (ug/mL)	% Theoretical
Freshly Prepared	Top	MAL-A-T-1	MAL-A-Assay-1	0.1	314721	399.3	79.9
		MAL-A-T-2	MAL-A-Assay-2	0.1	338022	428.9	85.8
		MAL-A-T-3	MAL-A-Assay-3	0.1	292568	371.2	74.2
	Middle	MAL-A-M-1	MAL-A-Assay-4	0.1	397102	503.8	100.8
		MAL-A-M-2	MAL-A-Assay-5	0.1	392264	497.7	99.5
		MAL-A-M-3	MAL-A-Assay-6	0.1	390825	495.8	99.2
	Bottom	MAL-A-B-1	MAL-A-Assay-7	0.1	393881	499.7	99.9
		MAL-A-B-2	MAL-A-Assay-8	0.1	408133	517.8	103.6
		MAL-A-B-3	MAL-A-Assay-9	0.1	403957	512.5	102.5
3 Hrs	Top	MAL-A-T-1	MAL-A-Assay-10	0.1	112028	142.1	28.4
		MAL-A-T-2	MAL-A-Assay-11	0.1	117995	149.7	29.9
		MAL-A-T-3	MAL-A-Assay-12	0.1	113416	143.9	28.8
	Middle	MAL-A-M-1	MAL-A-Assay-13	0.1	116932	148.4	29.7
		MAL-A-M-2	MAL-A-Assay-14	0.1	120166	152.5	30.5
		MAL-A-M-3	MAL-A-Assay-15	0.1	116419	147.7	29.5
	Bottom	MAL-A-B-1	MAL-A-Assay-16	0.1	122442	155.3	31.1
		MAL-A-B-2	MAL-A-Assay-17	0.1	123198	156.3	31.3
		MAL-A-B-3	MAL-A-Assay-18	0.1	121067	153.6	30.7
7 Day Redispersion	Top	MAL-A-T-1	MAL-A-Assay-7Day-1	1.0	1289138	163.6	32.7
		MAL-A-T-2	MAL-A-Assay-7Day-2	1.0	1334666	169.3	33.9
		MAL-A-T-3	MAL-A-Assay-7Day-3	1.0	1324753	168.1	33.6
	Middle	MAL-A-M-1	MAL-A-Assay-7Day-4	1.0	1406801	178.5	35.7
		MAL-A-M-2	MAL-A-Assay-7Day-5	1.0	1419063	180.0	36.0
		MAL-A-M-3	MAL-A-Assay-7Day-6	1.0	1447232	183.6	36.7
	Bottom	MAL-A-B-1	MAL-A-Assay-7Day-7	1.0	3265671	414.3	82.9
		MAL-A-B-2	MAL-A-Assay-7Day-8	1.0	3234240	410.3	82.1
		MAL-A-B-3	MAL-A-Assay-7Day-9	1.0	3180318	403.5	80.7

Samples Prepared on Date 7/13/2016 - 7/14/2016
Data Processed by and Date Matt Hayes 7/27/2016

Delivered Dose Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-A-1

Product Attribute Dose Uniformity
Analyte
Method

Testing Type Delivered Dose Uniformity
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 2.05 mL
Label Claim 50 ug per spray

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
	53.2667	2141220.091

22.77777778

		Pump Delivery				
Sample Lot No.	Sample No.	Dose Shot Weight (mg)	Peak Area	Concentration	Mass Delivered (ug)	% Label Claim
MAL-A-1-D1	1	90.4	384319	9.56	19.60	39.20
MAL-A-1-D2	2	90.5	358163	8.91	18.27	36.53
MAL-A-1-D3	3	91.5	392576	9.77	20.02	40.04
MAL-A-1-D4	4	93.6	393477	9.79	20.07	40.13
MAL-A-1-D5	5	90.4	374360	9.31	19.09	38.18
MAL-A-1-D6	6	92.9	376454	9.36	19.20	38.40
MAL-A-1-D7	7	92.7	466253	11.60	23.78	47.56
MAL-A-1-D8	8	93.7	593272	14.76	30.26	60.51
MAL-A-1-D9	9	93.0	690869	17.19	35.23	70.47
MAL-A-1-D10	10	93.1	713892	17.76	36.41	72.81
MAL-A-1-D51	11	96.6	741506	18.45	37.81	75.63
MAL-A-1-D52	12	96.9	809535	20.14	41.28	82.57
MAL-A-1-D53	13	95.7	801470	19.94	40.87	81.75
MAL-A-1-D54	14	94.5	798708	19.87	40.73	81.46
MAL-A-1-D55	15	95.3	804777	20.02	41.04	82.08
MAL-A-1-D56	16	94.1	792732	19.72	40.43	80.85
MAL-A-1-D57	17	94.2	795546	19.79	40.57	81.14
MAL-A-1-D58	18	95.9	814310	20.26	41.53	83.06
MAL-A-1-D59	19	95.7	820651	20.42	41.85	83.70
MAL-A-1-D60	20	95.3	807783	20.10	41.19	82.39
	Mean Pump Delivery (mg)	93.80				64.92 Mean
	Standard Deviation(mg)	2.01				19.62 Standard Deviation
	%RSD	2.14				30.22 %RSD
	Min	90.40				36.53 Min
	Max	96.90				83.70 Max

Samples Prepared on Date 7/13/2016 - 7/14/2016
Data Processed by and Date [signature] 7/27/2016

Delivered Dose Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-A-2

Product Attribute Dose Uniformity
Analyte
Method

Testing Type Delivered Dose Uniformity
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 2.05 mL
Label Claim 50 ug per spray

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
	53.2667	2141220.091

22.77777778

		Pump Delivery						
Sample Lot No.	Sample No.	Dose Shot Weight (mg)	Peak Area	Concentration	Mass Delivered (ug)	% Label Claim		
MAL-A-2-D1	1	91.8	545780	13.58	27.83	55.67		
MAL-A-2-D2	2	95.1	558563	13.90	28.49	56.97		
MAL-A-2-D3	3	95.6	618429	15.38	31.54	63.08		
MAL-A-2-D4	4	96.0	569673	14.17	29.05	58.10		
MAL-A-2-D5	5	94.7	537314	13.37	27.40	54.80		
MAL-A-2-D6	6	94.3	520911	12.96	26.57	53.13		
MAL-A-2-D7	7	96.0	552242	13.74	28.16	56.33		
MAL-A-2-D8	8	94.3	637127	15.85	32.49	64.98		
MAL-A-2-D9	9	96.5	735684	18.30	37.52	75.04		
MAL-A-2-D10	10	97.3	796752	19.82	40.63	81.26		
MAL-A-2-D51	11	95.5	701159	17.44	35.76	71.51		
MAL-A-2-D52	12	97.6	773729	19.25	39.46	78.92		
MAL-A-2-D53	13	96.1	834132	20.75	42.54	85.08		
MAL-A-2-D54	14	94.5	805004	20.03	41.05	82.11		
MAL-A-2-D55	15	95.3	808278	20.11	41.22	82.44		
MAL-A-2-D56	16	95.1	798066	19.85	40.70	81.40		
MAL-A-2-D57	17	95.0	817323	20.33	41.68	83.36		
MAL-A-2-D58	18	96.5	817115	20.33	41.67	83.34		
MAL-A-2-D59	19	95.2	823739	20.49	42.01	84.02		
MAL-A-2-D60	20	95.7	823316	20.48	41.99	83.97		
	Mean Pump Delivery (mg)	95.41				71.78	Mean	
	Standard Deviation(mg)	1.24				12.29	Standard Deviation	
	%RSD	1.30				17.12	%RSD	
	Min	91.80				53.13	Min	
	Max	97.60				85.08	Max	

Samples Prepared on Date 7/13/2016 - 7/14/2016

Data Processed by and Date Matt Hayes 7/27/2016

Delivered Dose Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-A-3

Product Attribute Dose Uniformity
Analyte
Method

Testing Type Delivered Dose Uniformity
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 2.05 mL
Label Claim 50 ug per spray

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
	53.2667	2141220.091

22.77777778

		Pump Delivery					
Sample Lot No.	Sample No.	Dose Shot Weight (mg)	Peak Area	Concentration (ug/mL	Mass Delivered (ug)	% Label Claim	
MAL-A-3-D1	1	91.2	388467	9.66	19.81	39.62	
MAL-A-3-D2	2	96.0	496790	12.36	25.34	50.67	
MAL-A-3-D3	3	94.2	660240	16.42	33.67	67.34	
MAL-A-3-D4	4	94.6	689291	17.15	35.15	70.30	
MAL-A-3-D5	5	94.5	676915	16.84	34.52	69.04	
MAL-A-3-D6	6	93.9	702958	17.49	35.85	71.70	
MAL-A-3-D7	7	95.8	743448	18.49	37.91	75.83	
MAL-A-3-D8	8	93.2	716930	17.83	36.56	73.12	
MAL-A-3-D9	9	99.7	745028	18.53	37.99	75.99	
MAL-A-3-D10	10	96.6	686371	17.07	35.00	70.01	
MAL-A-3-D51	11	96.2	638358	15.88	32.55	65.11	
MAL-A-3-D52	12	98.3	710702	17.68	36.24	72.49	
MAL-A-3-D53	13	97.4	765903	19.05	39.06	78.12	
MAL-A-3-D54	14	96.6	758870	18.88	38.70	77.40	
MAL-A-3-D55	15	97.0	760345	18.91	38.78	77.55	
MAL-A-3-D56	16	96.6	753660	18.75	38.43	76.87	
MAL-A-3-D57	17	95.4	751078	18.68	38.30	76.61	
MAL-A-3-D58	18	94.8	742007	18.46	37.84	75.68	
MAL-A-3-D59	19	95.1	740974	18.43	37.79	75.58	
MAL-A-3-D60	20	96.4	743835	18.50	37.93	75.87	
	Mean Pump Delivery (mg)	95.68				70.74	Mean
	Standard Deviation(mg)	1.87				9.66	Standard Deviation
	%RSD	1.96				13.65	%RSD
	Min	91.20				39.62	Min
	Max	99.70				78.12	Max

Samples Prepared on Date 7/13/2016 - 7/14/2016

Data Processed by and Date Matt Hyde 7/27/2016

Exhibit I - Mal-C Delivered Dose Uniformity and Assay

Bulk Blend Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-C

Product Attribute Bulk Blend Uniformity
Analyte Triamcinolone Acetonide
Method HPLC- Isocratic 40% CAN

HPMC Grade: E3 LV
Triamcinolone Micronized

Testing Type Bulk Uniformity Assay
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 5.1 mL
Theoretical Conc. 500 ug per sample

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
	53.2667	2141220.091

		Sample Lot No.	Sample No.	Sample Volume	Peak Area	Concentration (ug/mL)	% Theoretical
Freshly Prepared	Top	MAL-C-T-1	MAL-A-Assay-1	0.1	393590	499.4	99.9
		MAL-C-T-2	MAL-A-Assay-2	0.1	407648	517.2	103.4
		MAL-C-T-3	MAL-A-Assay-3	0.1	410803	521.2	104.2
	Middle	MAL-C-M-1	MAL-A-Assay-4	0.1	407469	517.0	103.4
		MAL-C-M-2	MAL-A-Assay-5	0.1	401585	509.5	101.9
		MAL-C-M-3	MAL-A-Assay-6	0.1	397062	503.8	100.8
	Bottom	MAL-C-B-1	MAL-A-Assay-7	0.1	410963	521.4	104.3
		MAL-C-B-2	MAL-A-Assay-8	0.1	406560	515.8	103.2
		MAL-C-B-3	MAL-A-Assay-9	0.1	410579	520.9	104.2
3 Hrs	Top	MAL-C-T-1	MAL-A-Assay-10	0.1	312031	395.9	79.2
		MAL-C-T-2	MAL-A-Assay-11	0.1	324622	411.9	82.4
		MAL-C-T-3	MAL-A-Assay-12	0.1	328653	417.0	83.4
	Middle	MAL-C-M-1	MAL-A-Assay-13	0.1	342757	434.9	87.0
		MAL-C-M-2	MAL-A-Assay-14	0.1	348382	442.0	88.4
		MAL-C-M-3	MAL-A-Assay-15	0.1	349216	443.1	88.6
	Bottom	MAL-C-B-1	MAL-A-Assay-16	0.1	367465	466.2	93.2
		MAL-C-B-2	MAL-A-Assay-17	0.1	359682	456.3	91.3
		MAL-C-B-3	MAL-A-Assay-18	0.1	369065	468.2	93.6
7 Day Redispersion	Top	MAL-C-T-1	MAL-A-Assay-7Day-1	1.0	3316568	420.8	84.2
		MAL-C-T-2	MAL-A-Assay-7Day-2	1.0	3472049	440.5	88.1
		MAL-C-T-3	MAL-A-Assay-7Day-3	1.0	3453757	438.2	87.6
	Middle	MAL-C-M-1	MAL-A-Assay-7Day-4	1.0	3395260	430.8	86.2
		MAL-C-M-2	MAL-A-Assay-7Day-5	1.0	3480739	441.6	88.3
		MAL-C-M-3	MAL-A-Assay-7Day-6	1.0	3479461	441.4	88.3
	Bottom	MAL-C-B-1	MAL-A-Assay-7Day-7	1.0	3485904	442.3	88.5
		MAL-C-B-2	MAL-A-Assay-7Day-8	1.0	3592919	455.8	91.2
		MAL-C-B-3	MAL-A-Assay-7Day-9	1.0	3615499	458.7	91.7

Samples Prepared on Date 7/13/2016 - 7/14/2016
Data Processed by and Date Matt Hugh 7/27/2016

Delivered Dose Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-C-1

Product Attribute Dose Uniformity
Analyte
Method

Testing Type Delivered Dose Uniformity
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 2.05 mL
Label Claim 50 ug per spray

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
#REF!	53.2667	2141220.091

22.77777778

		Pump Delivery						
Sample Lot No.	Sample No.	Dose Shot Weight (mg)	Peak Area	Concentration	Mass Delivered (ug)	% Label Claim		
MAL-C-1-D1	1	91.6	883386	21.98	45.05	90.10		
MAL-C-1-D2	2	88.1	861978	21.44	43.96	87.92		
MAL-C-1-D3	3	91.5	909069	22.61	46.36	92.72		
MAL-C-1-D4	4	93.5	915560	22.78	46.69	93.38		
MAL-C-1-D5	5	91.7	904654	22.50	46.14	92.27		
MAL-C-1-D6	6	93.6	924588	23.00	47.15	94.30		
MAL-C-1-D7	7	94.6	924619	23.00	47.15	94.31		
MAL-C-1-D8	8	92.0	902395	22.45	46.02	92.04		
MAL-C-1-D9	9	96.3	941412	23.42	48.01	96.02		
MAL-C-1-D10	10	97.4	899487	22.38	45.87	91.74		
MAL-C-1-D51	11	95.2	901492	22.43	45.97	91.95		
MAL-C-1-D52	12	95.1	919692	22.88	46.90	93.80		
MAL-C-1-D53	13	95.3	935705	23.28	47.72	95.44		
MAL-C-1-D54	14	95.8	942959	23.46	48.09	96.18		
MAL-C-1-D55	15	95.7	951399	23.67	48.52	97.04		
MAL-C-1-D56	16	95.2	940076	23.39	47.94	95.88		
MAL-C-1-D57	17	95.4	943899	23.48	48.14	96.27		
MAL-C-1-D58	18	95.1	940820	23.40	47.98	95.96		
MAL-C-1-D59	19	96.8	950258	23.64	48.46	96.92		
MAL-C-1-D60	20	95.6	943139	23.46	48.10	96.20		
	Mean Pump Delivery (mg)	94.28				94.02	Mean	
	Standard Deviation(mg)	2.27				2.48	Standard Deviation	
	%RSD	2.41				2.63	%RSD	
	Min	88.10				87.92	Min	
	Max	97.40				97.04	Max	

Samples Prepared on Date 7/13/2016 - 7/27/2016

Data Processed by and Date Matt Hayes 7/27/2016

Delivered Dose Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-C-2

Product Attribute Dose Uniformity
Analyte
Method

Testing Type Delivered Dose Uniformity
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 2.05 mL
Label Claim 50 ug per spray

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
	53.2667	2141220.091

22.77777778

		Pump Delivery				
Sample Lot No.	Sample No.	Dose Shot Weight (mg)	Peak Area	Concentration	Mass Delivered (ug)	% Label Claim
MAL-C-2-D1	1	86.0	851183	21.17	43.41	86.82
MAL-C-2-D2	2	87.7	863755	21.49	44.05	88.10
MAL-C-2-D3	3	89.7	888543	22.10	45.31	90.63
MAL-C-2-D4	4	91.2	894917	22.26	45.64	91.28
MAL-C-2-D5	5	91.9	909693	22.63	46.39	92.78
MAL-C-2-D6	6	91.7	900664	22.41	45.93	91.86
MAL-C-2-D7	7	92.6	904939	22.51	46.15	92.30
MAL-C-2-D8	8	93.6	913583	22.73	46.59	93.18
MAL-C-2-D9	9	92.3	902018	22.44	46.00	92.00
MAL-C-2-D10	10	92.7	906954	22.56	46.25	92.50
MAL-C-2-D51	11	92.7	887416	22.08	45.26	90.51
MAL-C-2-D52	12	93.7	910281	22.64	46.42	92.84
MAL-C-2-D53	13	95.9	932866	23.21	47.57	95.15
MAL-C-2-D54	14	93.6	920440	22.90	46.94	93.88
MAL-C-2-D55	15	95.3	928125	23.09	47.33	94.66
MAL-C-2-D56	16	93.7	913397	22.72	46.58	93.16
MAL-C-2-D57	17	93.9	913455	22.72	46.58	93.17
MAL-C-2-D58	18	92.4	905100	22.52	46.16	92.32
MAL-C-2-D59	19	76.7	751335	18.69	38.32	76.63
MAL-C-2-D60	20	79.0	774138	19.26	39.48	78.96
	Mean Pump Delivery (mg)	90.82				90.64 Mean
	Standard Deviation(mg)	5.01				4.82 Standard Deviation
	%RSD	5.52				5.32 %RSD
	Min	76.70				76.63 Min
	Max	95.90				95.15 Max

Samples Prepared on Date 7/13/2016 - 7/14/2016

Data Processed by and Date [signature] 7/27/2016

Delivered Dose Uniformity for Triamcinolone Acetonide

Product Name Triamcinolone Acetonide /Azelastine Nasal Spray
Product Lot No. MAL-C-3

Product Attribute Dose Uniformity
Analyte
Method

Testing Type Delivered Dose Uniformity
HPLC Run Log N/A
Medium Formulation Matrix + 70%ACN

Sample Volume 2.05 mL
Label Claim 50 ug per spray

System suitability Working Standard A		
Reference	Concentration (ug/mL)	Peak Area
#REF!	53.2667	2141220.091

22.77777778

		Pump Delivery						
Sample Lot No.	Sample No.	Dose Shot Weight (mg)	Peak Area	Concentration	Mass Delivered (ug)	% Label Claim		
MAL-C-3-D1	1	81.0	545573	13.57	27.82	55.65		
MAL-C-3-D2	2	89.6	768647	19.12	39.20	78.40		
MAL-C-3-D3	3	91.6	938351	23.34	47.85	95.71		
MAL-C-3-D4	4	90.6	949997	23.63	48.45	96.89		
MAL-C-3-D5	5	94.4	973566	24.22	49.65	99.30		
MAL-C-3-D6	6	93.9	946823	23.55	48.29	96.57		
MAL-C-3-D7	7	94.1	936160	23.29	47.74	95.48		
MAL-C-3-D8	8	94.2	934169	23.24	47.64	95.28		
MAL-C-3-D9	9	93.9	933174	23.21	47.59	95.18		
MAL-C-3-D10	10	93.6	922441	22.95	47.04	94.08		
MAL-C-3-D51	11	65.5	901703	22.43	45.98	91.97		
MAL-C-3-D52	12	93.9	905648	22.53	46.19	92.37		
MAL-C-3-D53	13	94.2	918922	22.86	46.86	93.73		
MAL-C-3-D54	14	94.0	918210	22.84	46.83	93.65		
MAL-C-3-D55	15	93.3	914183	22.74	46.62	93.24		
MAL-C-3-D56	16	93.9	911727	22.68	46.50	92.99		
MAL-C-3-D57	17	92.6	900444	22.40	45.92	91.84		
MAL-C-3-D58	18	93.3	908540	22.60	46.33	92.67		
MAL-C-3-D59	19	94.4	919272	22.87	46.88	93.76		
MAL-C-3-D60	20	94.2	917349	22.82	46.78	93.56		
	Mean Pump Delivery (mg)	91.31				91.62	Mean	
	Standard Deviation(mg)	6.79				9.37	Standard Deviation	
	%RSD	7.44				10.22	%RSD	
	Min	65.50				55.65	Min	
	Max	94.40				99.30	Max	

Samples Prepared on Date 7/13/2016 - 7/14/2016

Data Processed by and Date Matt Hayes 7/27/2016

Exhibit J - Delivered Dose Uniformity

Delivered Dose Uniformity

Formulation: **Mal-A**

	Bottle #1	Bottle #2	Bottle #3
Mean Dose % Label Claim	**60.88**	**67.31**	**66.34**
Standard Deviation	**18.40**	**11.53**	**9.06**
%RSD	**30.22**	**17.12**	**13.65**
Min	**34.26**	**49.82**	**37.15**
Max	**78.49**	**79.78**	**73.25**

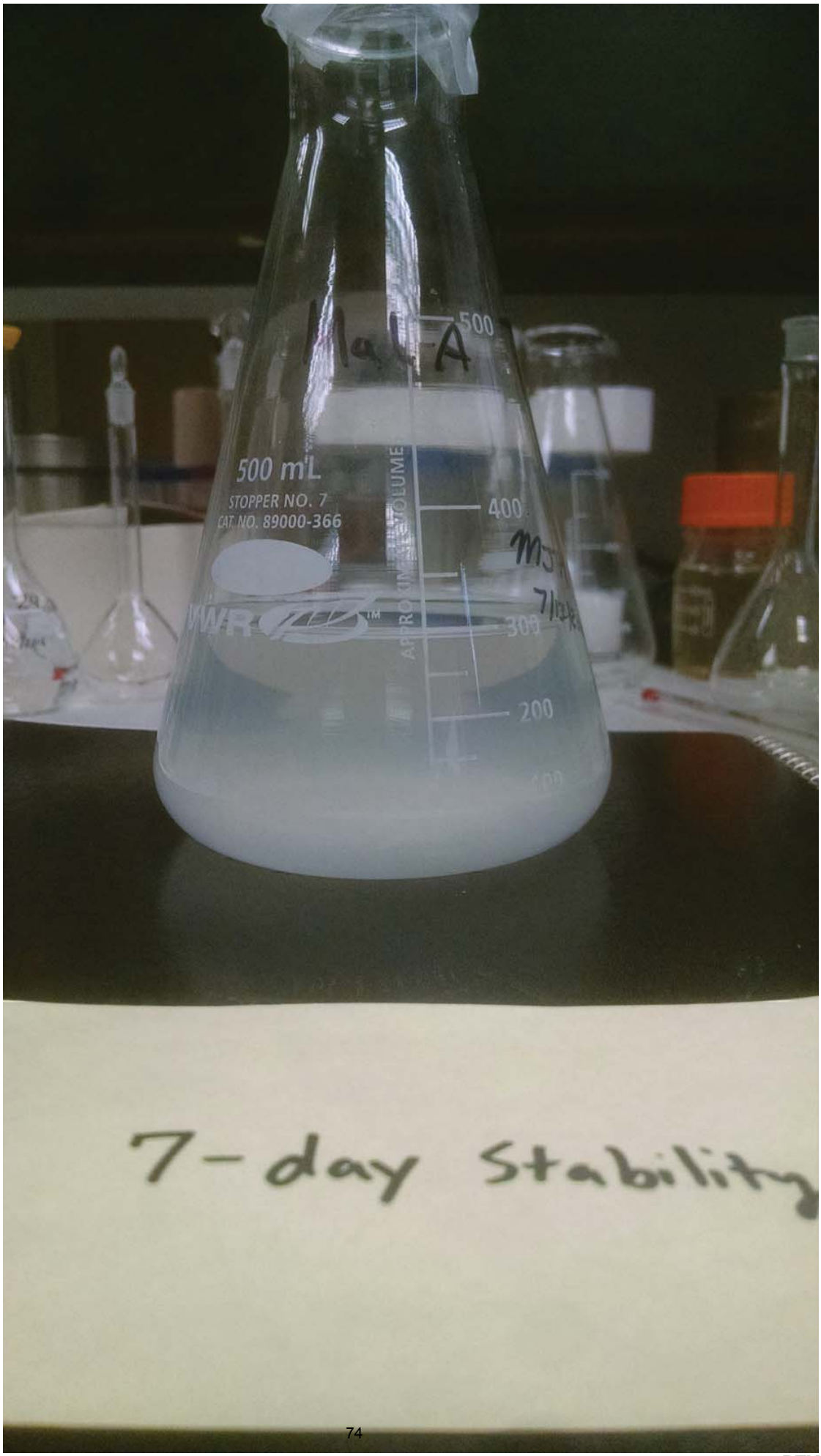
* Results calculated from the first 10 emitted doses after priming device. The middle 40 doses were wasted, and the final 10 doses were analyzed and averaged with the first 10 doses.

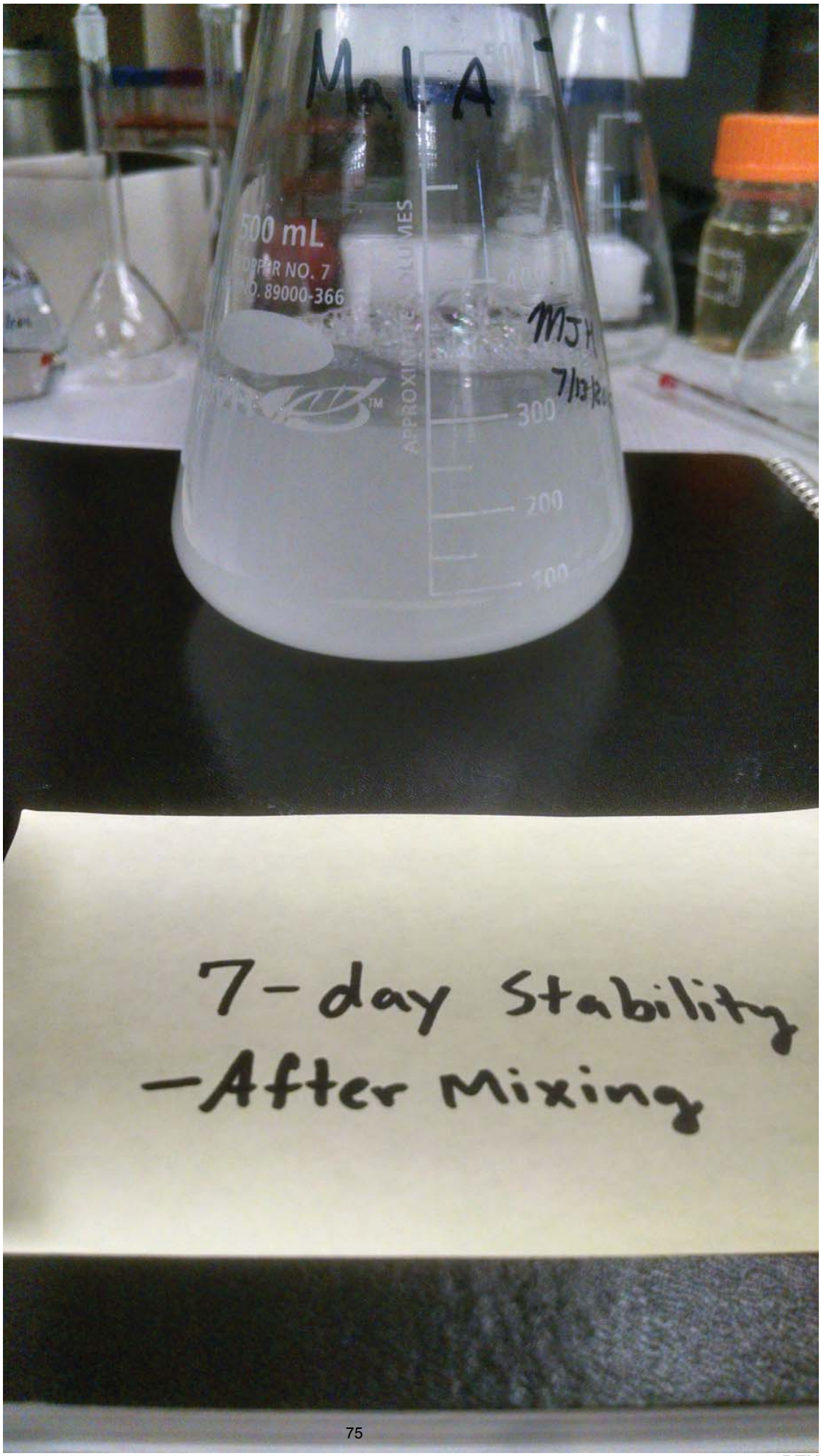
Formulation: **Mal-C**

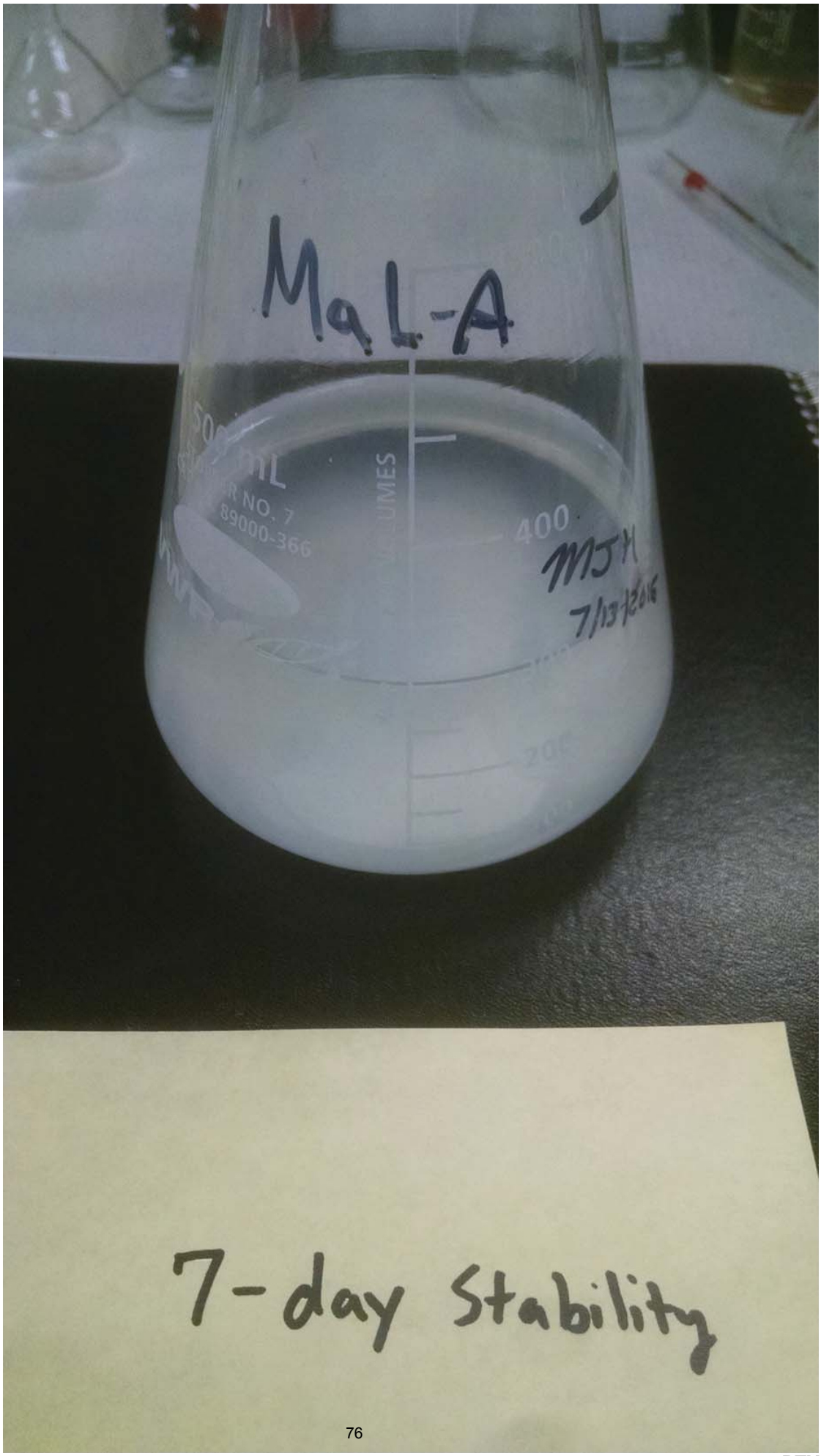
	Bottle #1	Bottle #2	Bottle #3
Mean Dose % Label Claim	**88.17**	**84.99**	**85.91**
Standard Deviation	**2.32**	**4.52**	**8.78**
%RSD	**2.63**	**5.32**	**10.22**
Min	**82.44**	**71.86**	**52.18**
Max	**91.00**	**89.22**	**93.12**

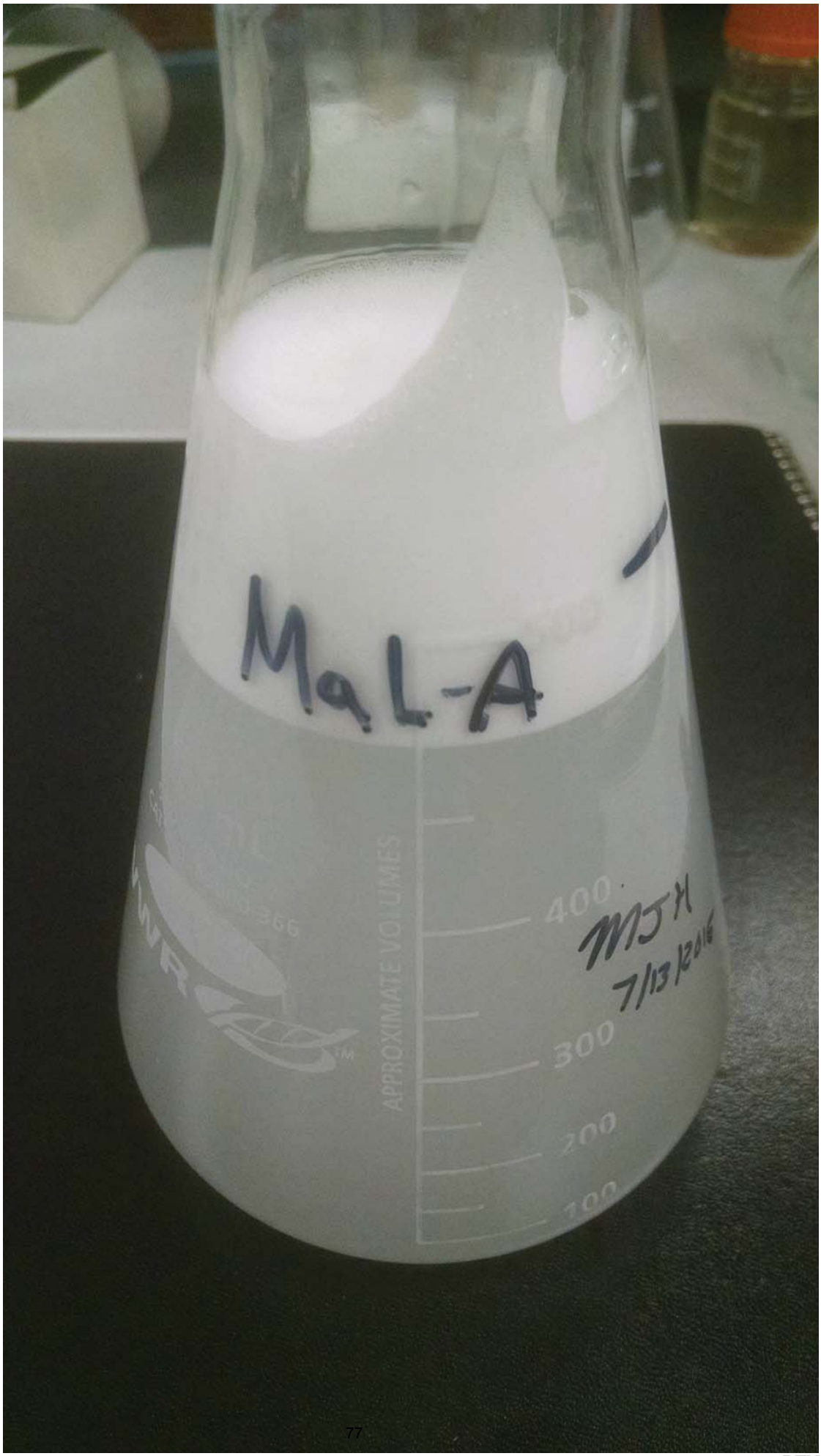
* Tests performed consistent with FDA Guidelines

Exhibit K – Mal A


500 mL
STOPPER NO. 7
CAT. NO. 89000-366
500
400
300
200
7-day Stability


MoLA
500 mL
APPROXIMATE VOLUMES
300
200
100
7-day Stability
-After Mixing


MaL-A
400
MJH
7/13/2016
7-day Stability


MaL-A
MJH
7/13/2016
APPROXIMATE VOLUMES
400
300
200
100

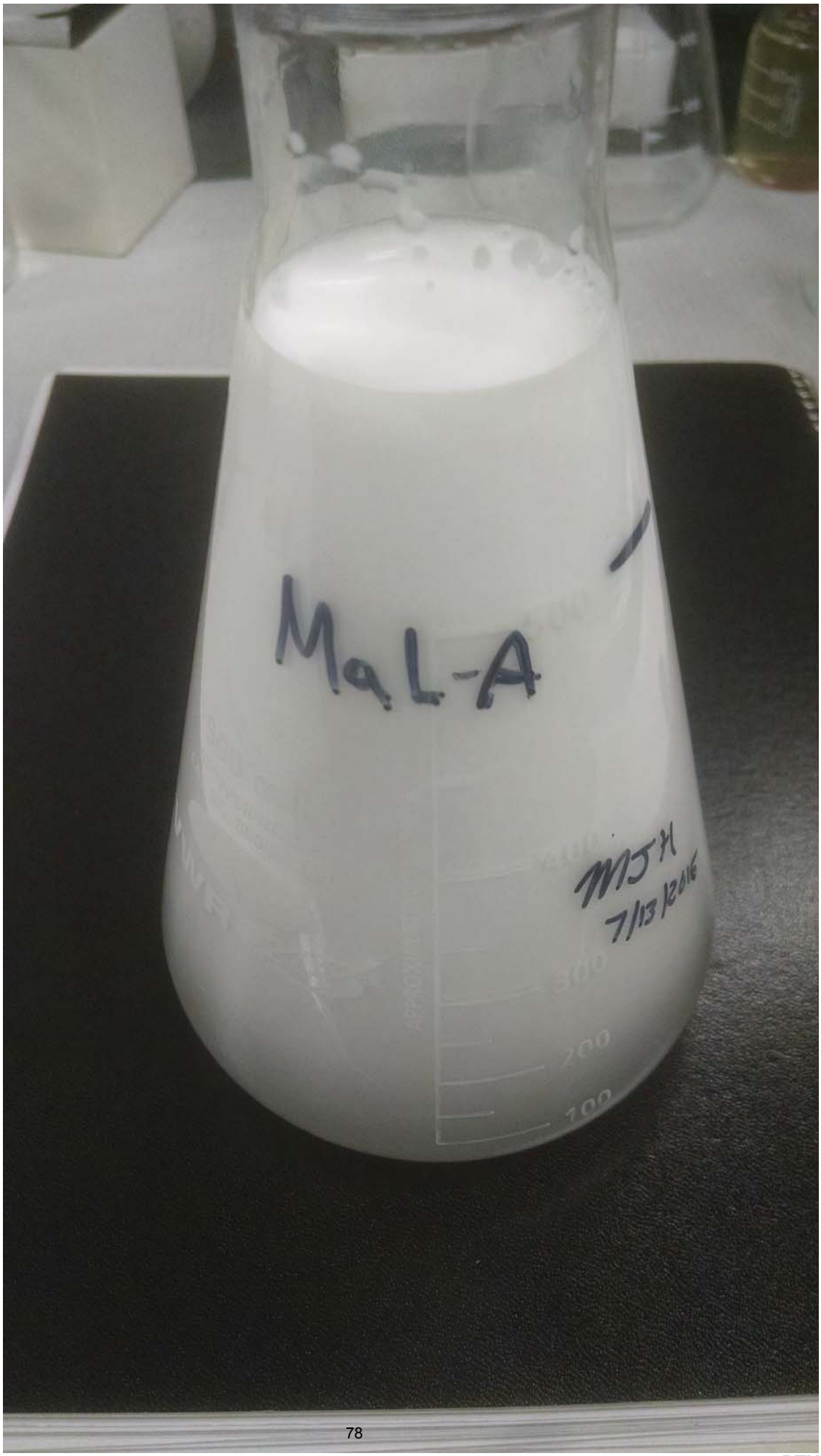
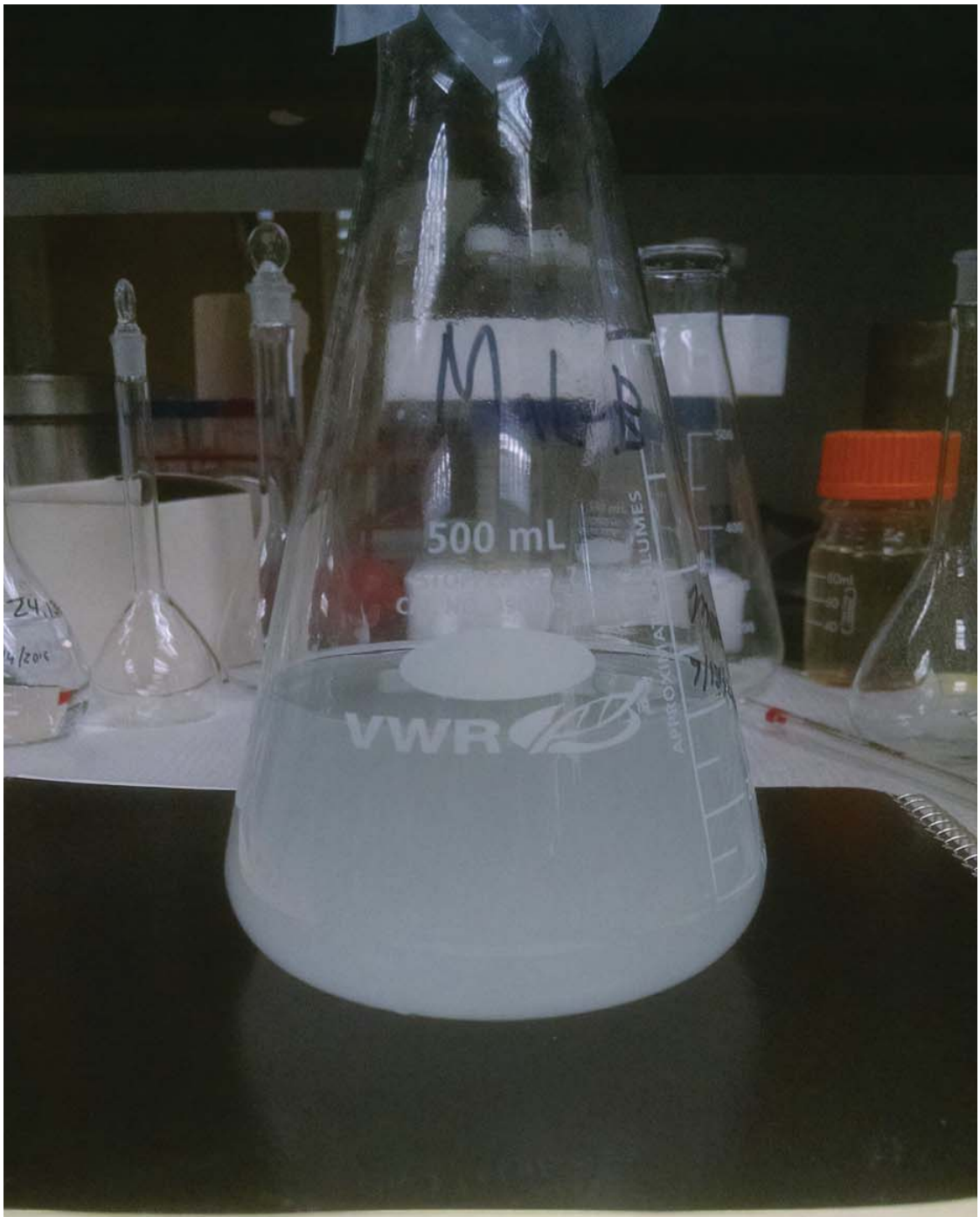
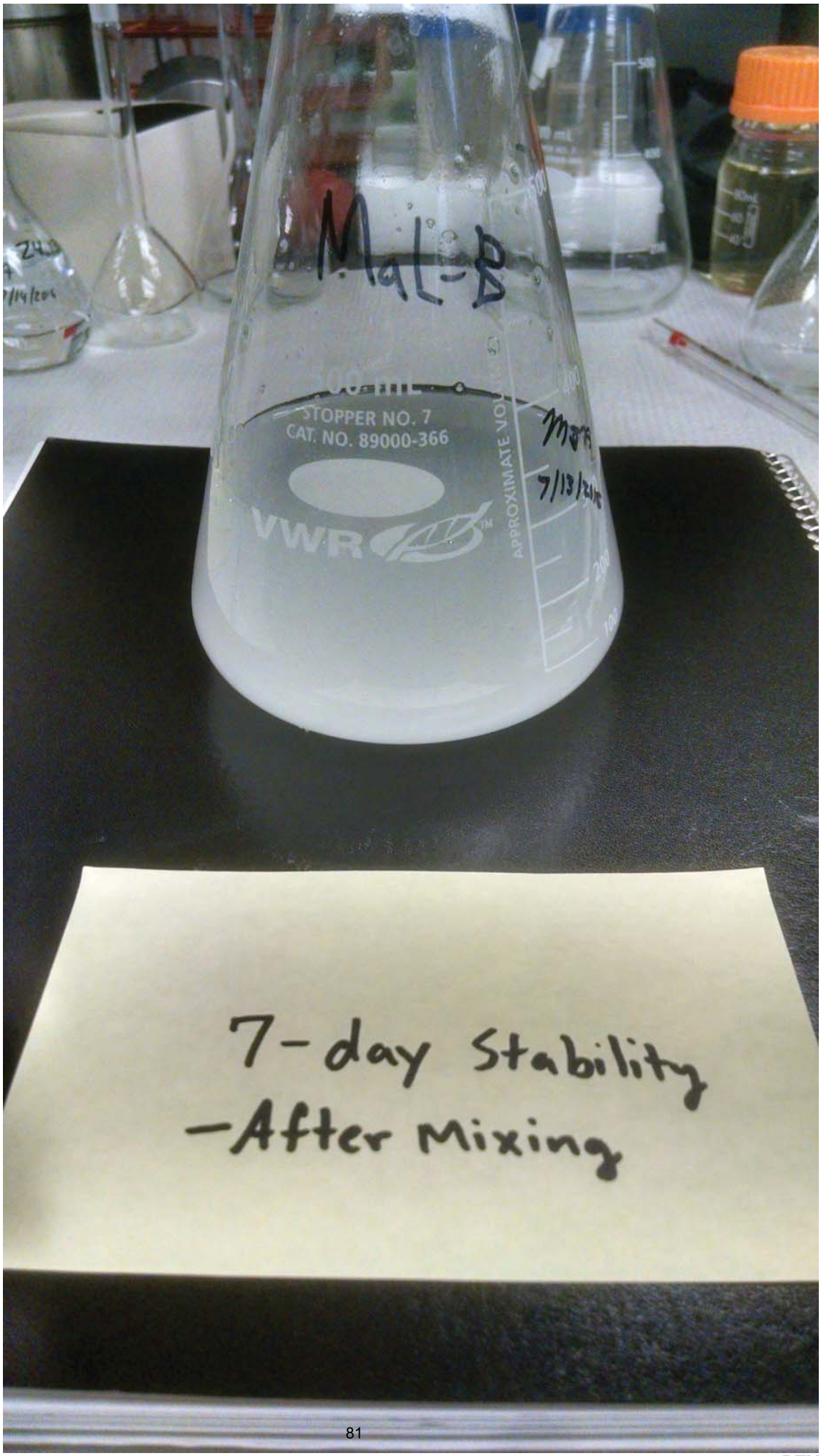
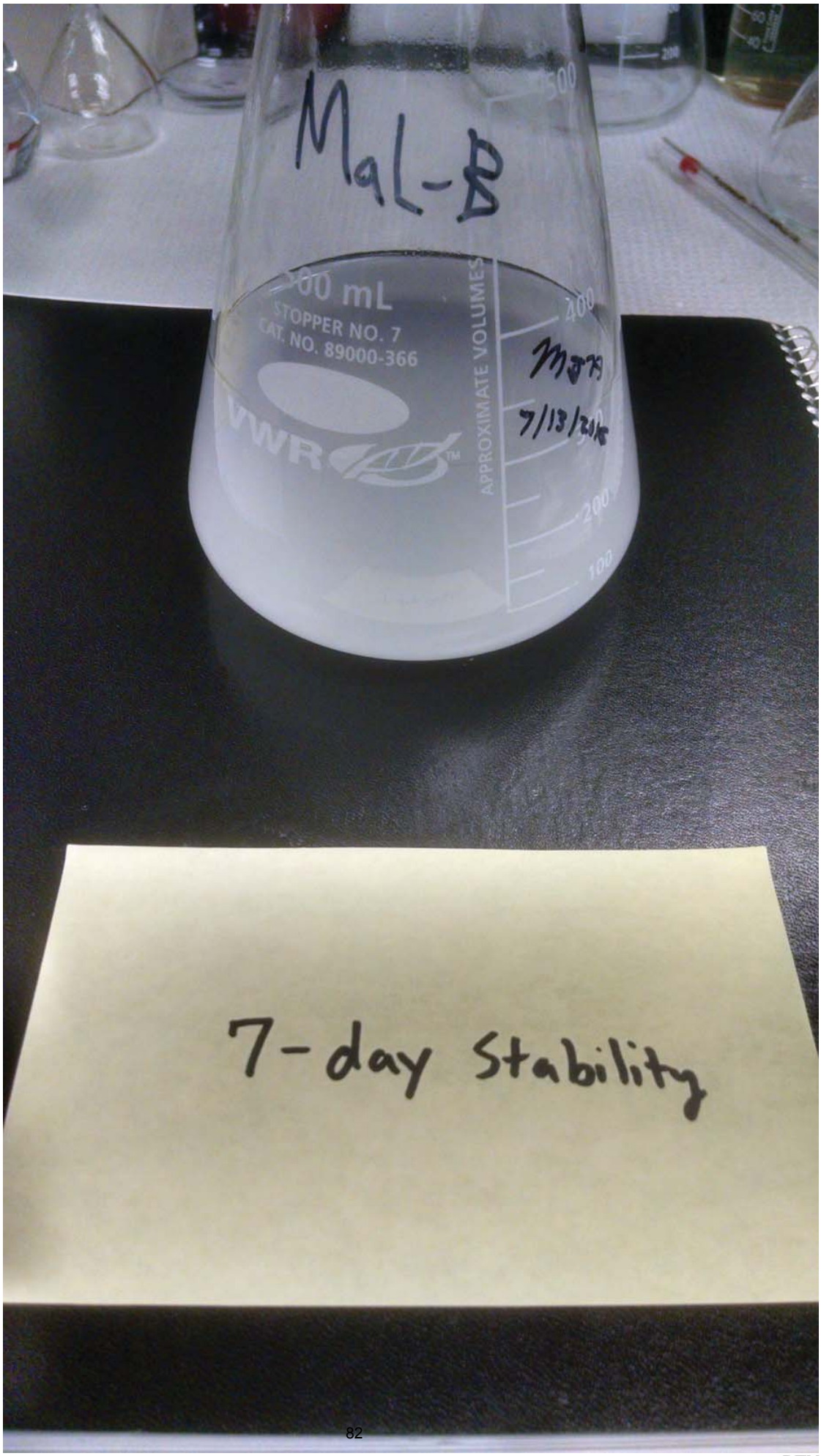

MaL-A
MJH
7/13/2016

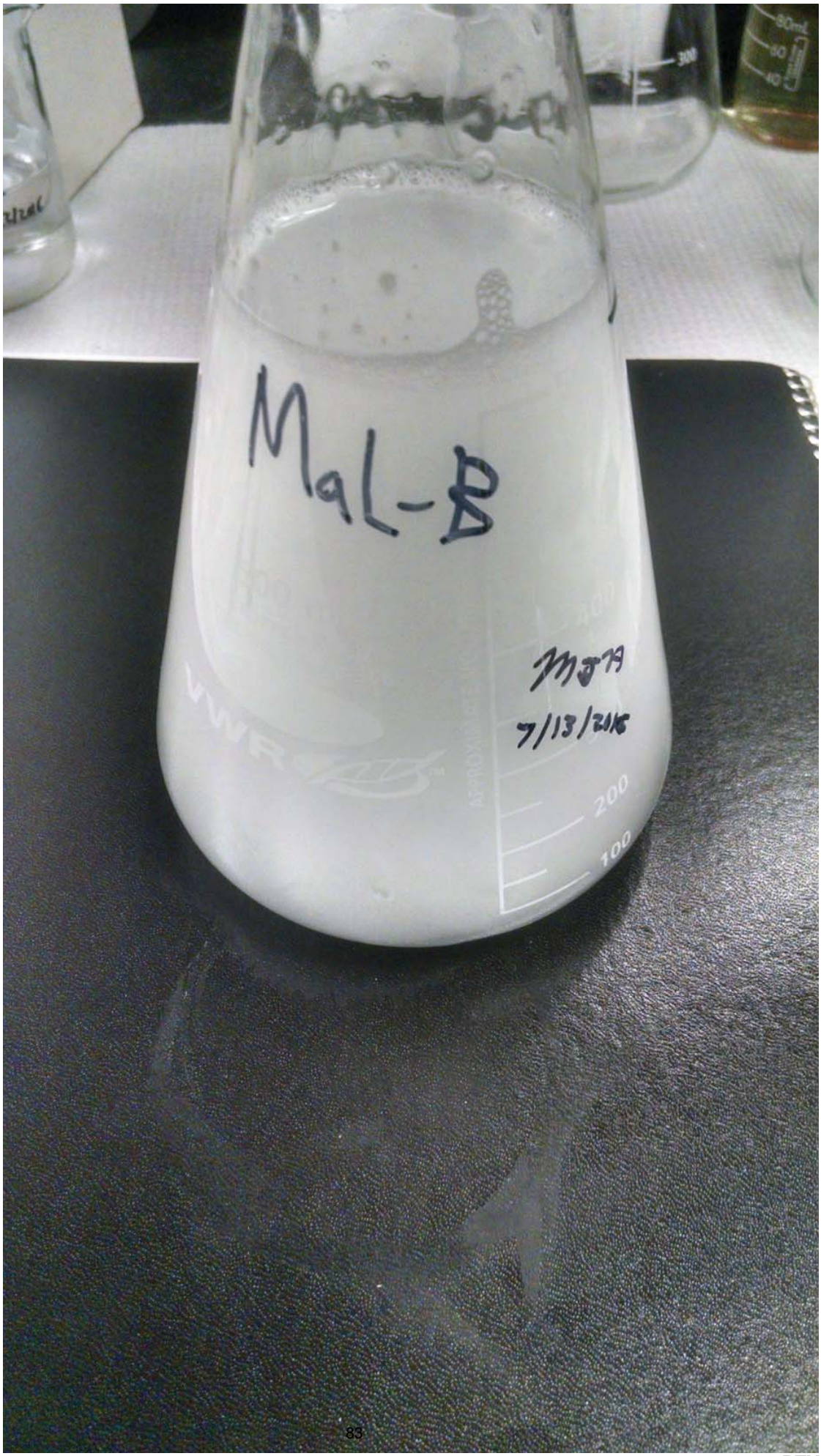
Exhibit L – Mal B



7-day Stability


Mal-B
STOPPER NO. 7
CAT. NO. 89000-366
VWR
7/13/24
7-day Stability
-After Mixing


MaL-B
APPROXIMATE VOLUMES
STOPPER NO. 7
CAT. NO. 89000-366
VWR
7/13/2016
7-day Stability


MaL-B
7/13/216
200
100

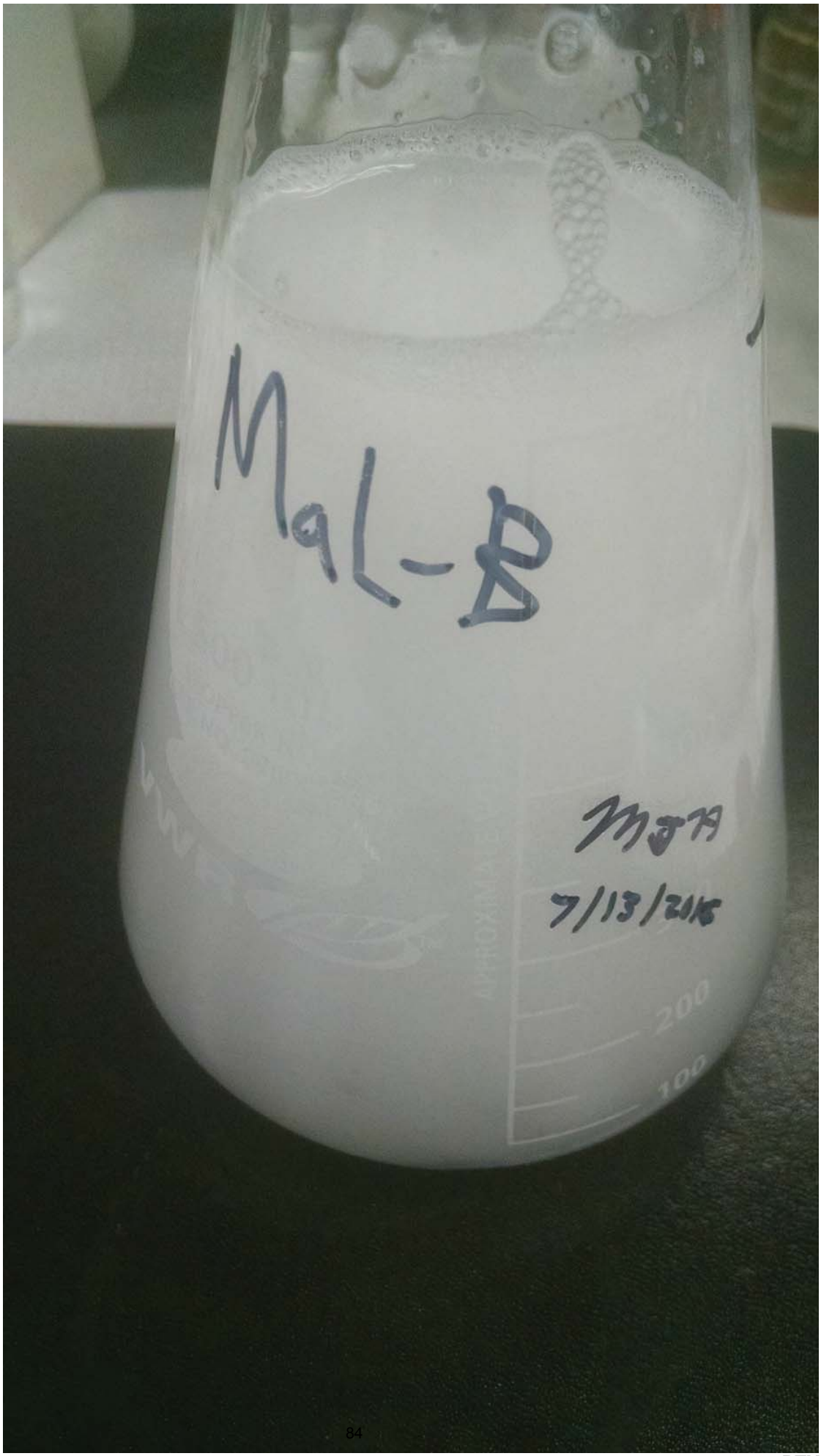
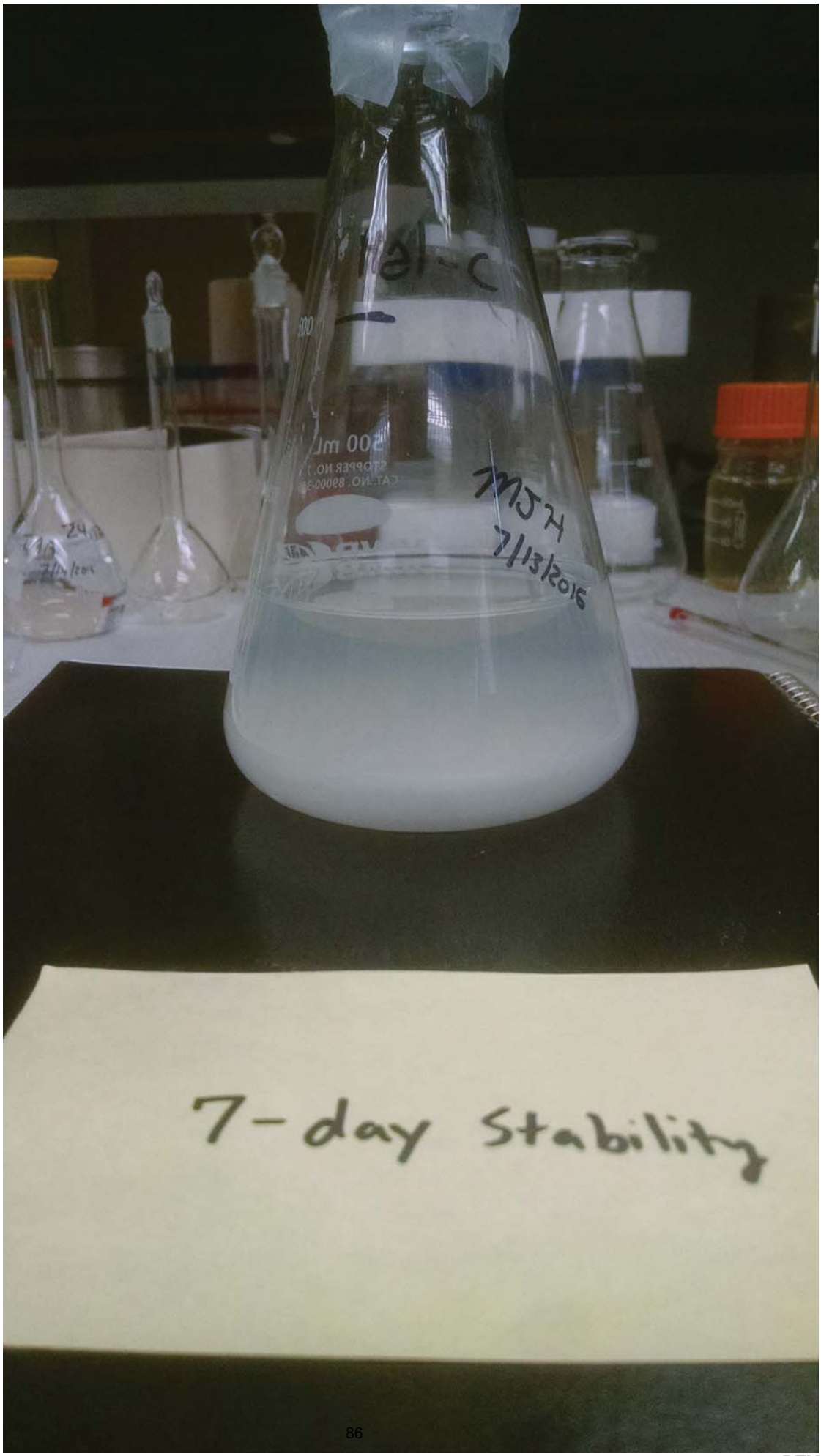
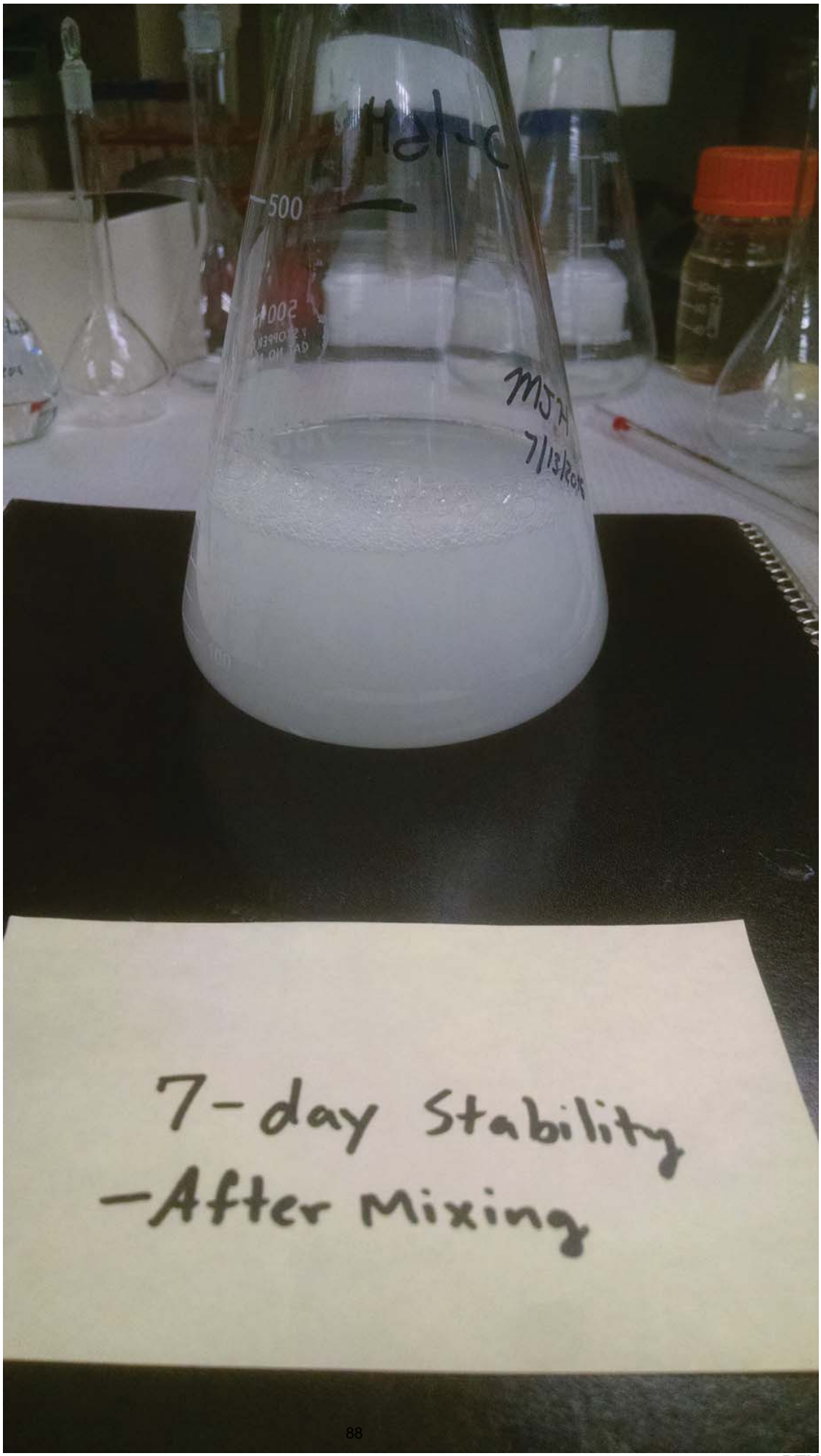
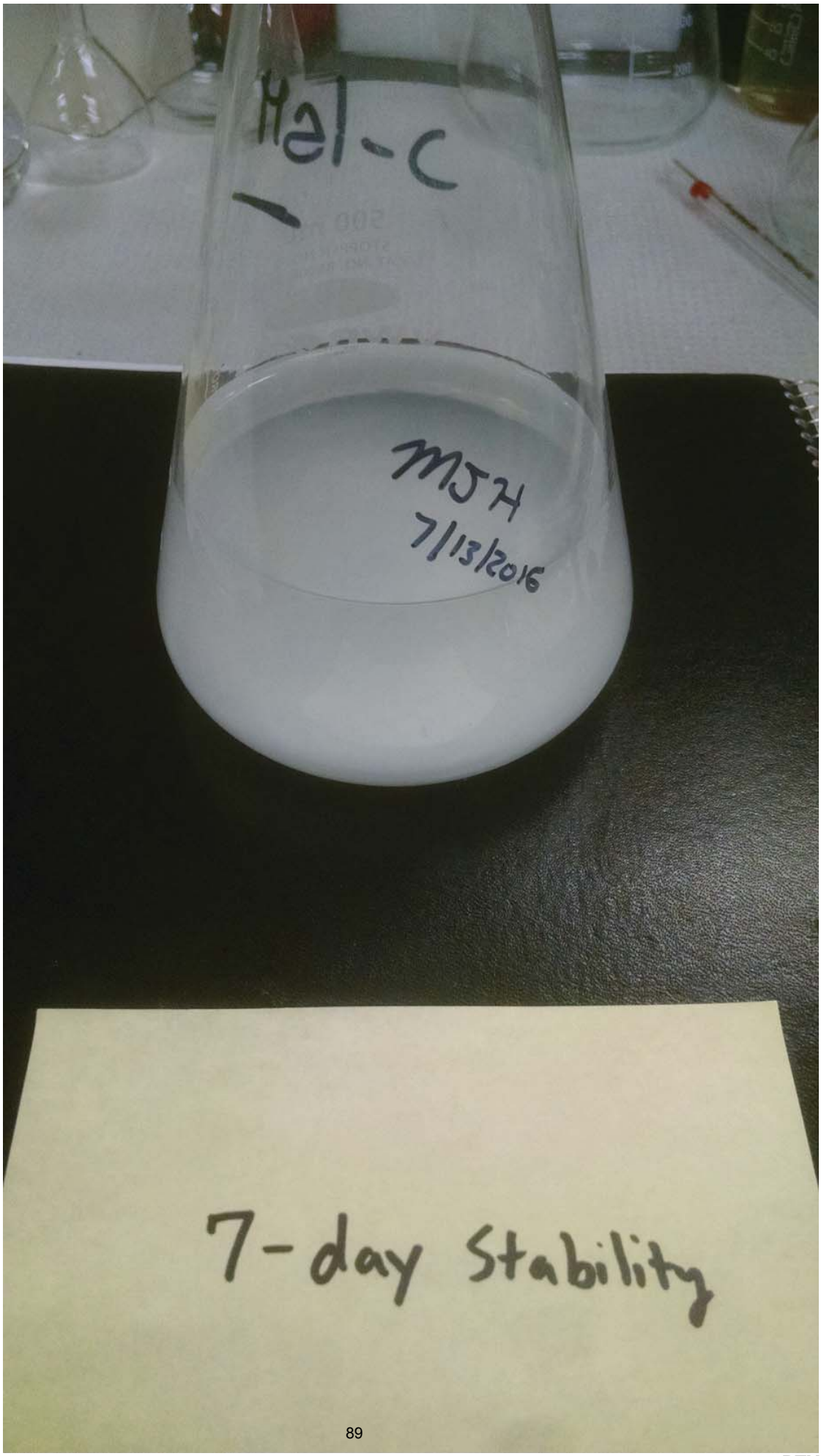
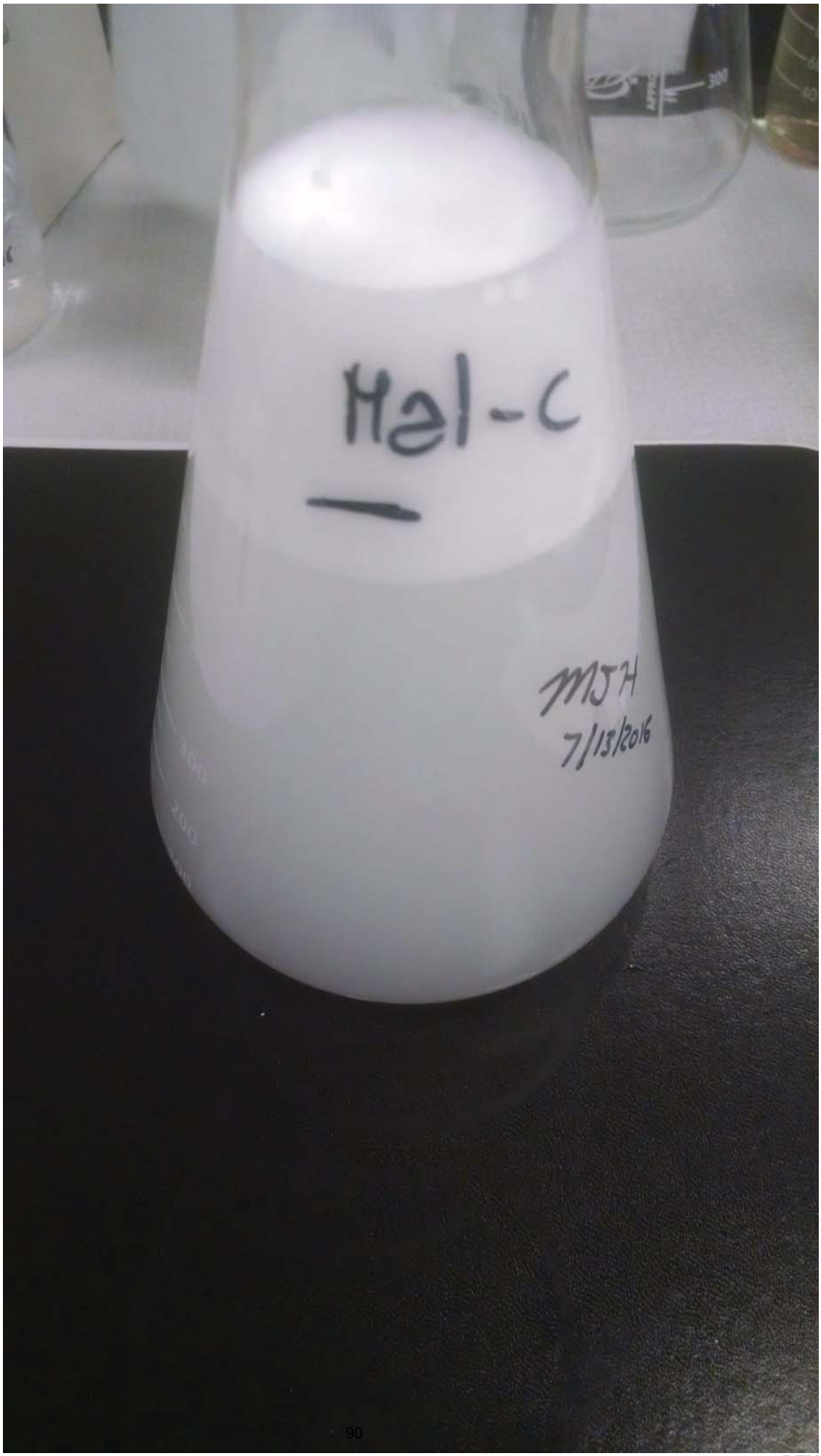

MaL-B
7/13/2015
200
100

Exhibit M – Mal C


7-day Stability


7-day Stability
-After Mixing


Hal-C
MJH
7/13/2016
7-day Stability


H21-C
MJH
7/13/2016

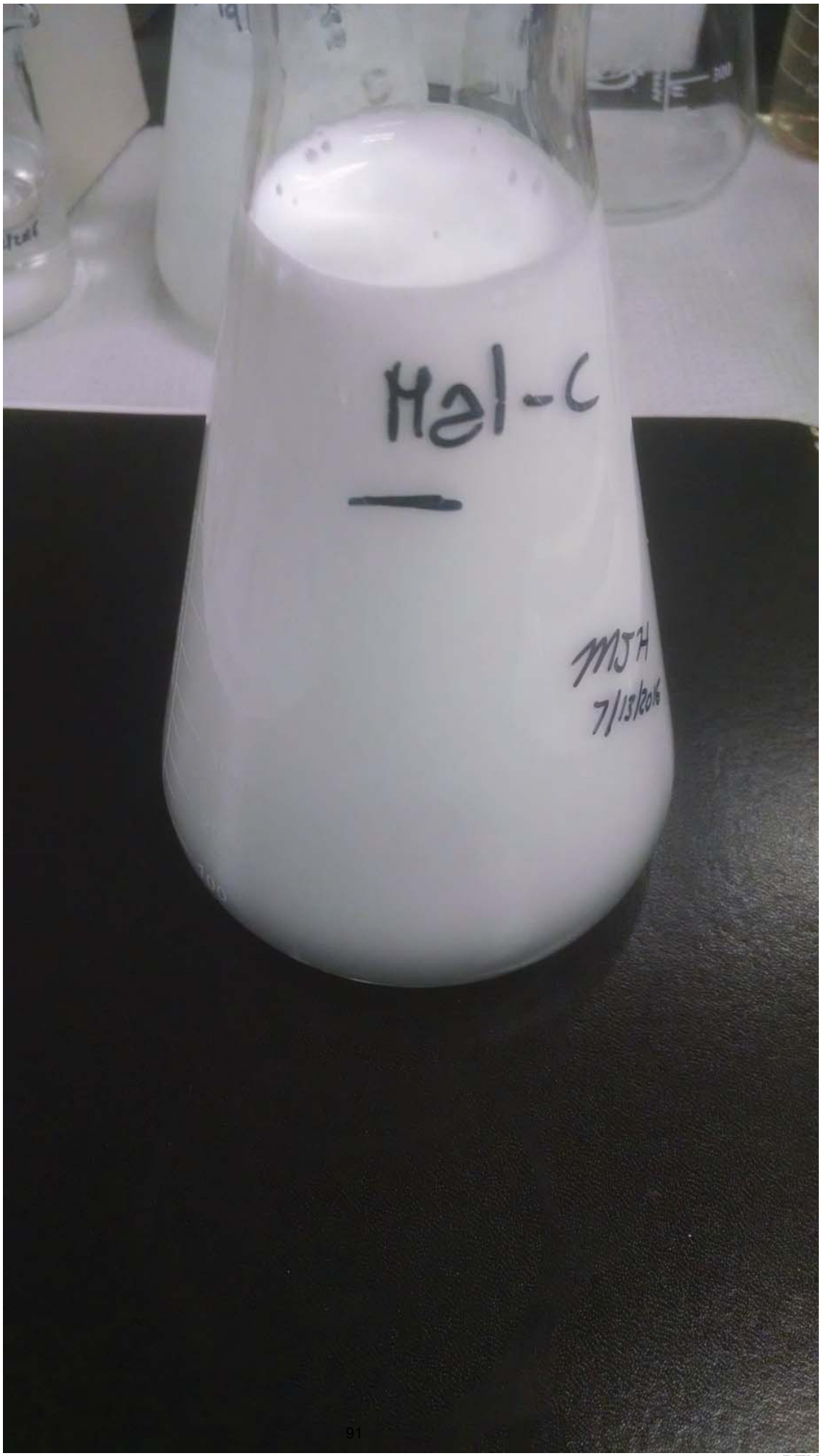
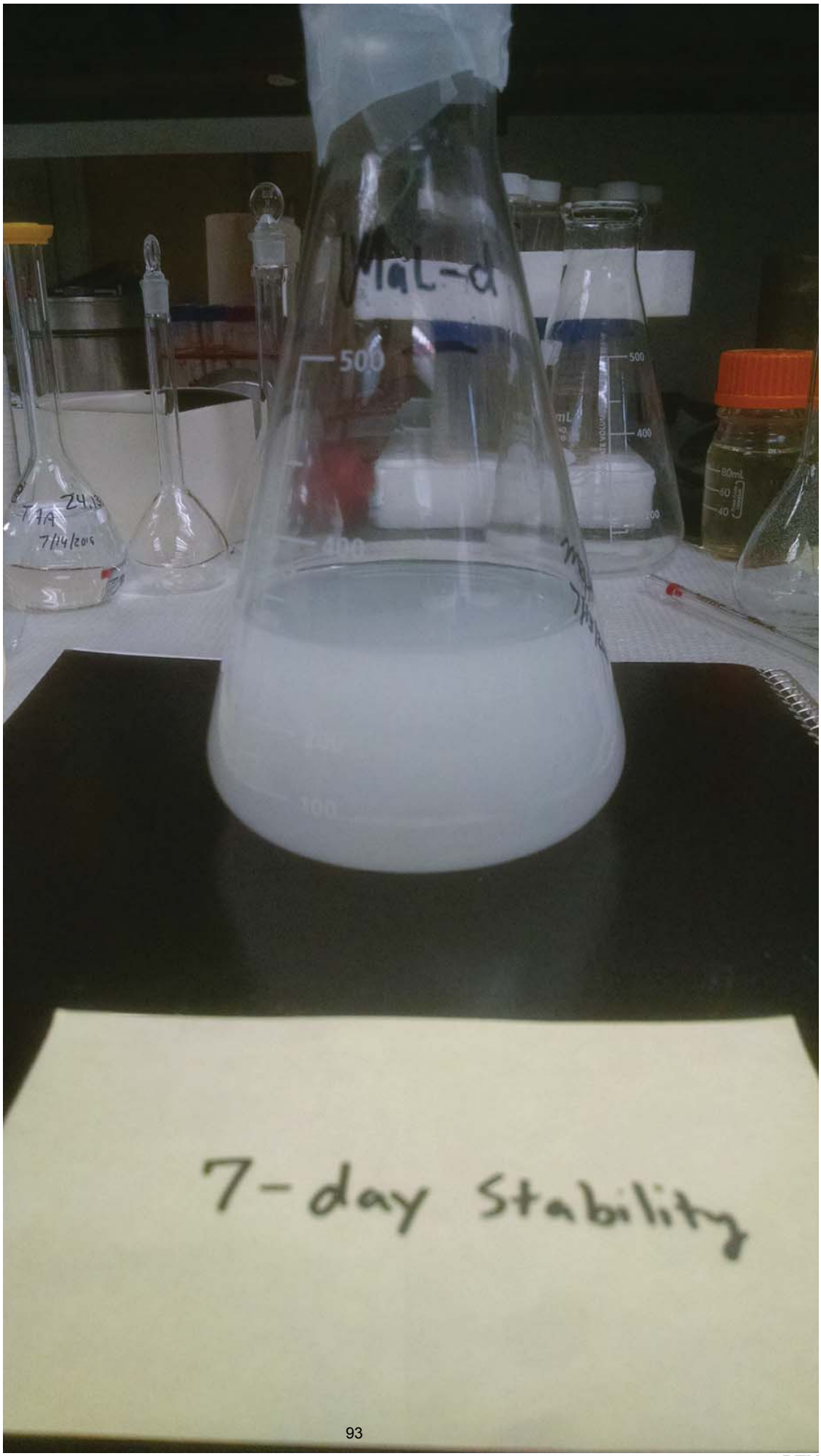
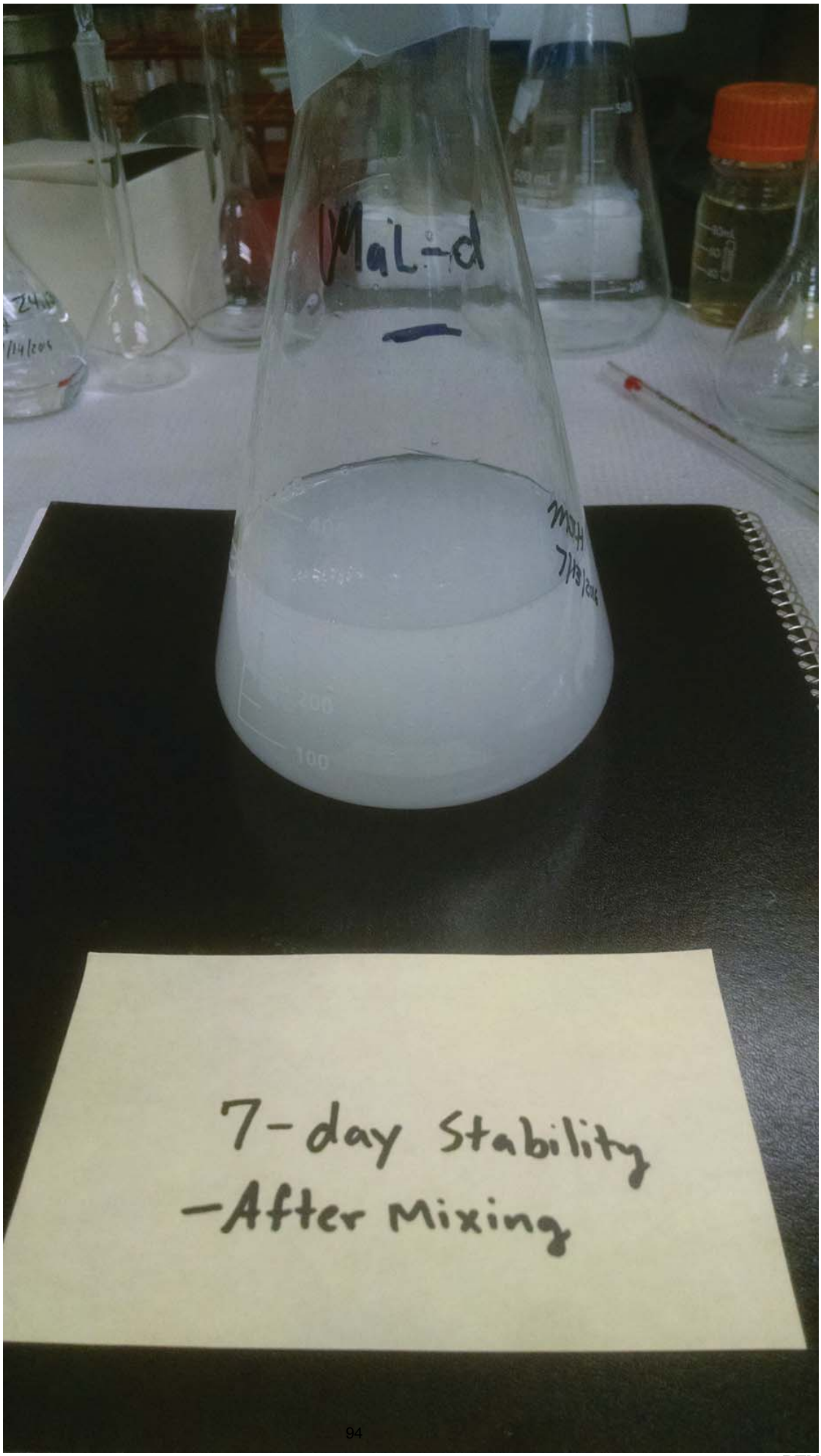
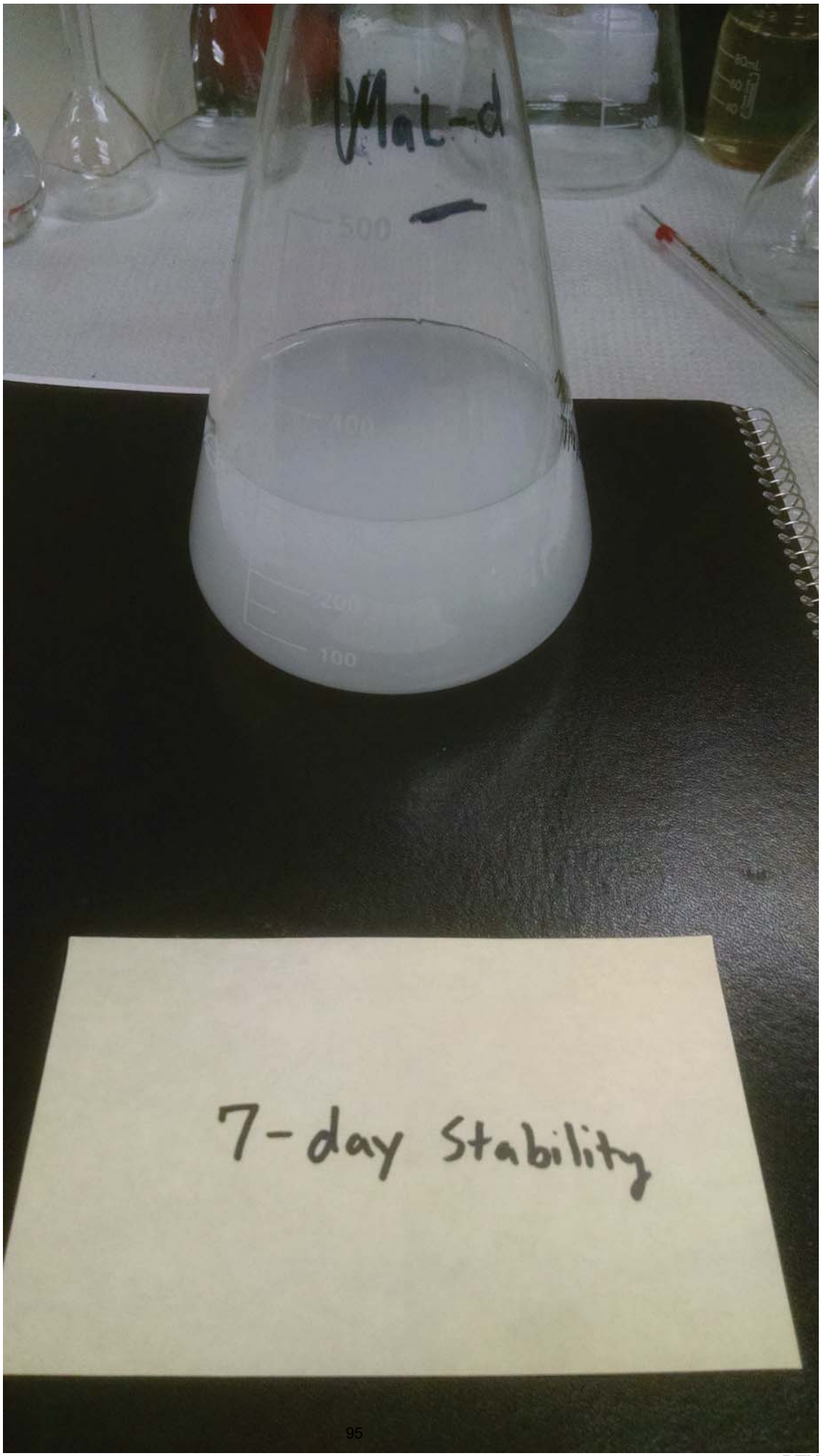
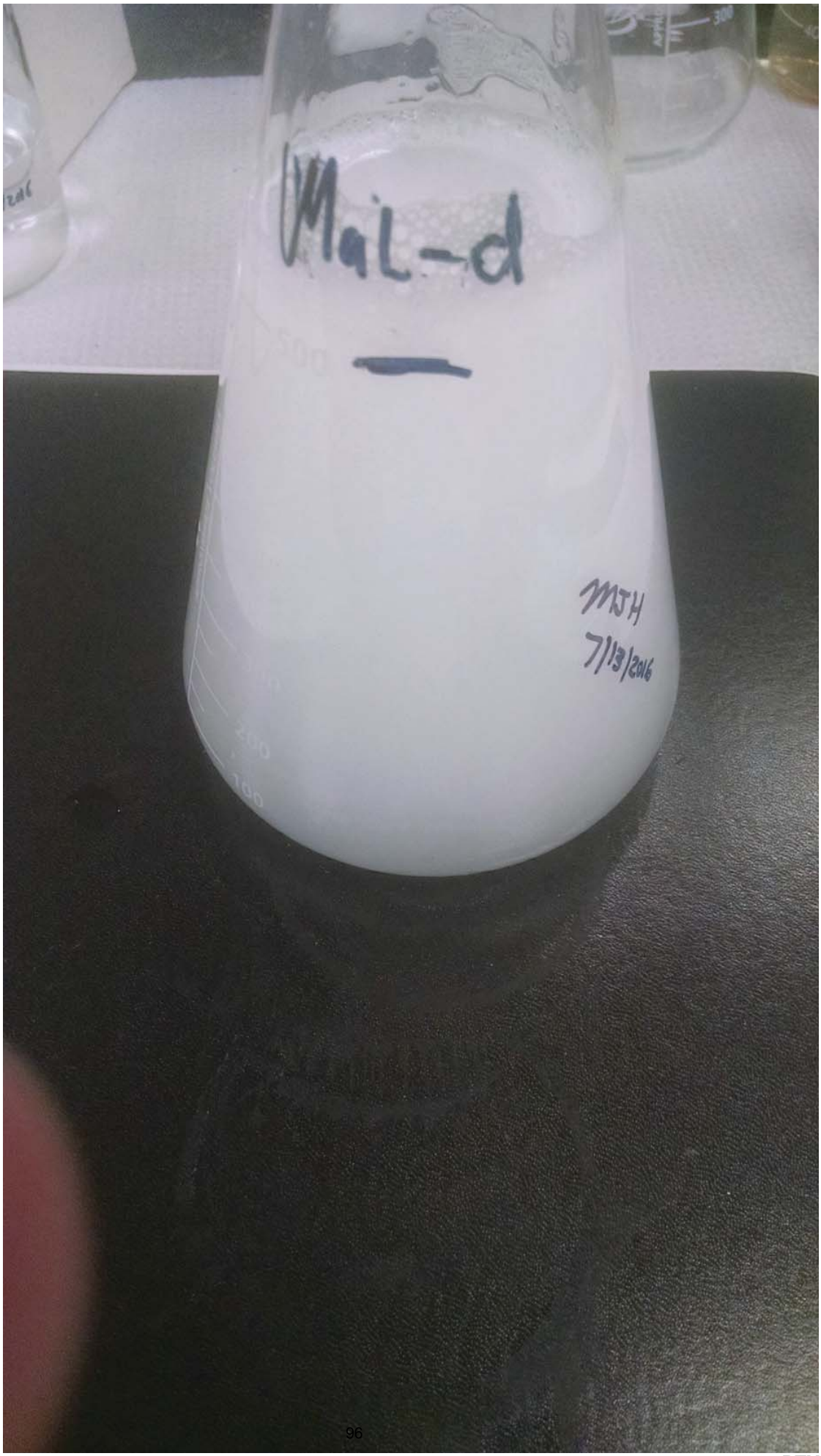

Hal-C
MJH
7/13/2016

Exhibit N – Mal D


Mal-d
500
400
7-day Stability


MaL-d
7-day Stability
-After Mixing


MaL-d
500
400
200
100
7-day Stability


MaL-d
MJH
7/13/2016

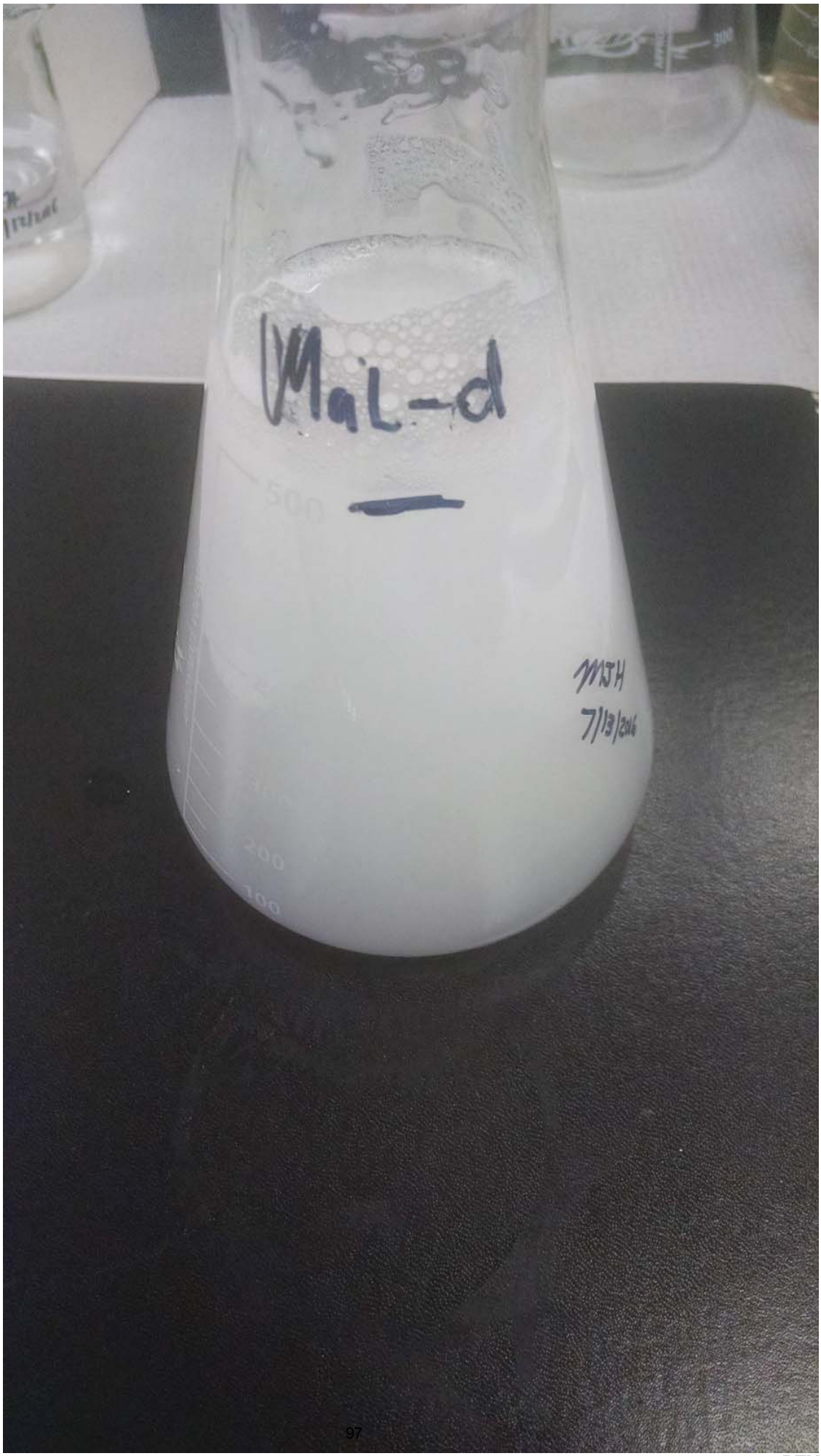
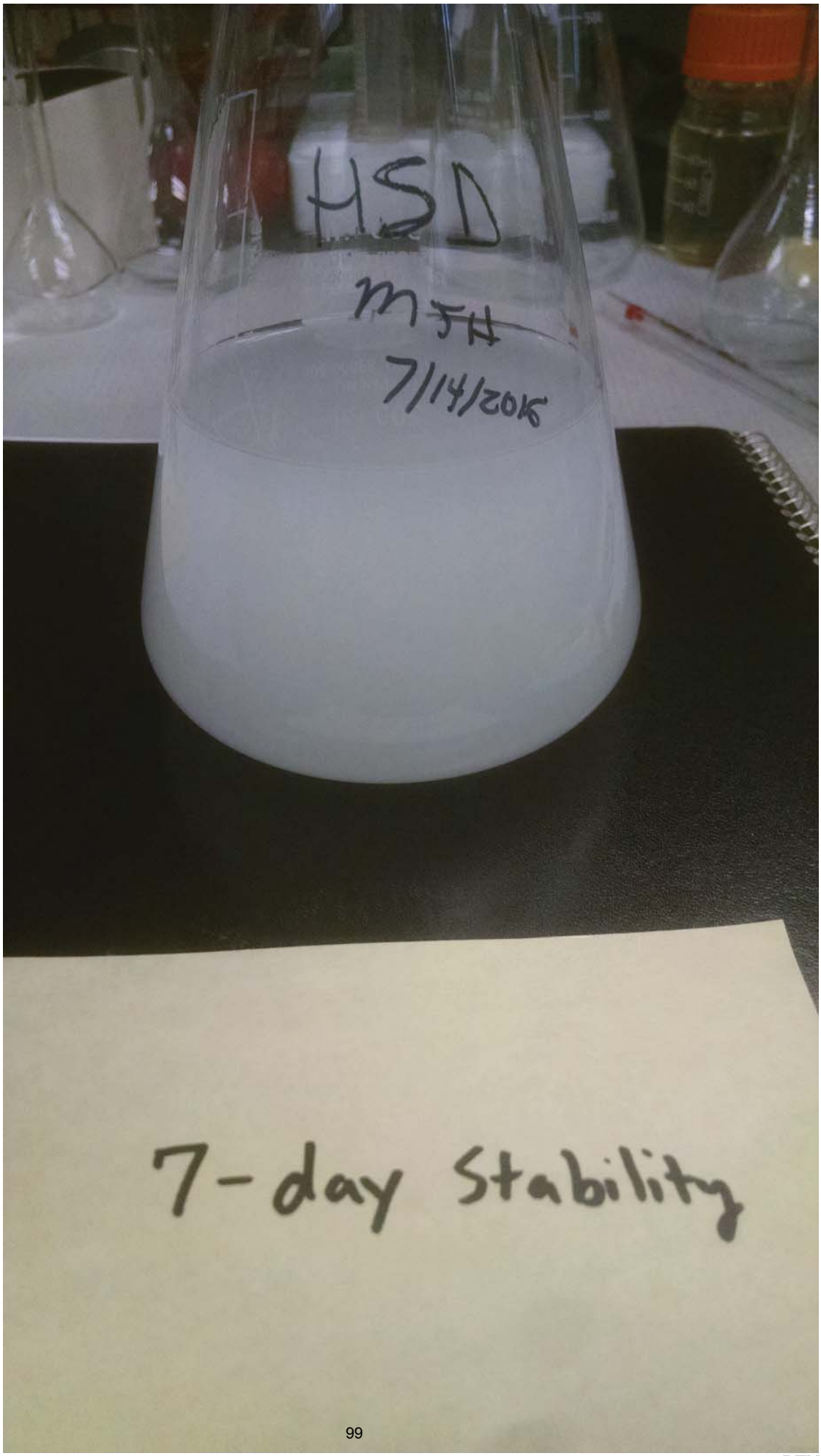
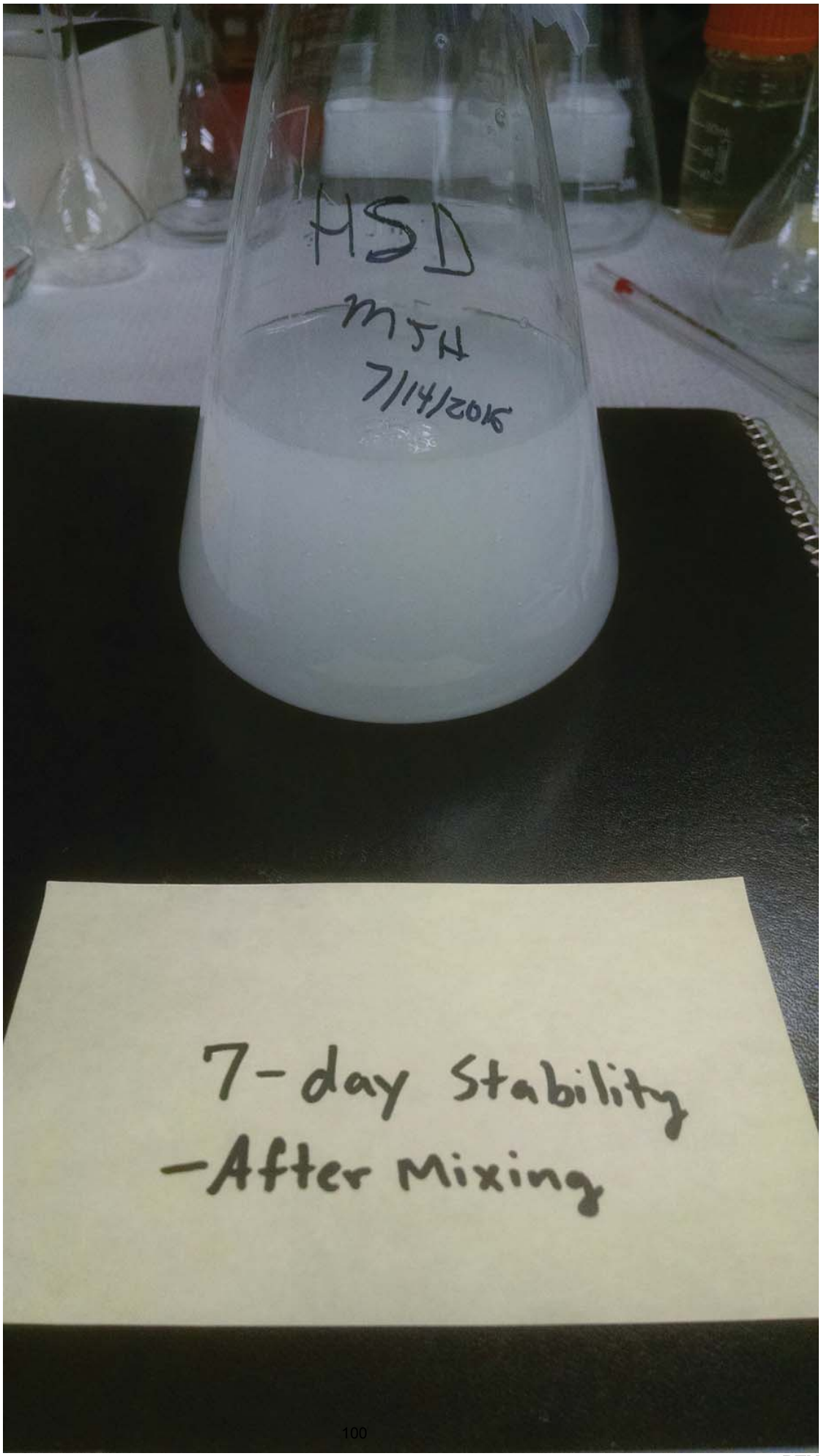
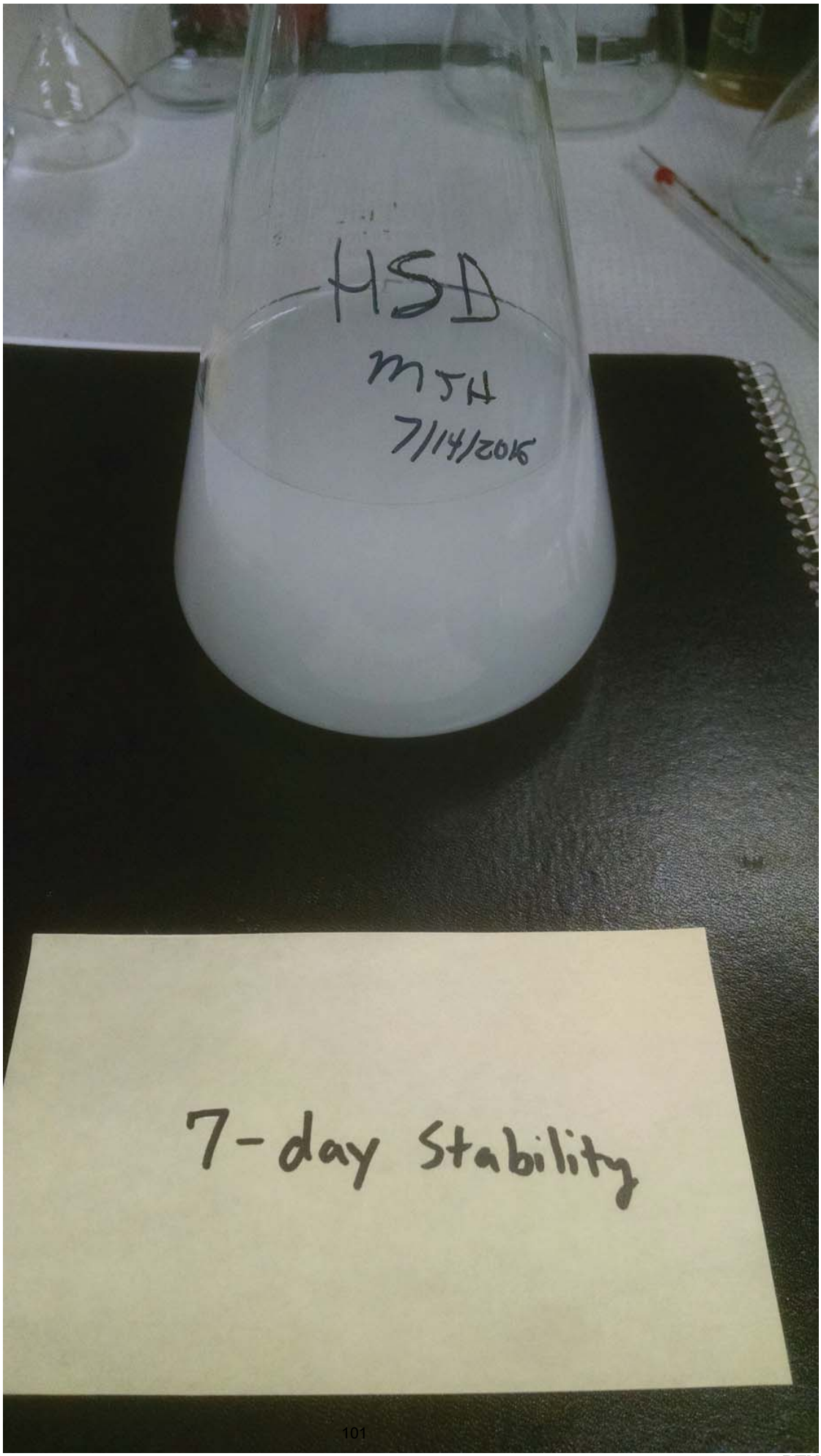
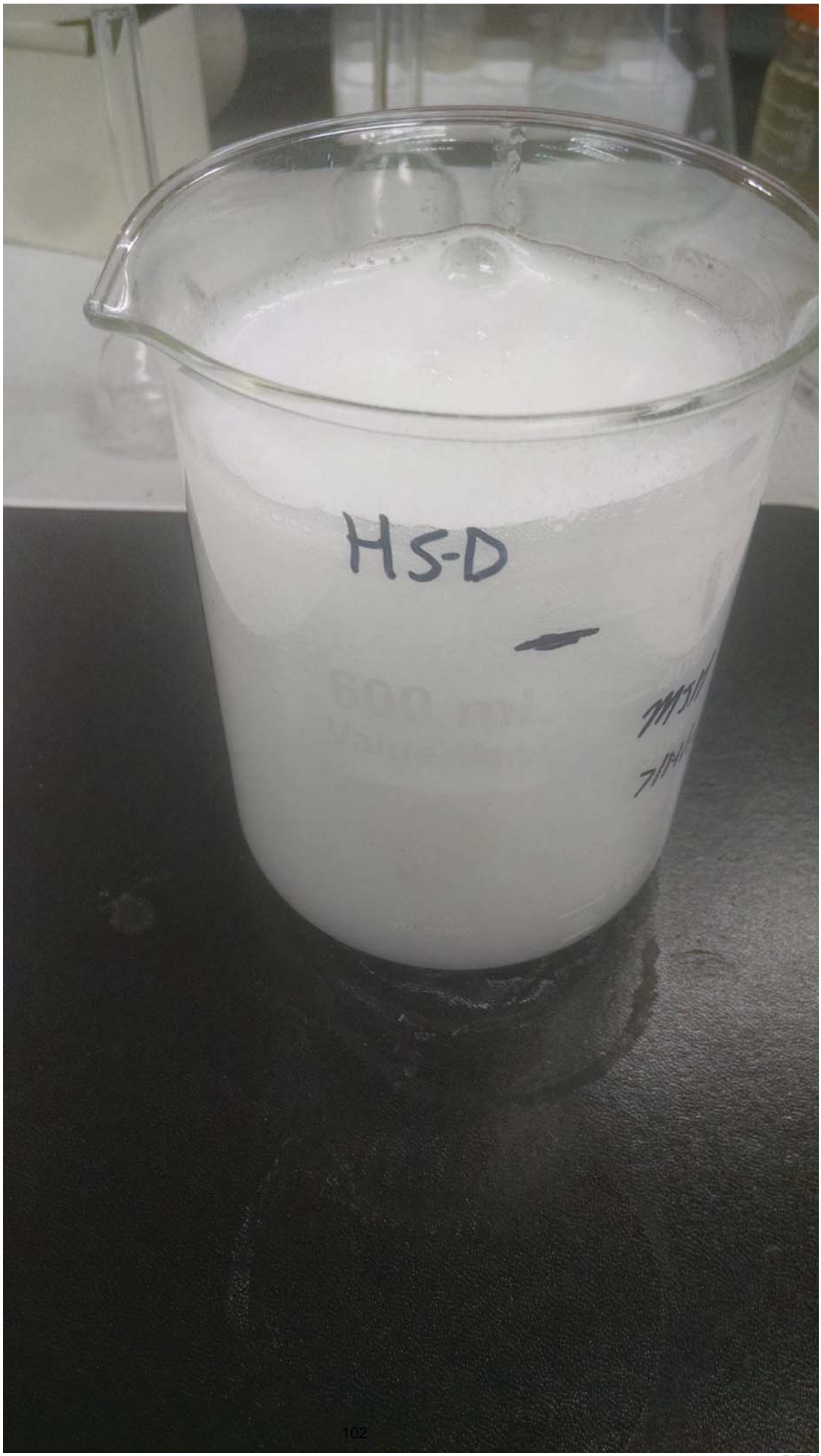

MaL-d
MJH
7/13/2016

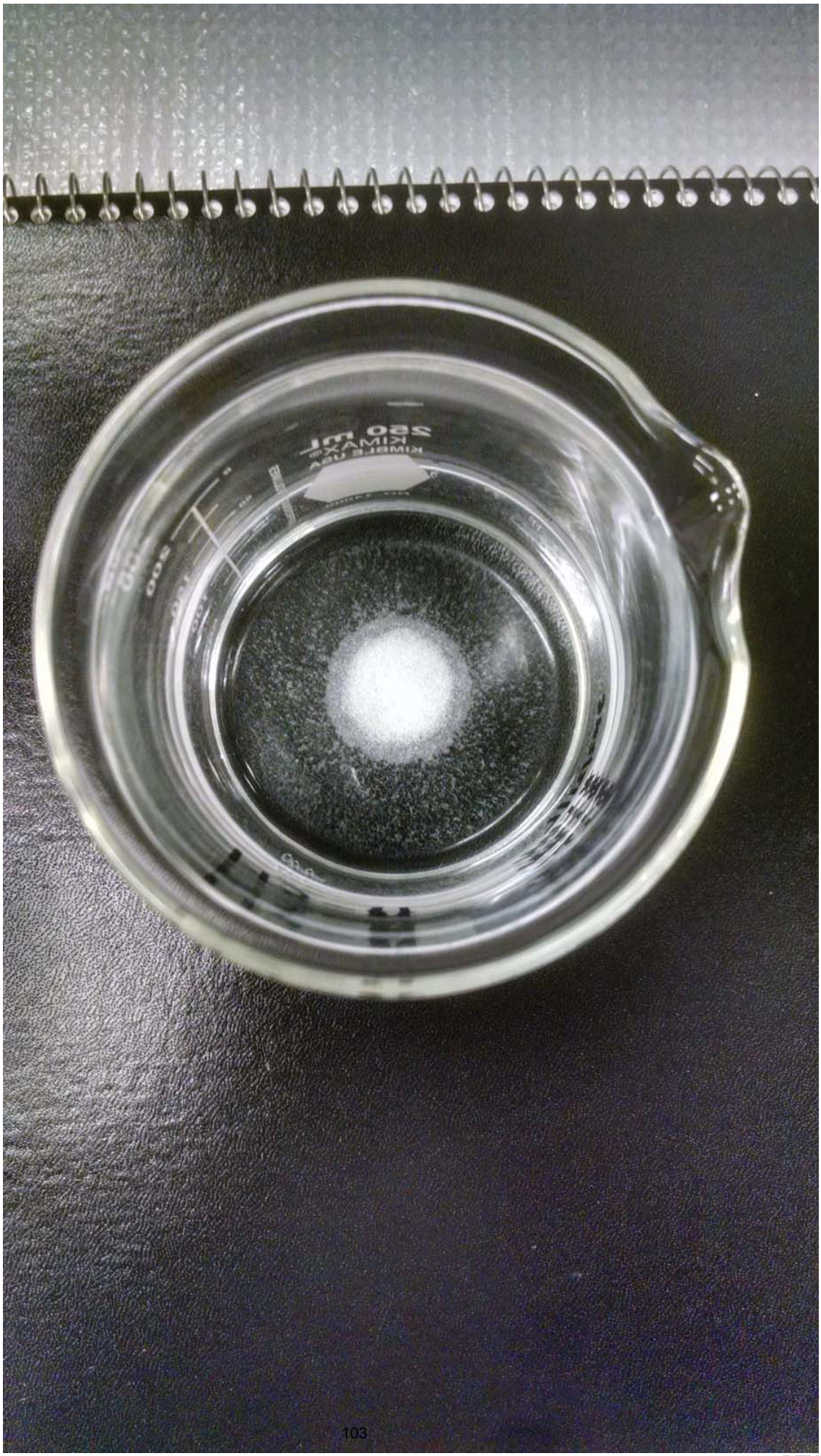
Exhibit O – HS-D

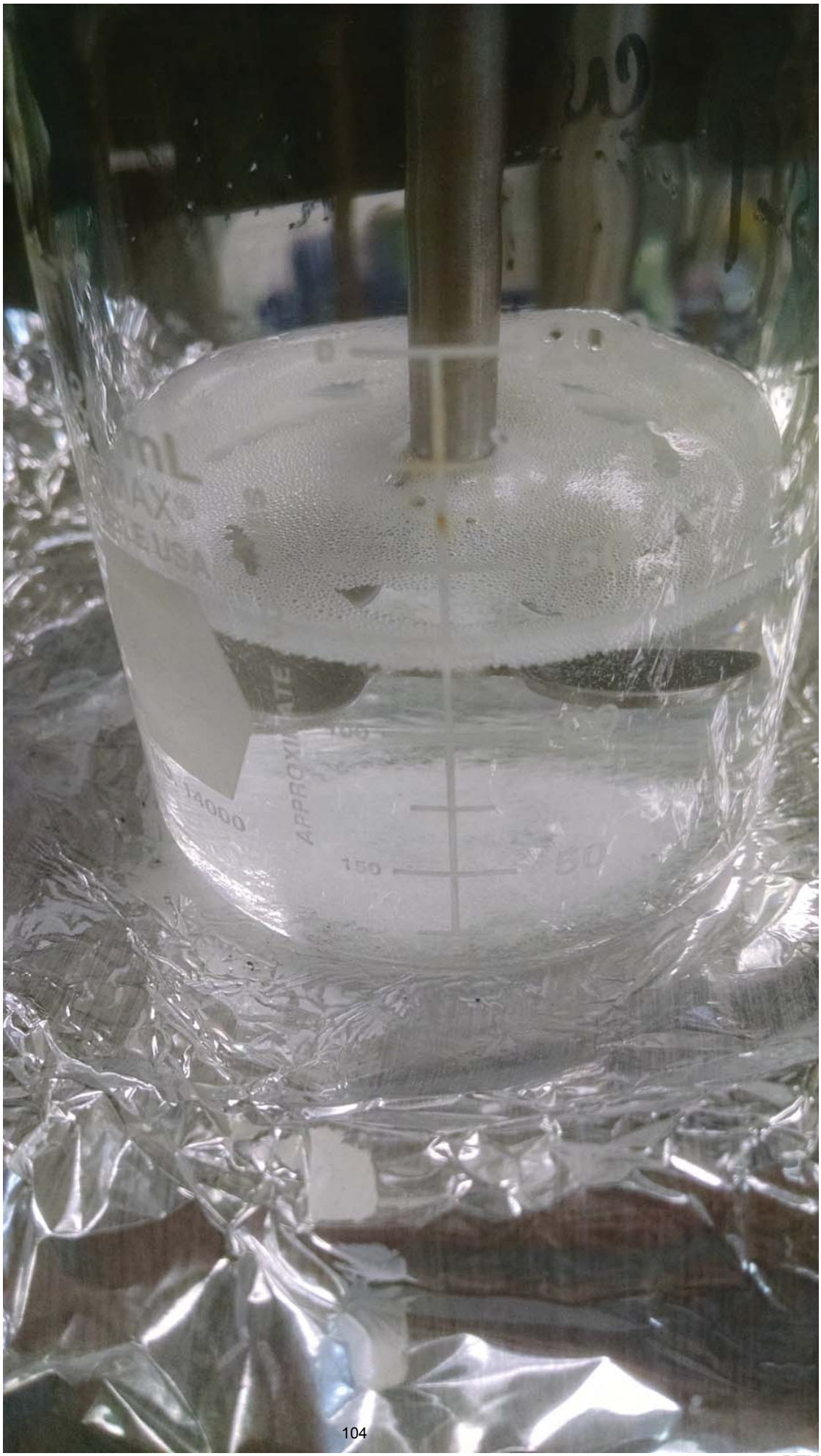

HSD
MFH
7/14/2016
7-day Stability

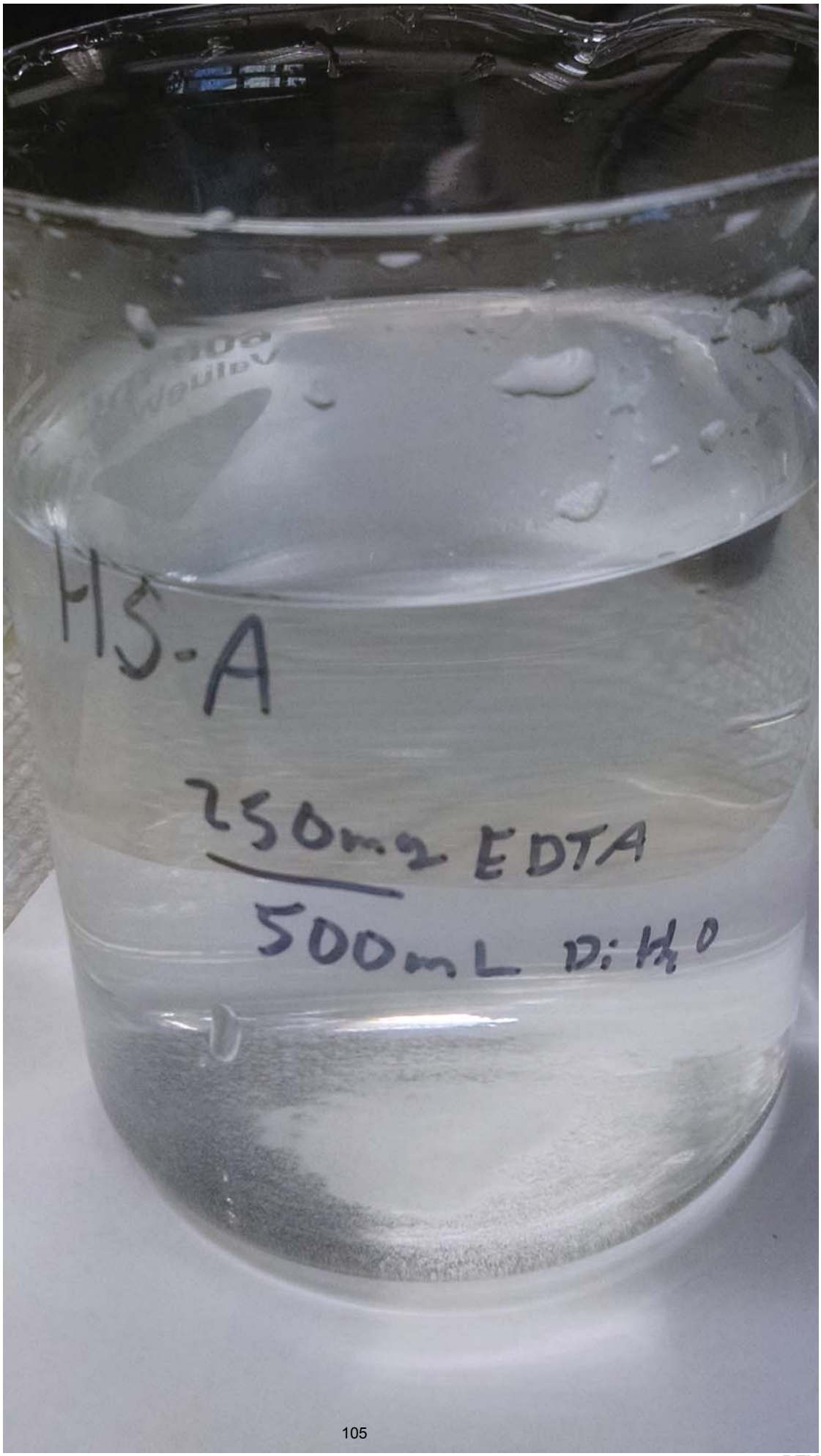

HSD
MJH
7/14/2016
7-day Stability
-After Mixing

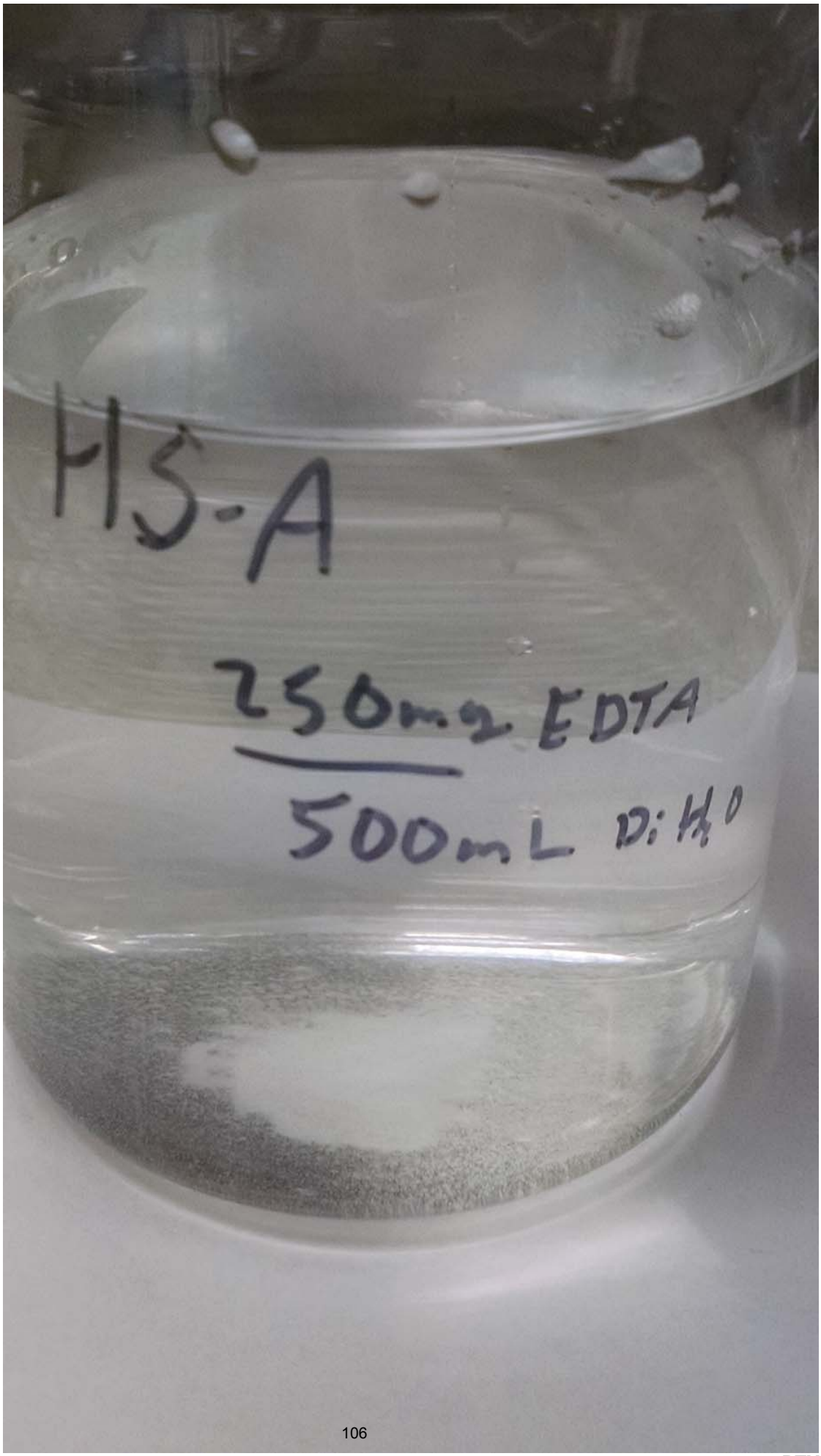

HSD
MJH
7/14/2016
7-day Stability


HS-D


250 mL
KIMAX®
KIMBLE USA


mL
APPROX
14000
150
60

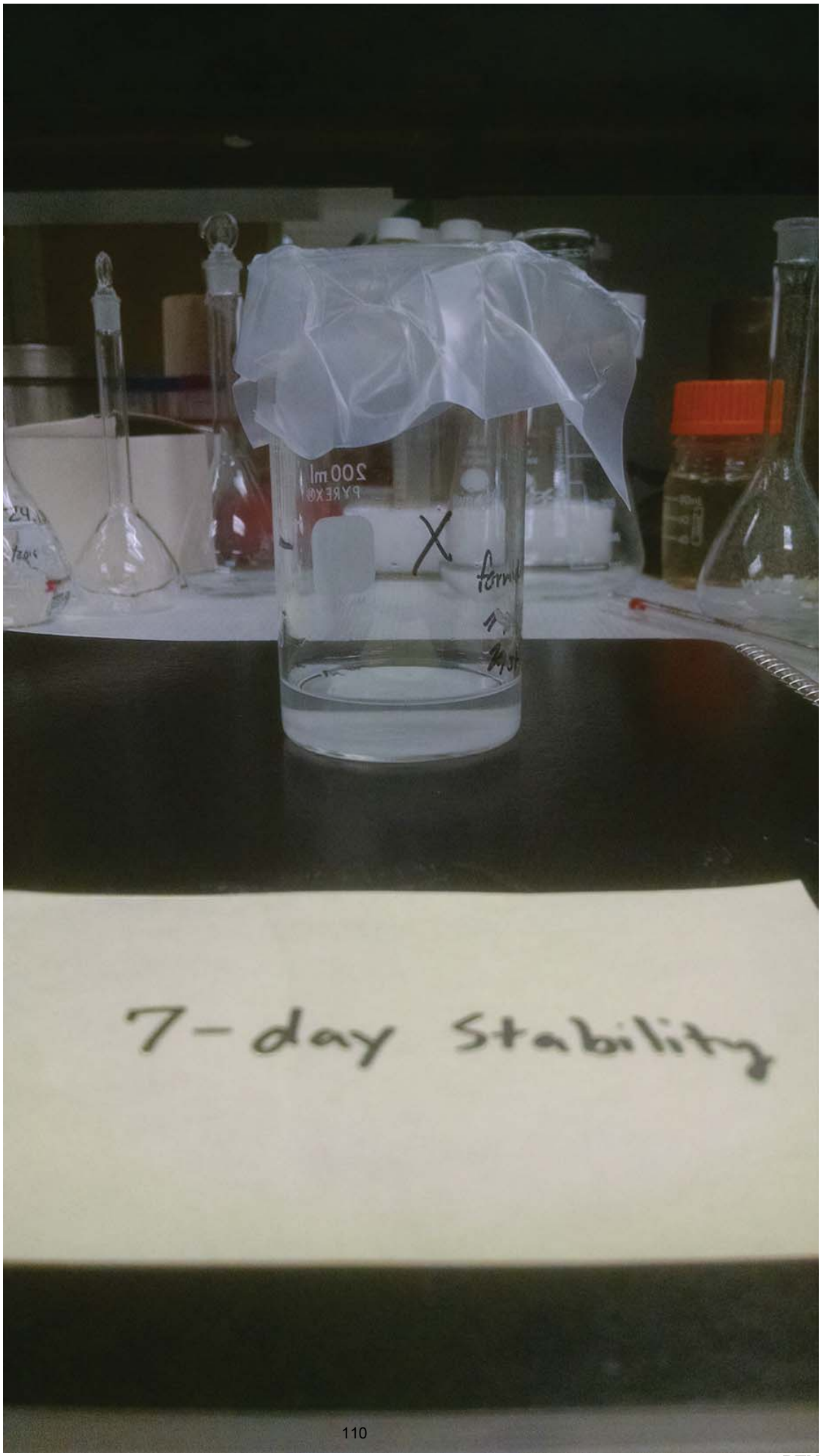

HS-A
250mg EDTA
500mL DiH2O

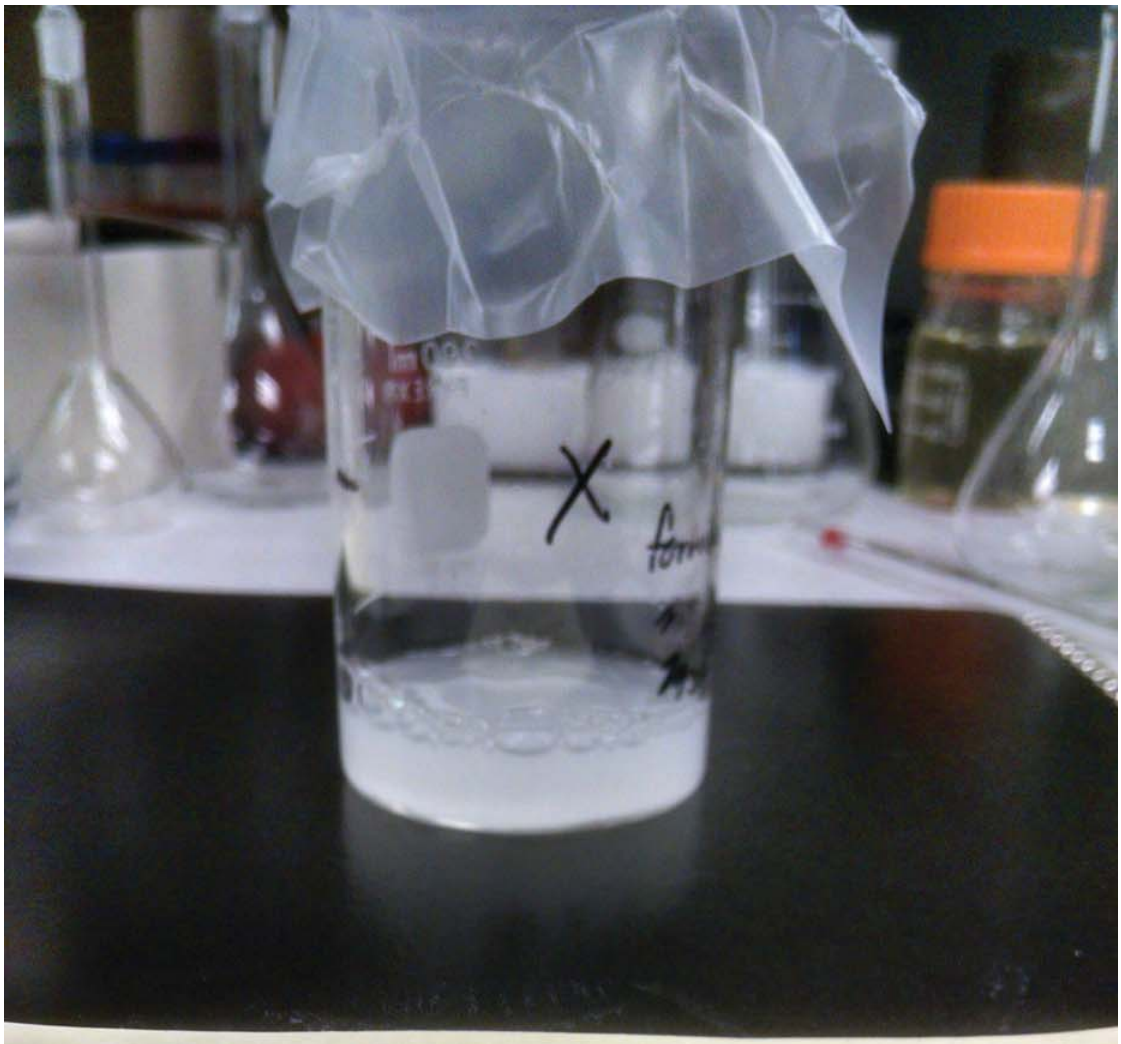

HS-A
250mg EDTA
500mL DI H2O

HS-A

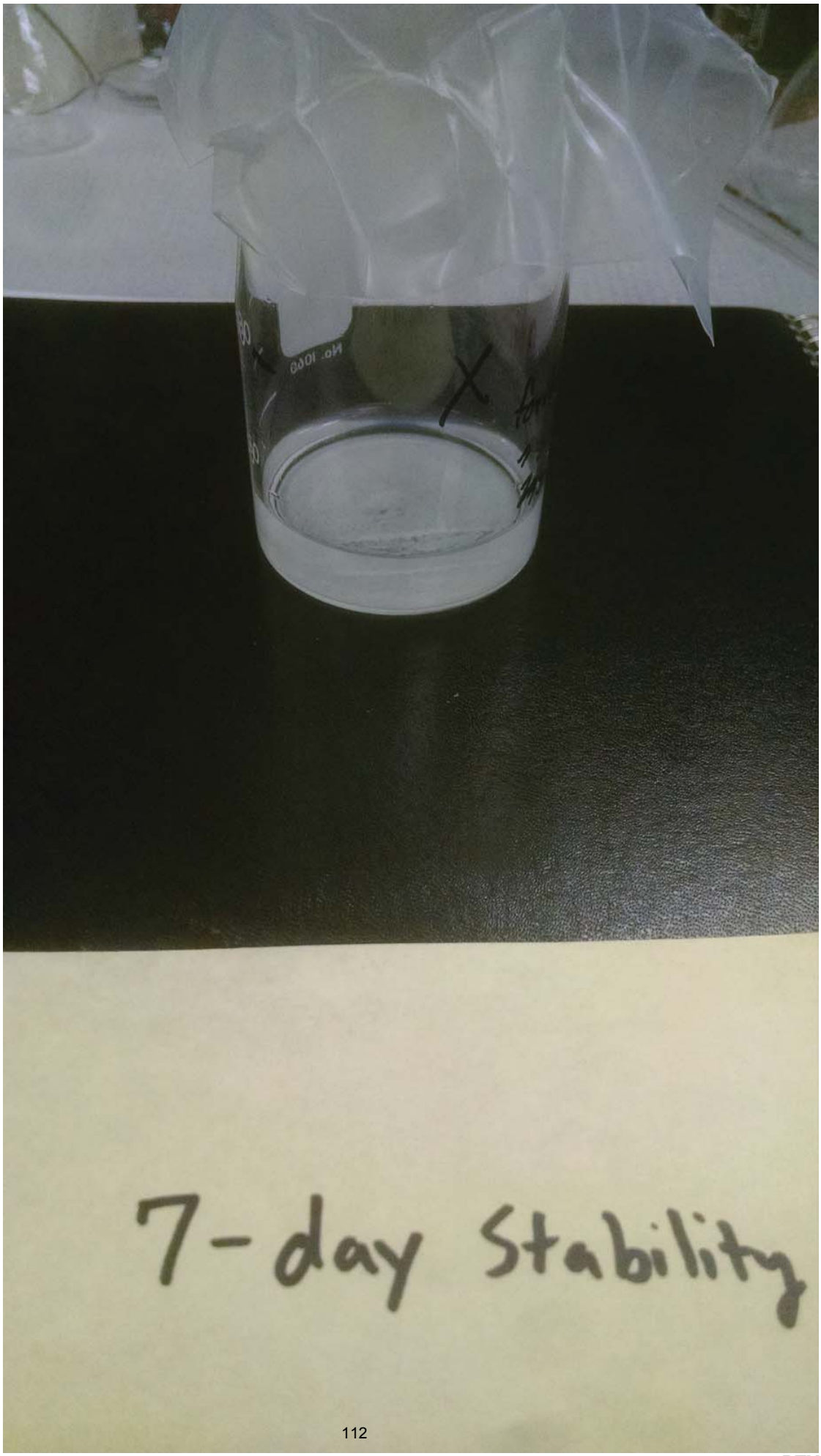
HS-A
EDTA
in ~100mL soln.

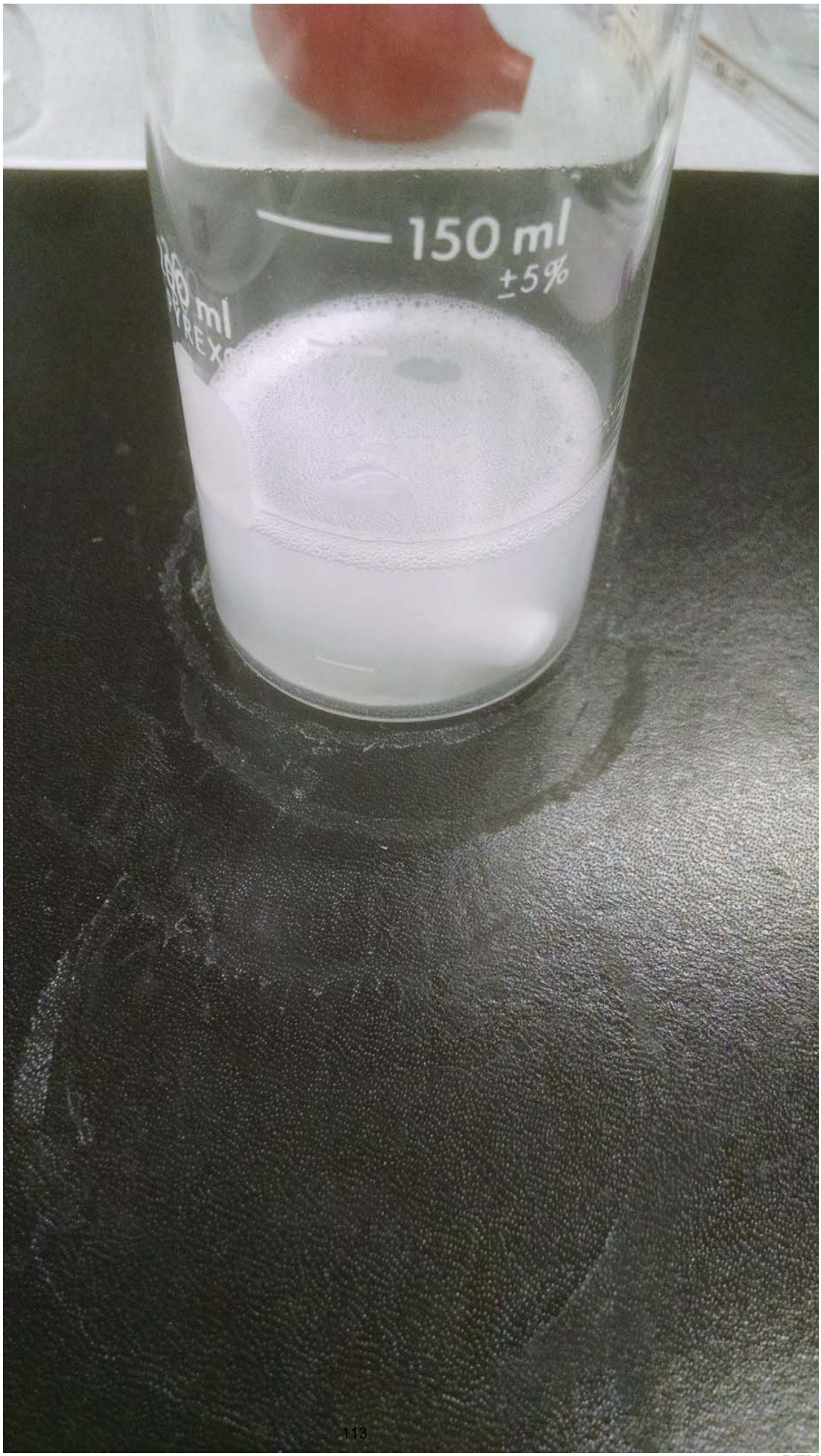
Exhibit P – X-Form

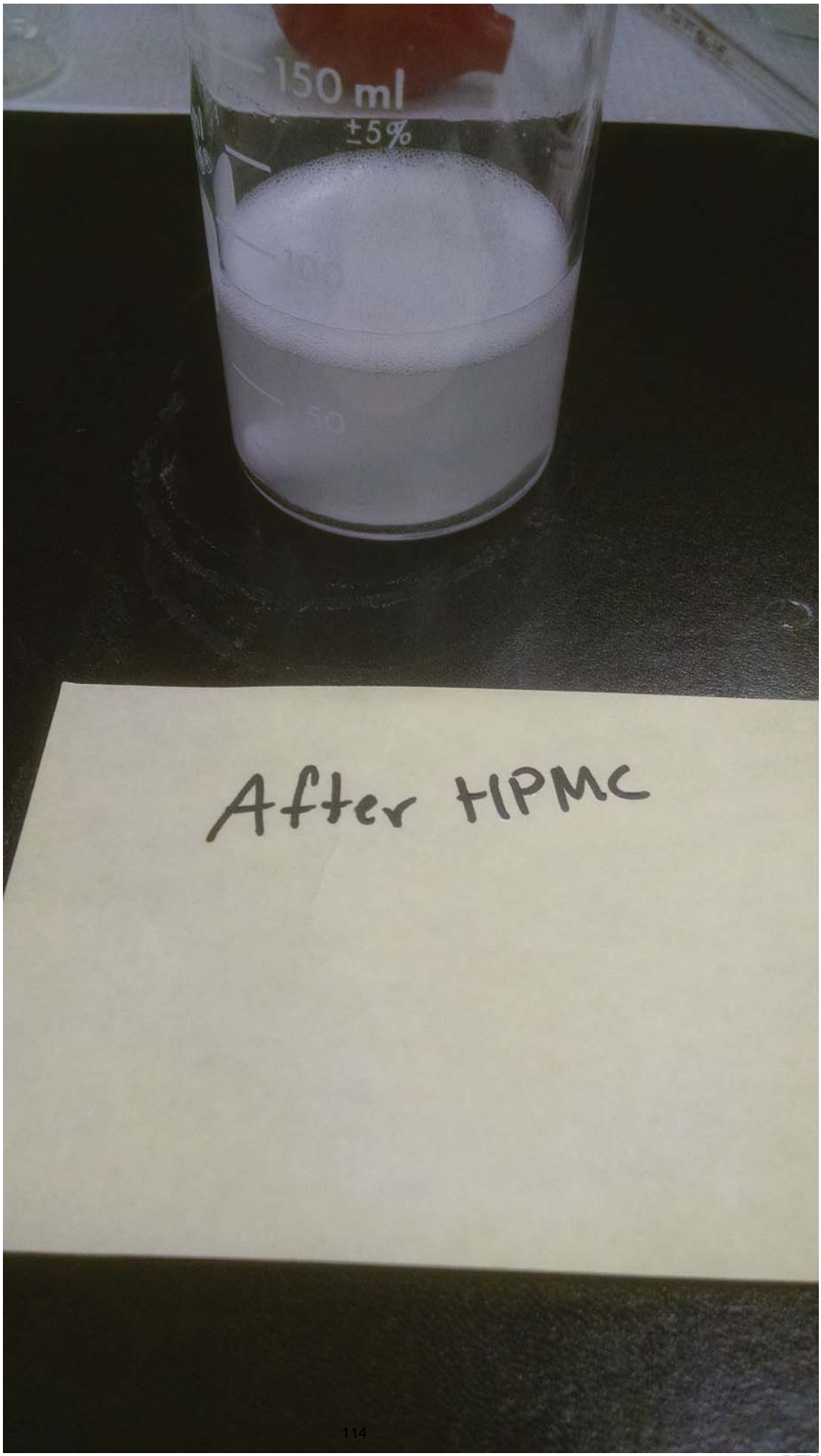

200 ml
PYREX
7-day Stability



7-day Stability
-After Mixing


7-day Stability


150 ml
±5%


150 ml
±5%
After HPMC


150 ml
±5%
200 ml
PYREX®
100

Exhibit R - Pump Delivery Shot Weight raw data and Sprayability Check

Mal-A 1

- primed shines / good spray

1	90.4 mg	Label: Initial I
2	90.5	
3	91,5	
4	93,6	
5	90.4	
6	92,9	
7	92,7	
8	93,7	
9	93,0	
10	93,1	

- wasted 40 sprays

1	96,6	End E
2	96,9	
3	95,7	
4	94,5	
5	95,3	
6	94,1	
7	94,2	
8	95,9	
9	95,7	
10	95,3	

Hal-A 2

- Primed 3 times / good Spray

1	91,8	mg
2	95,1	
3	95,6	
4	96	
5	94,7	
6	94,3	
7	96,0	
8	94,3	
9	96,5	
10	97,3	

Initial - I

Wasted 4 sprays

1	95,5
2	97,6
3	96,1
4	94,5
5	95,3
6	95,1
7	95
8	96,5
9	95,2
10	95,7

End - E

Mod # 3

Primed 3 times / spray good

1	91,2	
2	96	
3	94,2	
4	94,6	
5	94,5	
6	93,9	
7	95,8	
8	93,2	
9	99,7	??
10	96,6	

Initial - I

Wasted 40 sprays

1	96,2
2	98,3
3	97,4
4	96,6
5	97
6	96,6
7	95,4
8	94,8
9	95,1
10	96,4

end E

Mod-B 1

primed 3 times / spray not good, it's a set

1	93,3	Initial I
2	97	
3	98,8	
4	99,3	
5	98,2	
6	99,5	
7	99,6	
8	98,7	
9	98,7	
10	99,7	

wasted 40 sprays

1	100,8	Mod-E
2	99,1	
3	98,4	
4	98,1	
5	97,4	
6	96,4	
7	97,5	
8	100,9	
9	97,1	
10	98,3	

Mal - B 2

primed 3 times / spray not good, it's a Lot

1	97,2
2	98,7
3	97,6
4	100,3
5	97,8
6	99,7
7	99,3
8	99,7
9	100,1
10	100

waste 40 sprays

1	94,9
2	102,6
3	99,2
4	101,5
5	99,7
6	102,3
7	98,8
8	100,2
9	96,4
10	98,8

Hd B- 3

Primed 3 times (spray not good, it's a set

1	98,4
2	102,5
3	101,5
4	100,4
5	99,3
6	99
7	100,3
8	101,7
9	10,4,8
10	105,2

Waste 40 sprays

1	98,5
2	102,6
3	99,7
4	100,5
5	99,8
6	— → I accidentally take before getting the wait
7	105,6
8	99,0
9	101,2
10	996
11	100,6

Hdc 1

Primed 3 times / spray good

1	91,6
2	88,1
3	91,5
4	93,4
5	91,7
6	93,6
7	94,6
8	92,0
9	96,3
10	92,4

waste 40 sprays

1	95,2
2	95,1
3	95,3
4	95,8
5	95,7
6	95,2
7	95,4
8	95,1
9	96.8
10	95,6

Val-C 2

Primed 3 times / spray good

1	86,0 mg
2	87,7
3	89,7
4	91,2
5	91,9
6	91,7
7	92,6
8	93,6
9	92,3
10	92,7

waste 40 sprays

1	92,7
2	93,7
3	95,9
4	93,6
5	95,3
6	93,7
7	93,9
8	92,4
9	76,7
10	79,0

Hal-C 3

Primed 3 times / spray good

1 81.0
2 -170.6
3 91.6
4 90.6
5 185.0
6 93.9
7 94.1
8 94.2
9 93.9
10 93.6

waste 40

51 95.5
52 93.9
53 94.2
54 94.0
55 187.3
56 93.9
57 92.6
58 93.3
59 187.7
60 94.2

Mal D - 1, 2, 3

Bottle #1

Prime - 3 sprays
3 sprays
3 spray

1	96.6
2	101.5
3	101.0
4	102.5
5	101.6
6	100.6
7	101.1 mg
8	102.7 mg
9	102.5
10	102.8
51	101.5
52	101.9
53	101.2
54	103.0
55	101.8
56	203.7
57	101.0
58	101.6
59	100.2
60	101.2

✓ waste 40

#2

#1 - Spray is a Jet/Stream
#2 - Spray is a Jet or Jet
#3 - Spray is Stream/Jet

1	100.4
2	100.6
3	101.8
4	100.9
5	101.4
6	101.5
7	102.2
8	101.1
9	102.6
10	101.1
51	101.0
52	101.5
53	102.3
54	100.5
55	102.5
56	101.2
57	102.7
58	100.9
59	100.7
60	101.9

✓ waste 40

#3

1	100.1
2	101.1
3	
4	101.3
5	100.7
	99.2
6	100.2
7	99.8
8	99.7
9	99.8
10	~~103~~. 102.4
51	~~100.0~~ 99.6
52	100.4
53	100.1
54	99.9
55	100.6
56	100.7
57	100.6
58	100.4
59	99.91
60	

✓ waste 40

Delivered Dose Uniformity

Primed 3 times

Formulation: HSD

Bottle # 1, 2, 3

#1 - No Spray/Formed a Narrow Jet #2 No Spray/Formed a Narrow Jet #3 No Spray/Formed a Narrow Jet

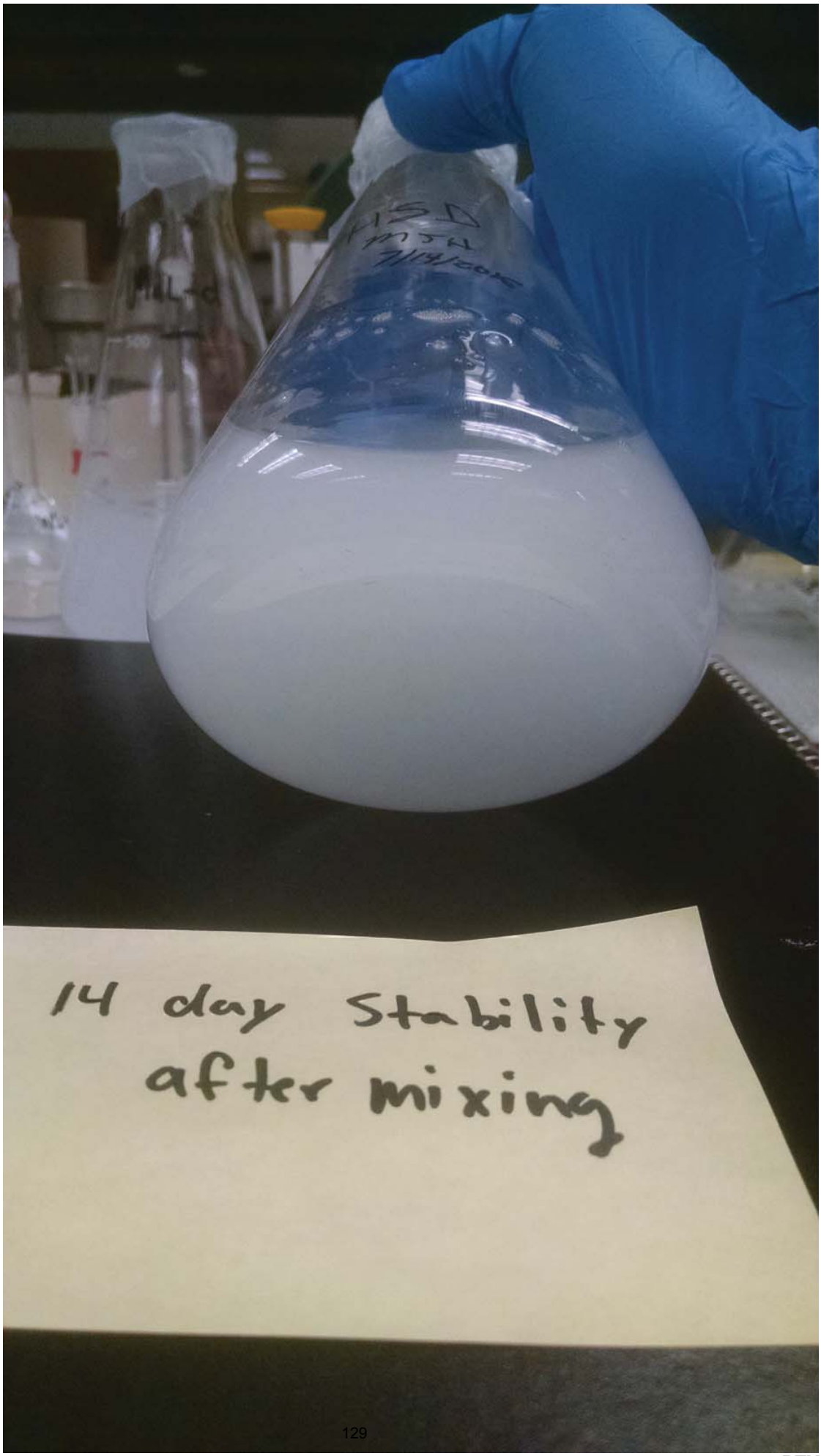
	Dose #	#1 shot weight(mg)	#2	#3
First 10 Doses	1	101.3	97.4	101.7
	2	* ⇒202.0 →	97.7	103.9
	3	101.6	98.2	102.8
	4	101.9	100.1	102.8
	5	101.0	99.7	100.9
	6	103.0	103.1	104.4
	7	102.8	102.4	103.0
	8	101.8	101.2	102
	9	101.1	100.5	103.5
	10	101.3	103.7	105.2
Middle 40 Doses Wasted				
Last 10 Dose	51	107.0	98.0	106.2
	52	103.0	103.5	102.7
	53	103.2	103.3	102.8
	54	102.8	99.9	102.9
	55	102.2	98.8	99.3
	56	100.1	100.0	103.7
	57	86.7	101.5	103.3
	58	96.2	100.2	102.1
	59	94.8	100.7	102.8
	60	96.0	104.6	103.9

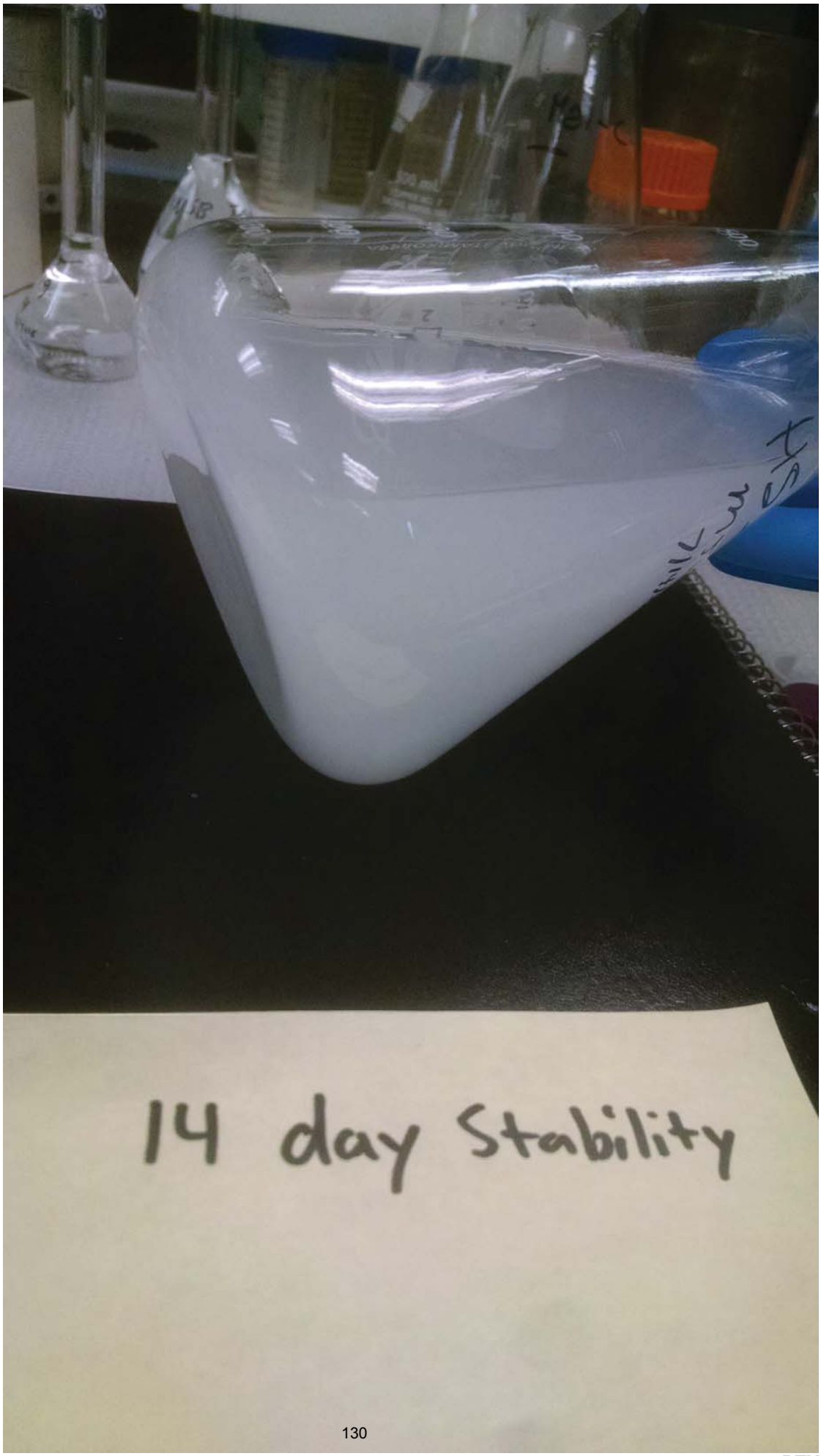
* Subtract from previous shot weight

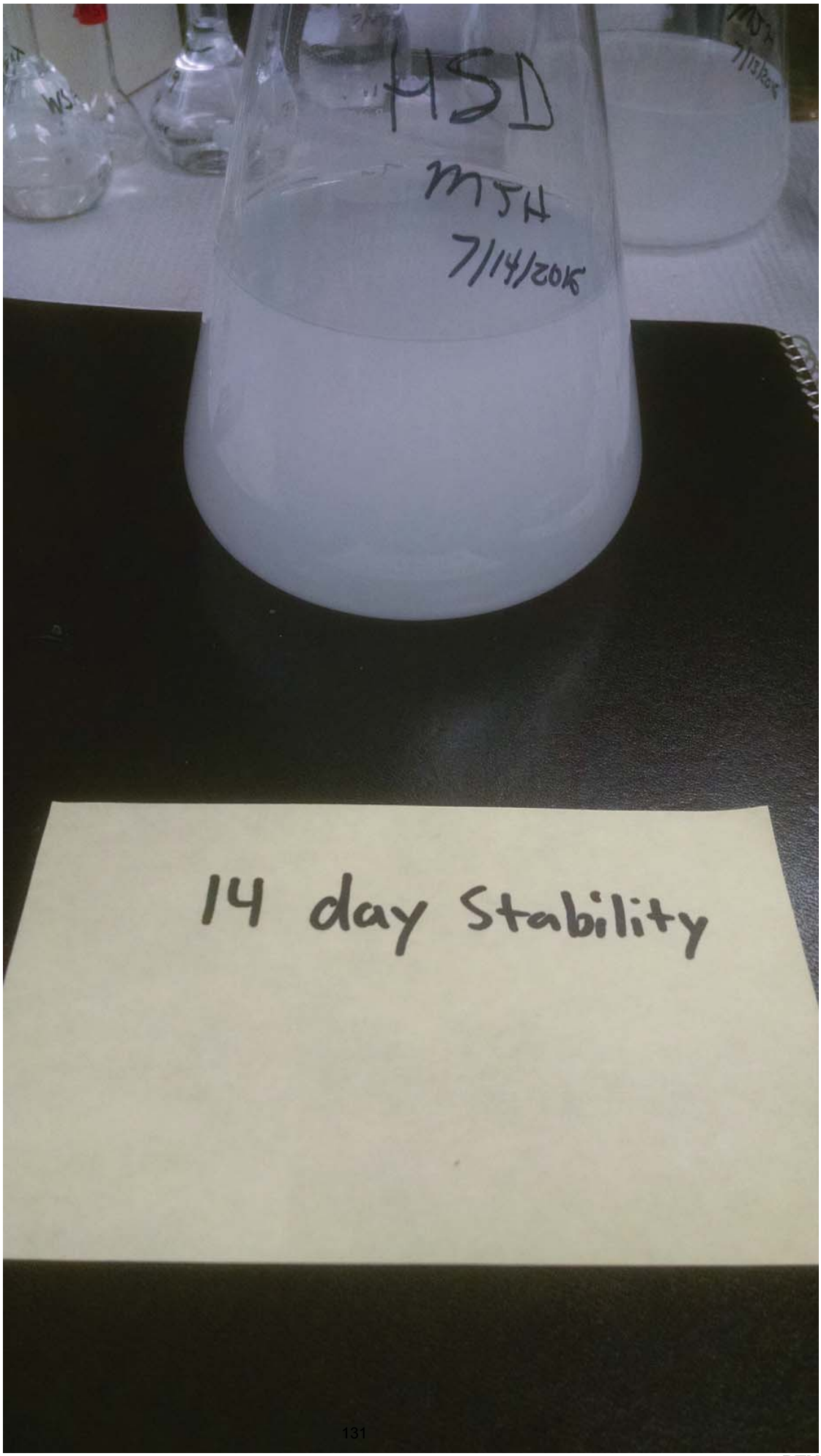
☐ Diluent Volume: 2mL

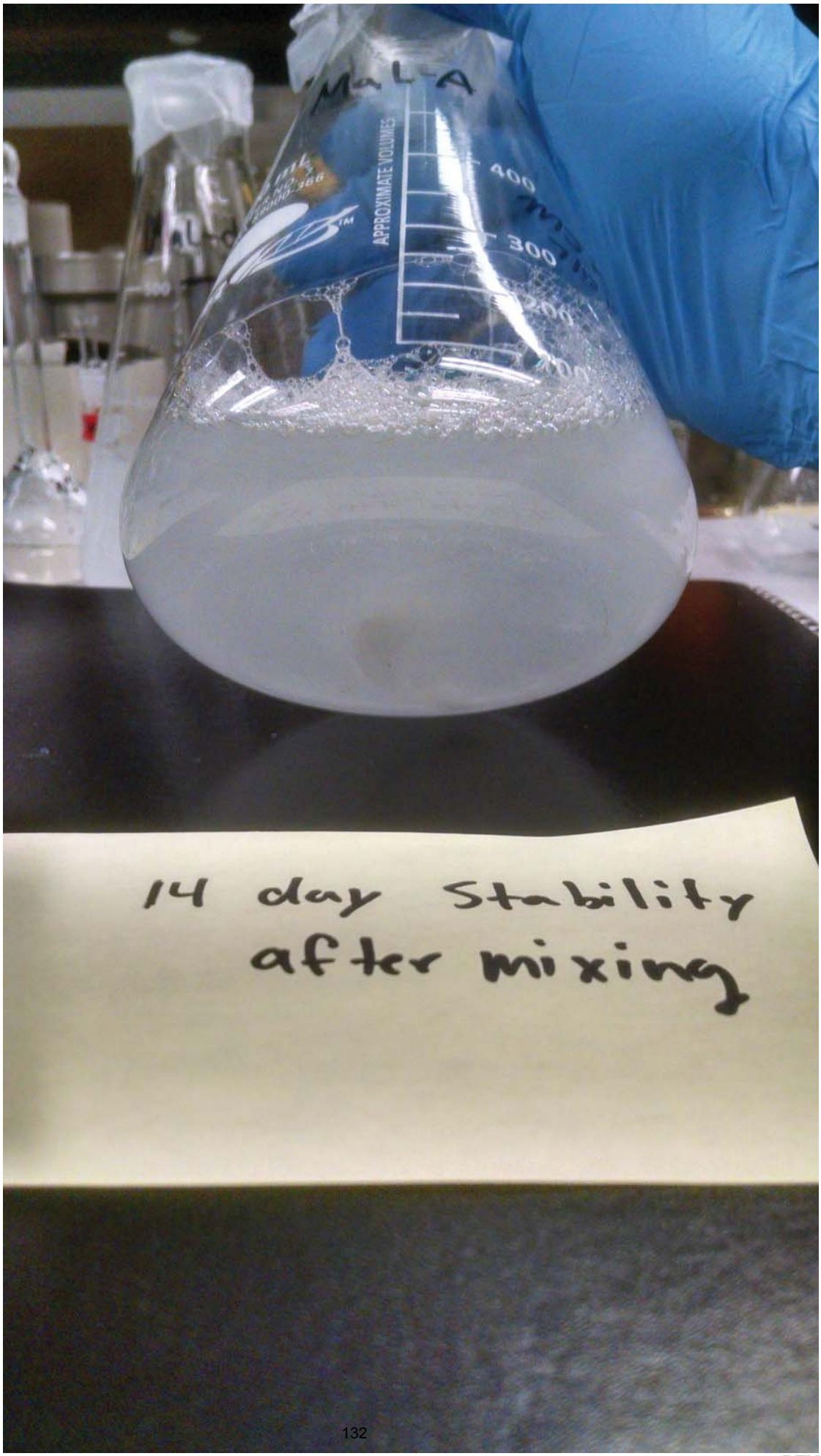
▭ Diluent Comp: 70% ACN

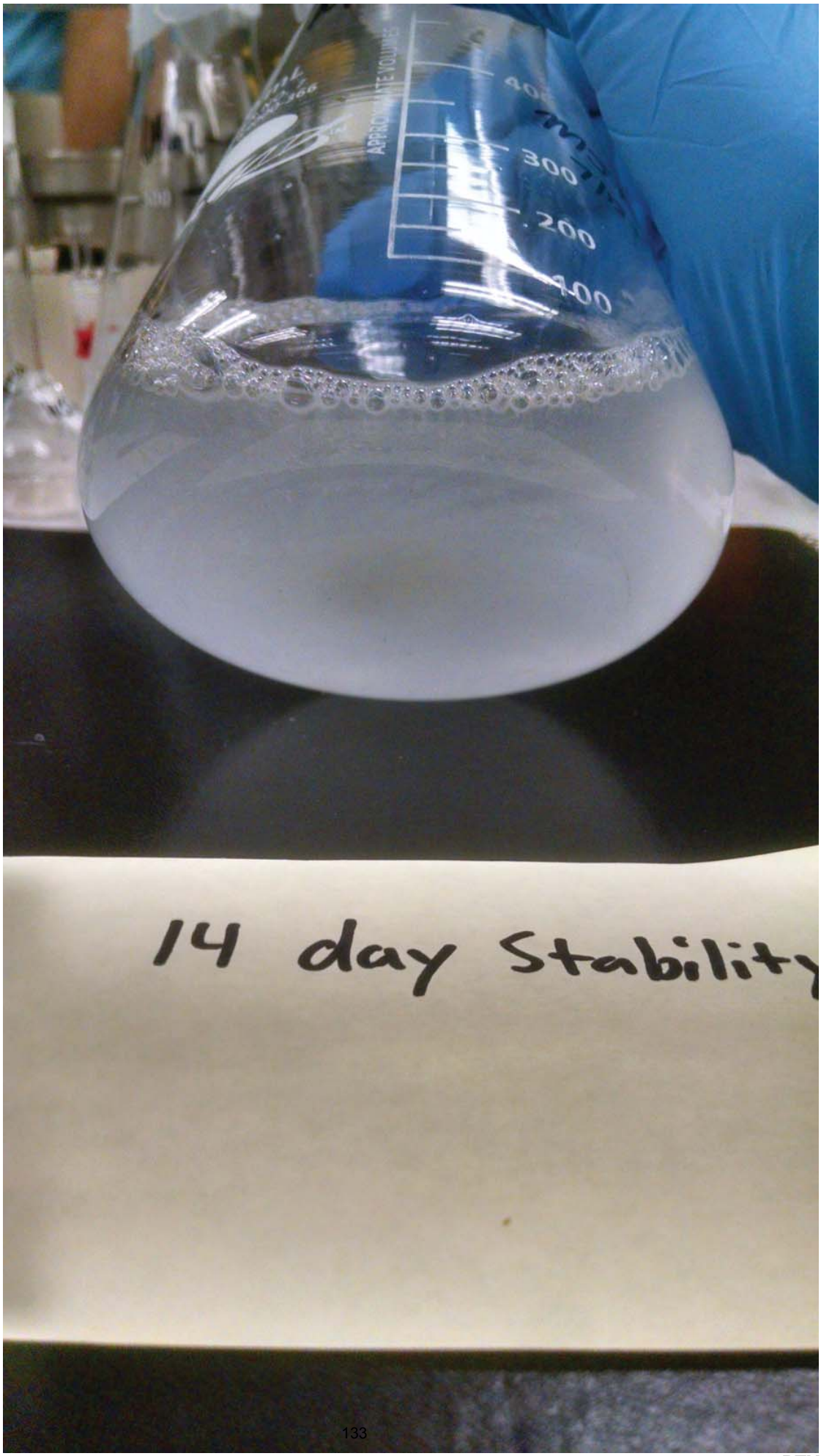
Exhibit S – 14 Day Stability Photos

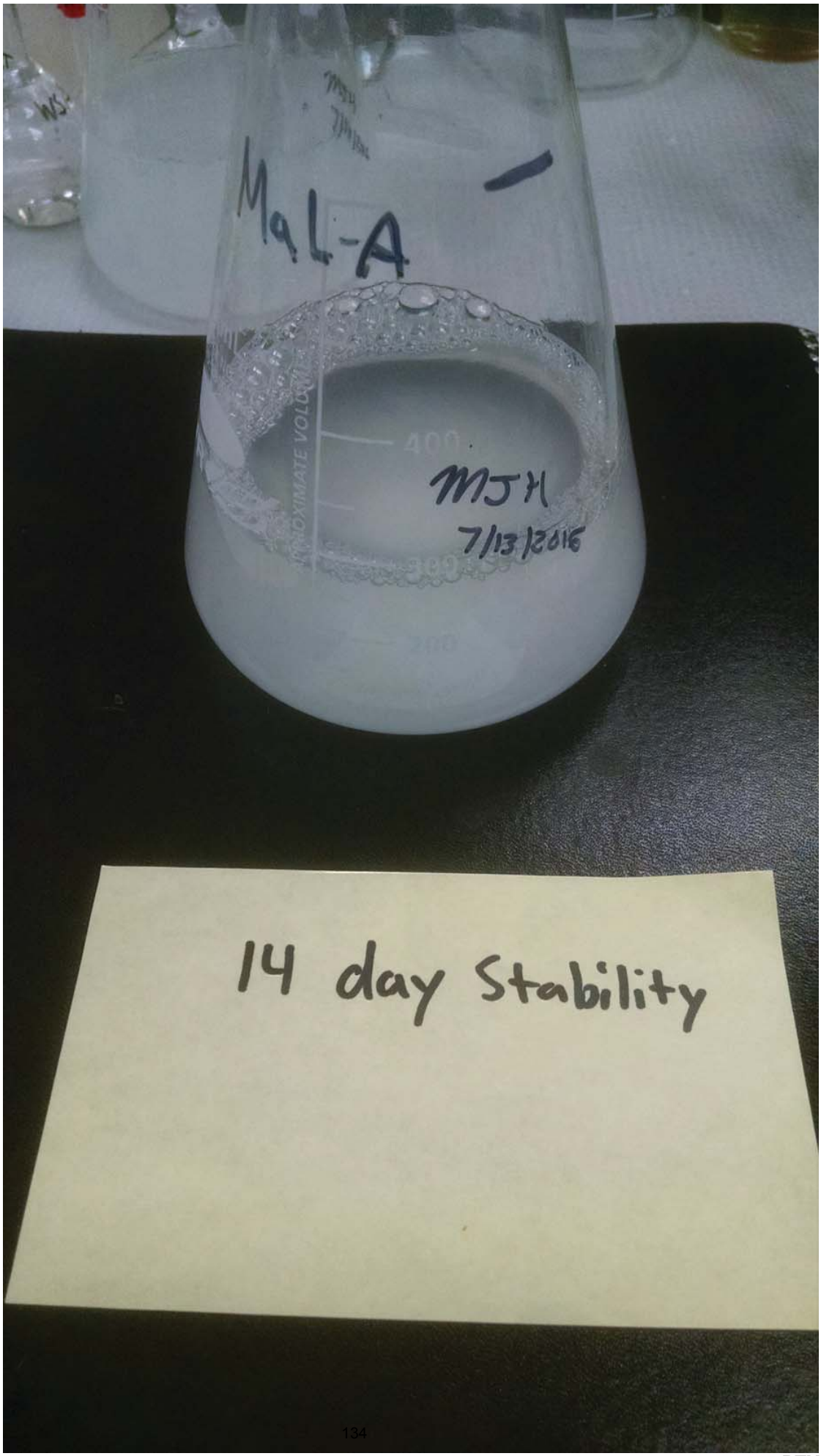

14 day Stability
after mixing

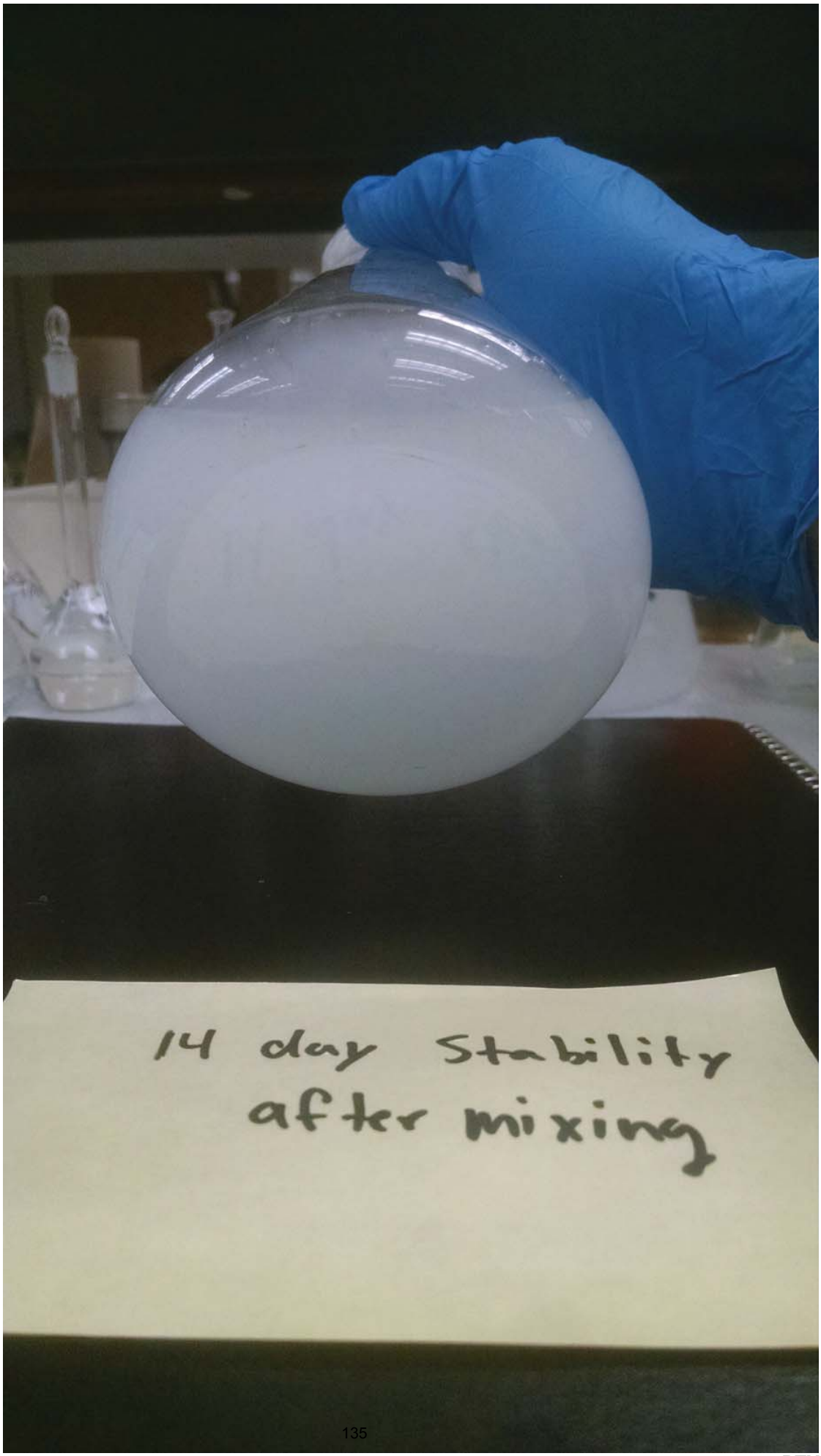

14 day Stability

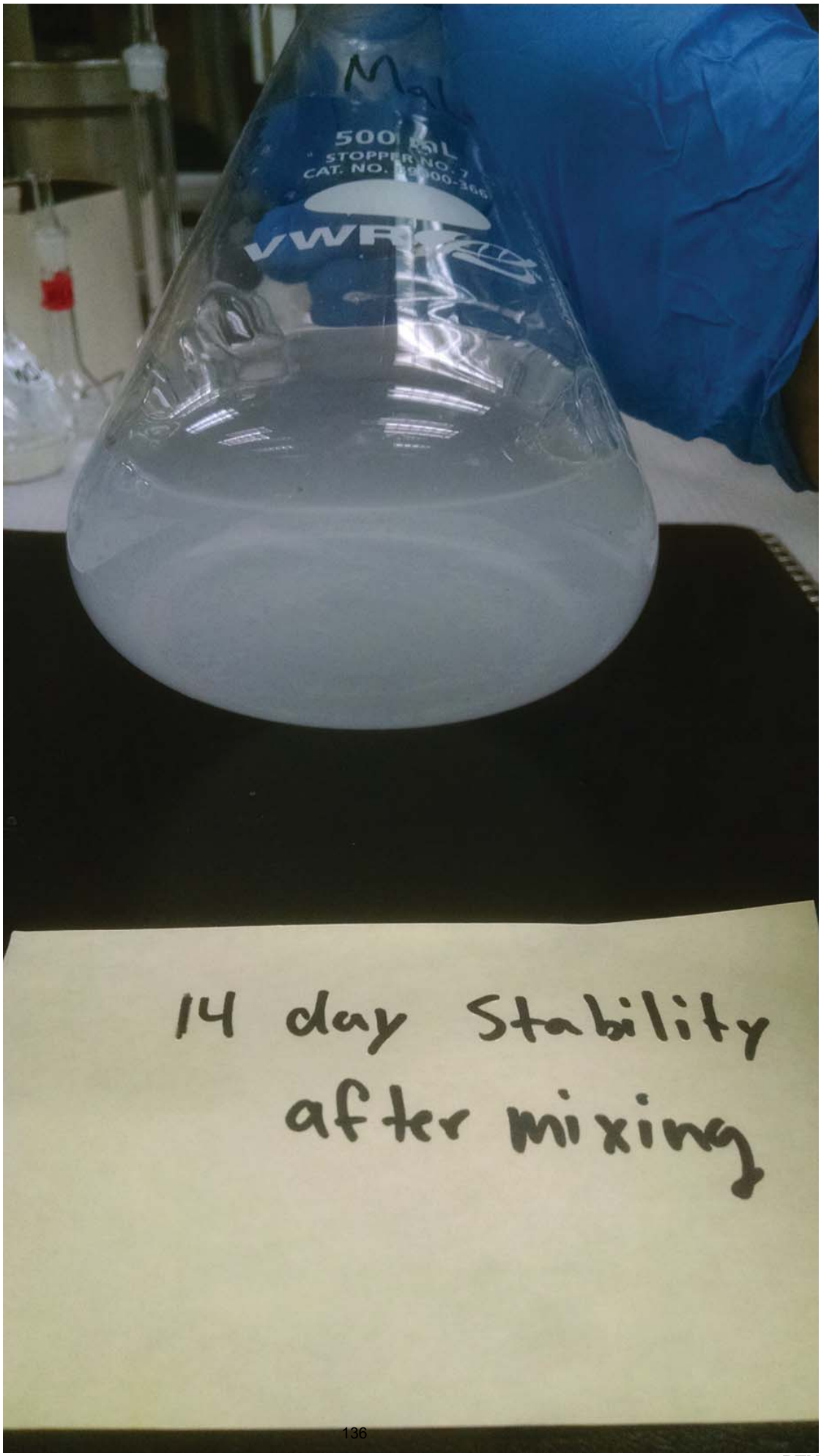

HSD
MJH
7/14/2015
14 day Stability

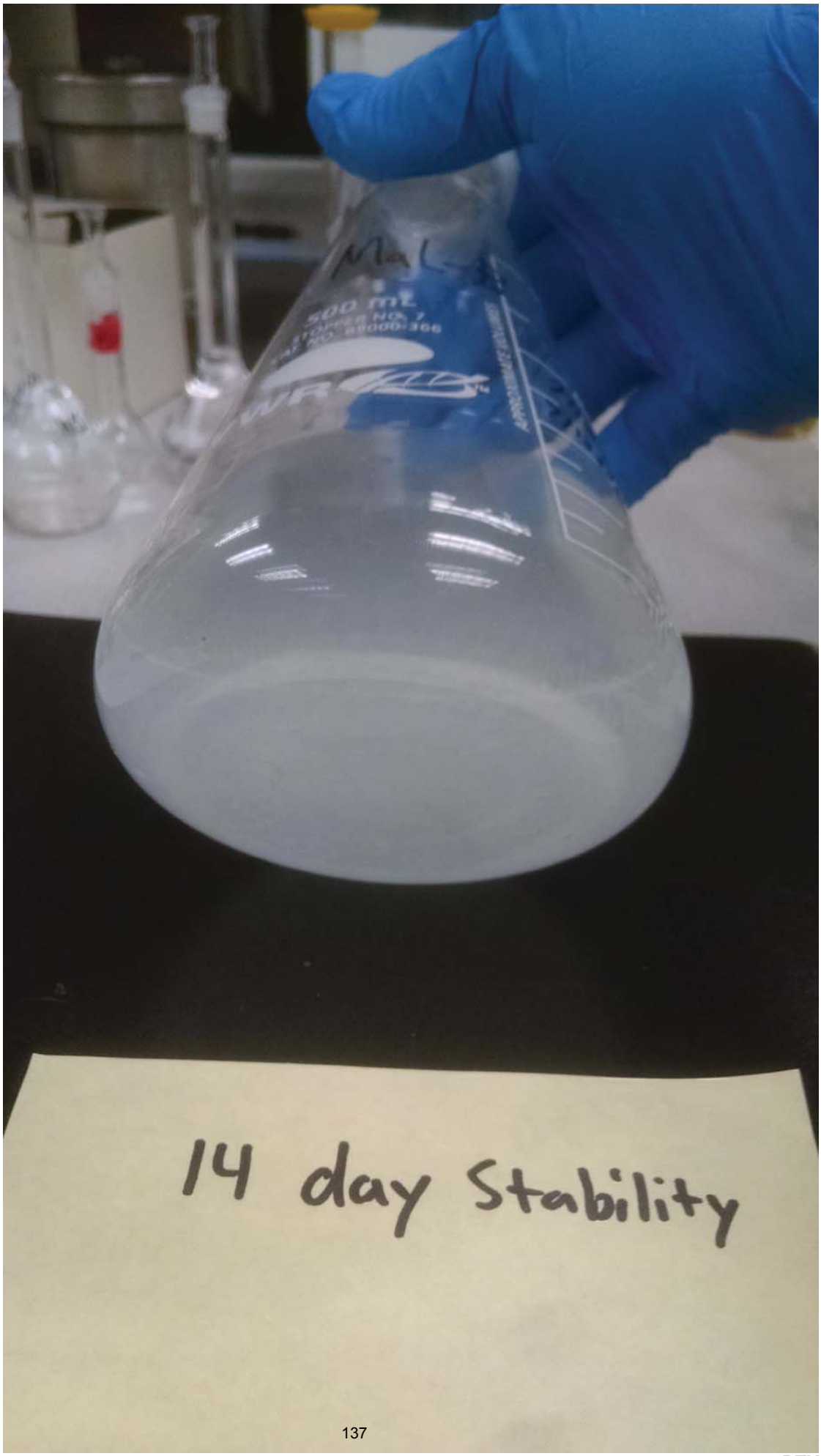

MaL-A
APPROXIMATE VOLUMES
400
300
14 day Stability
after mixing

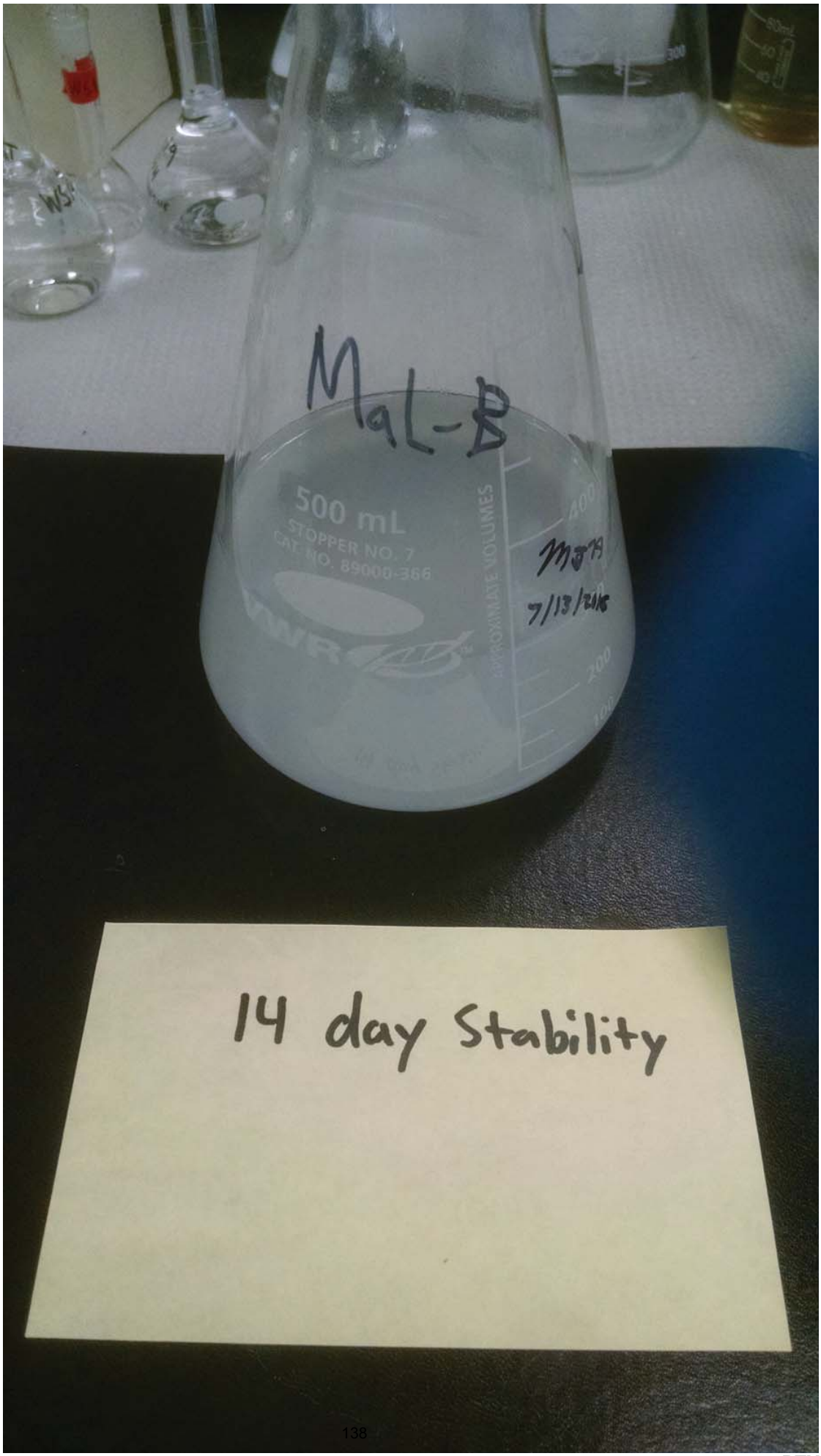

300
200
14 day Stability

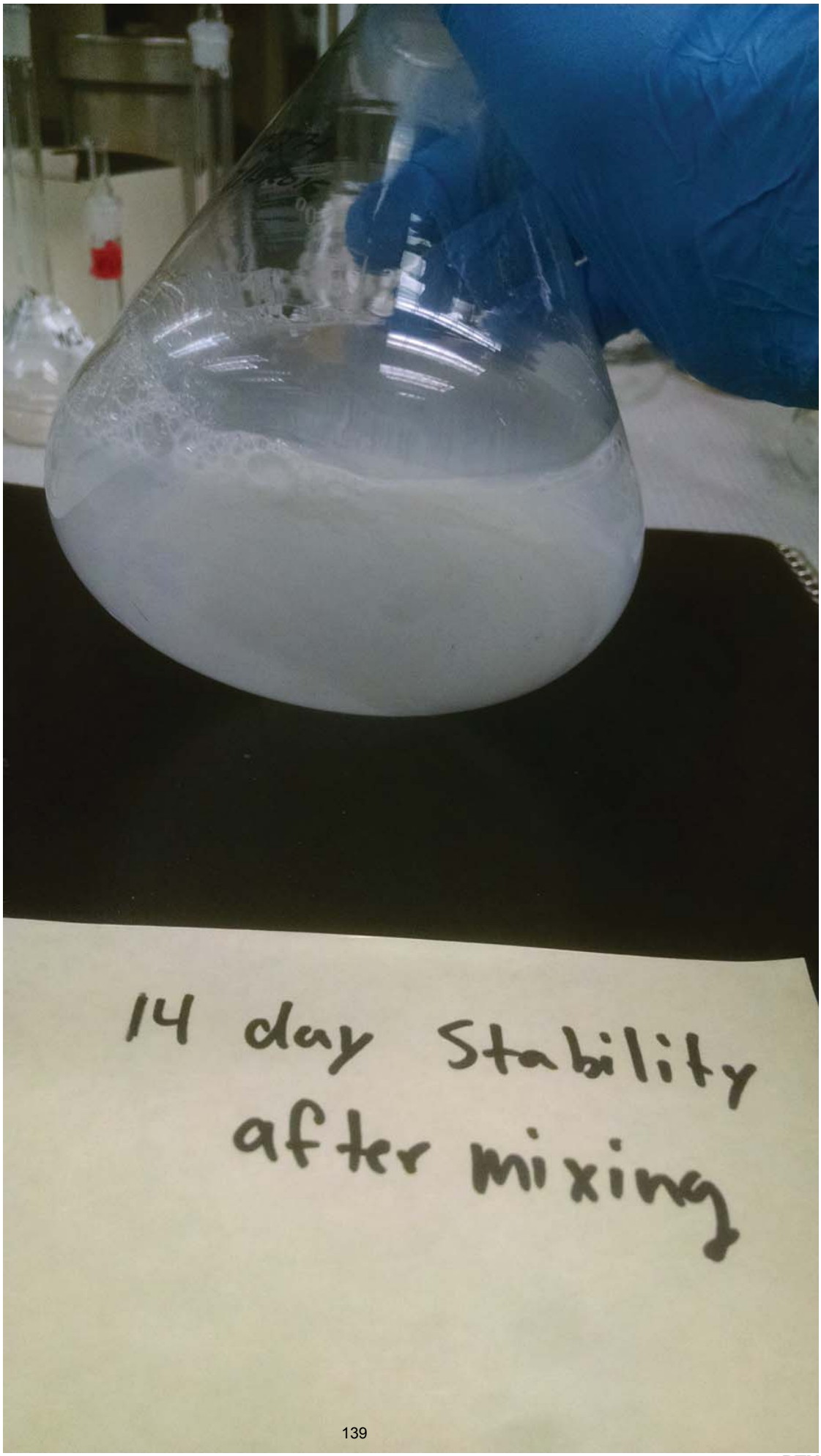

MgL-A
MJH
7/13/2016
14 day Stability

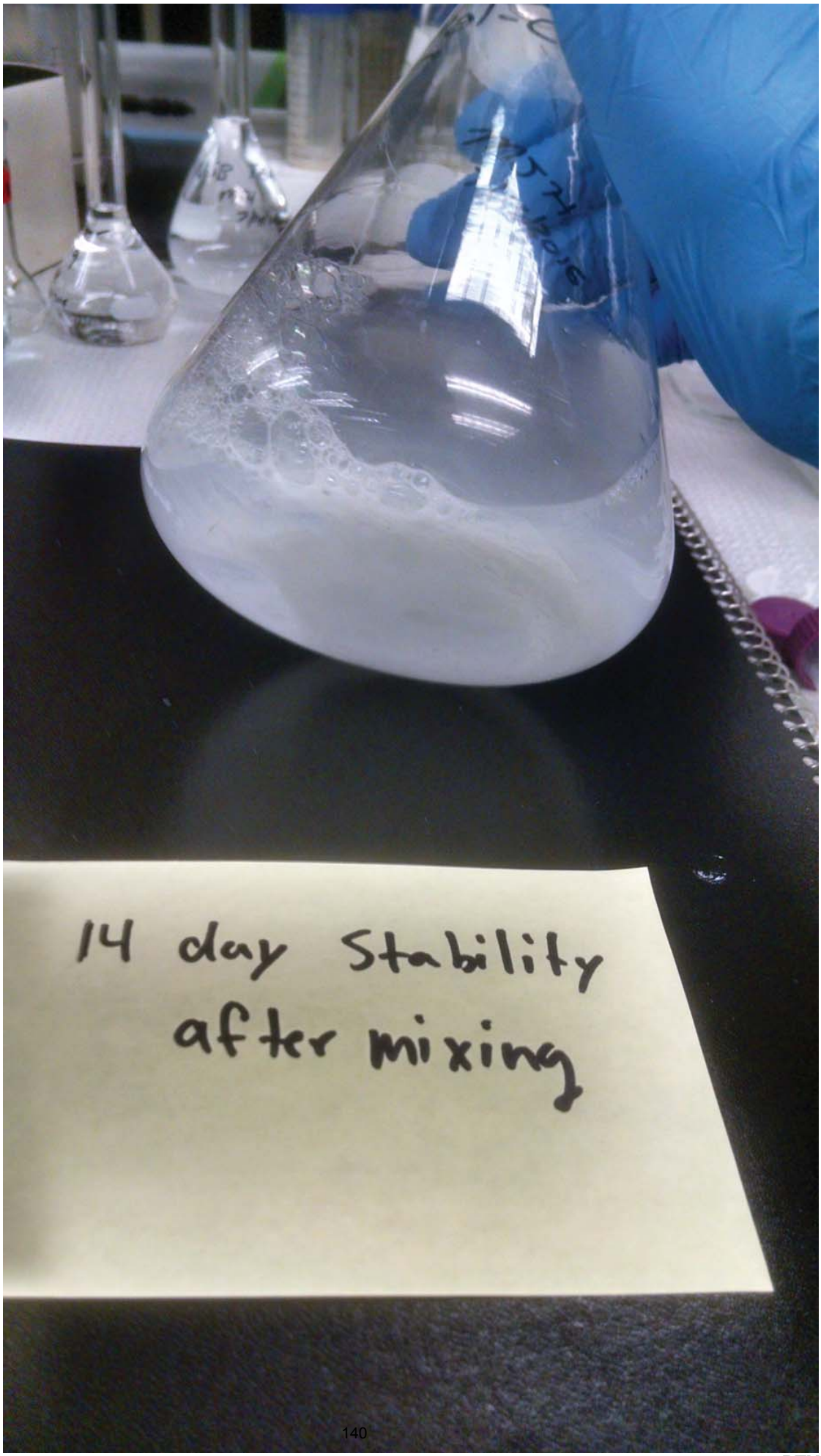

14 day Stability
after mixing

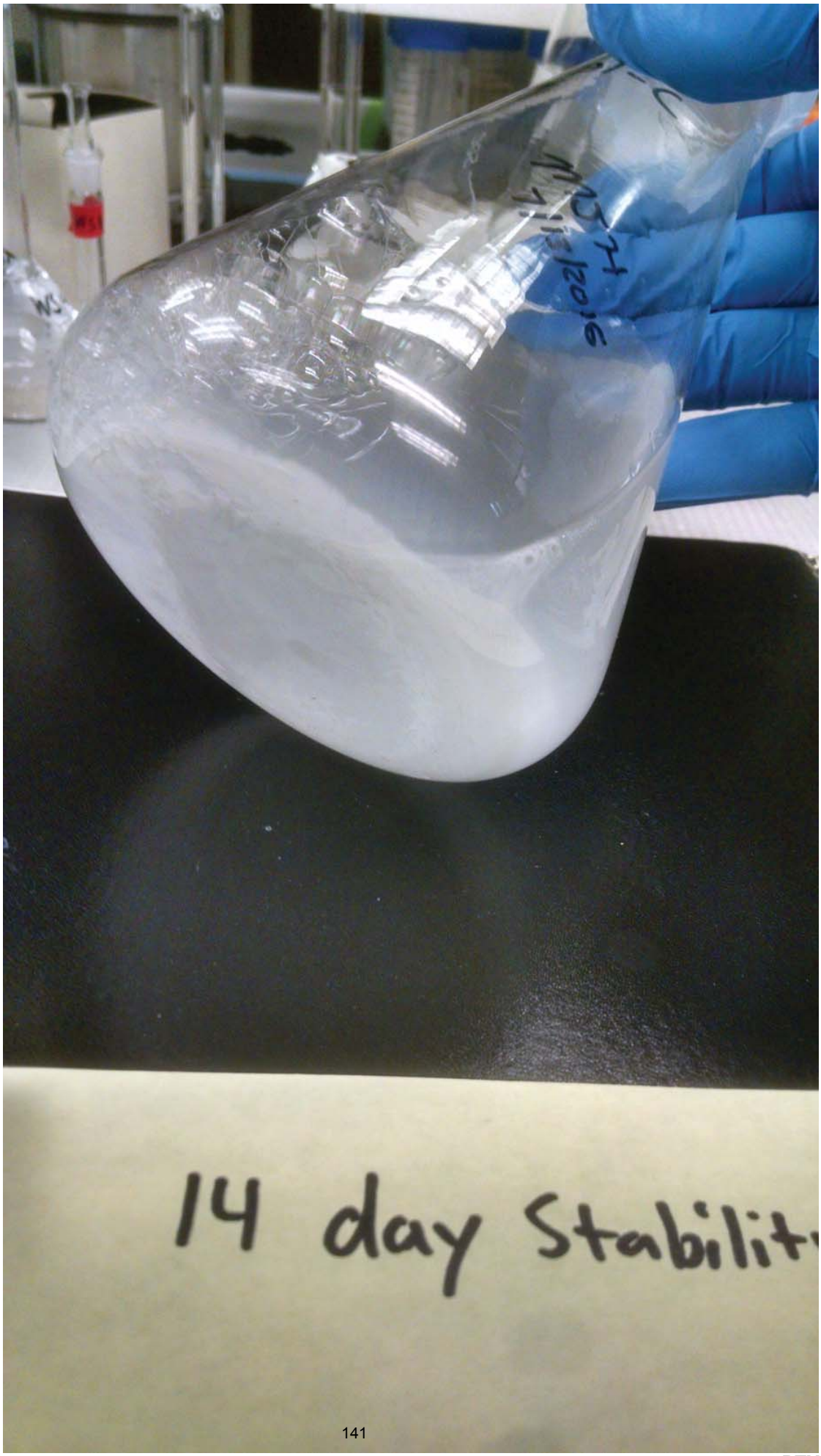

Mal
VWR
14 day Stability
after mixing

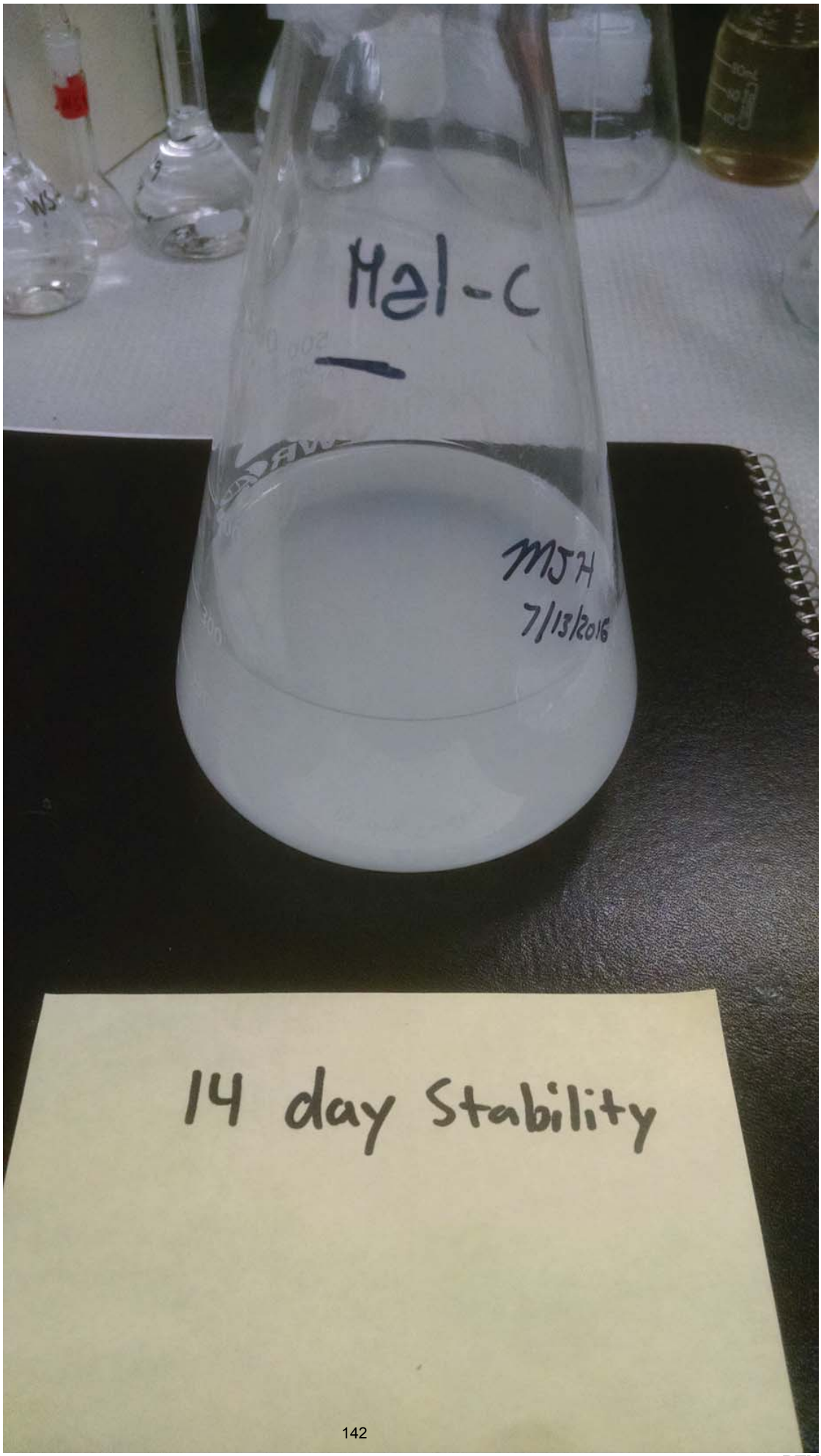

500 mL
14 day Stability

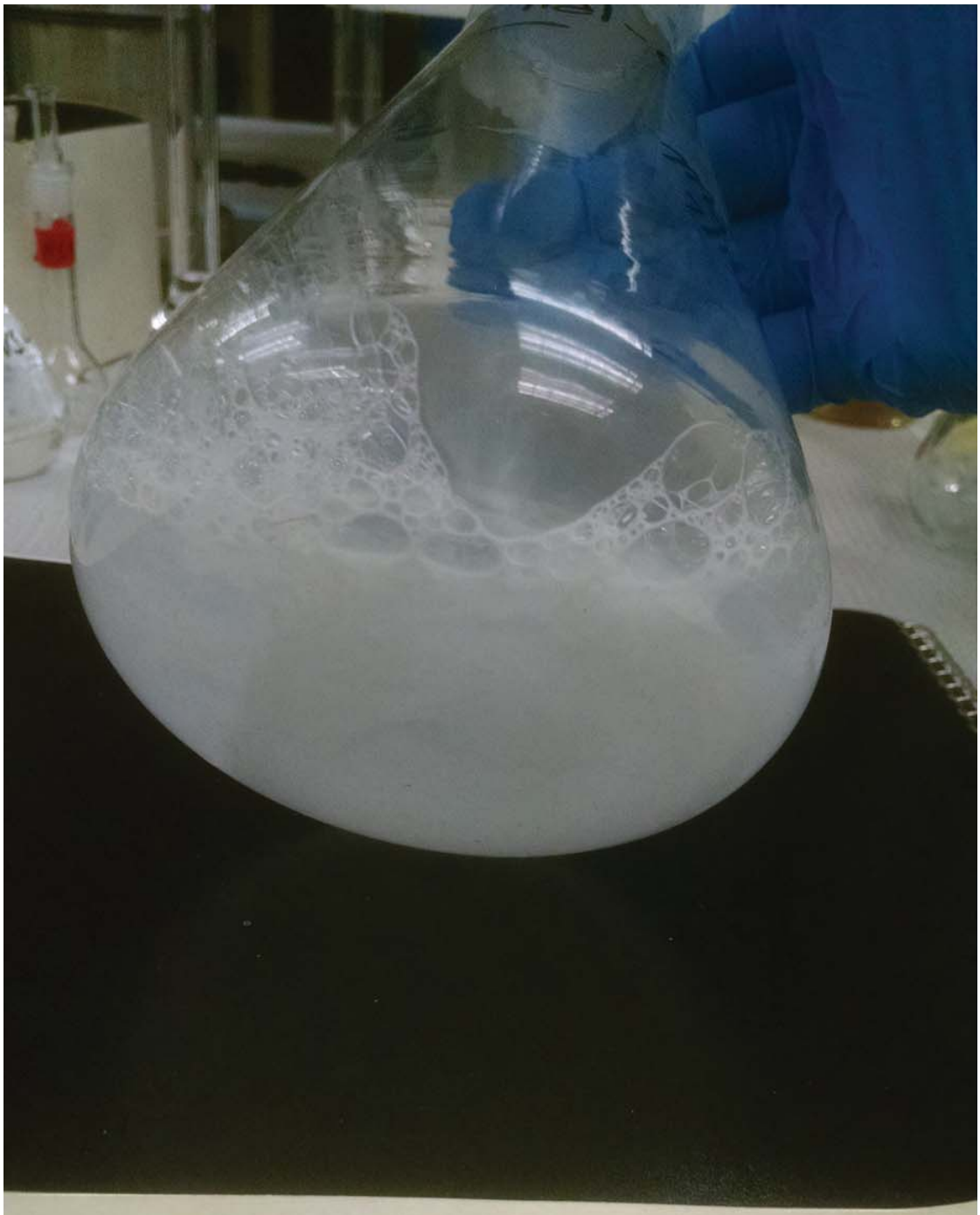

MaL-B
500 mL
STOPPER NO. 7
CAT. NO. 89000-366
MJB
7/13/2016
14 day Stability


14 day Stability
after mixing

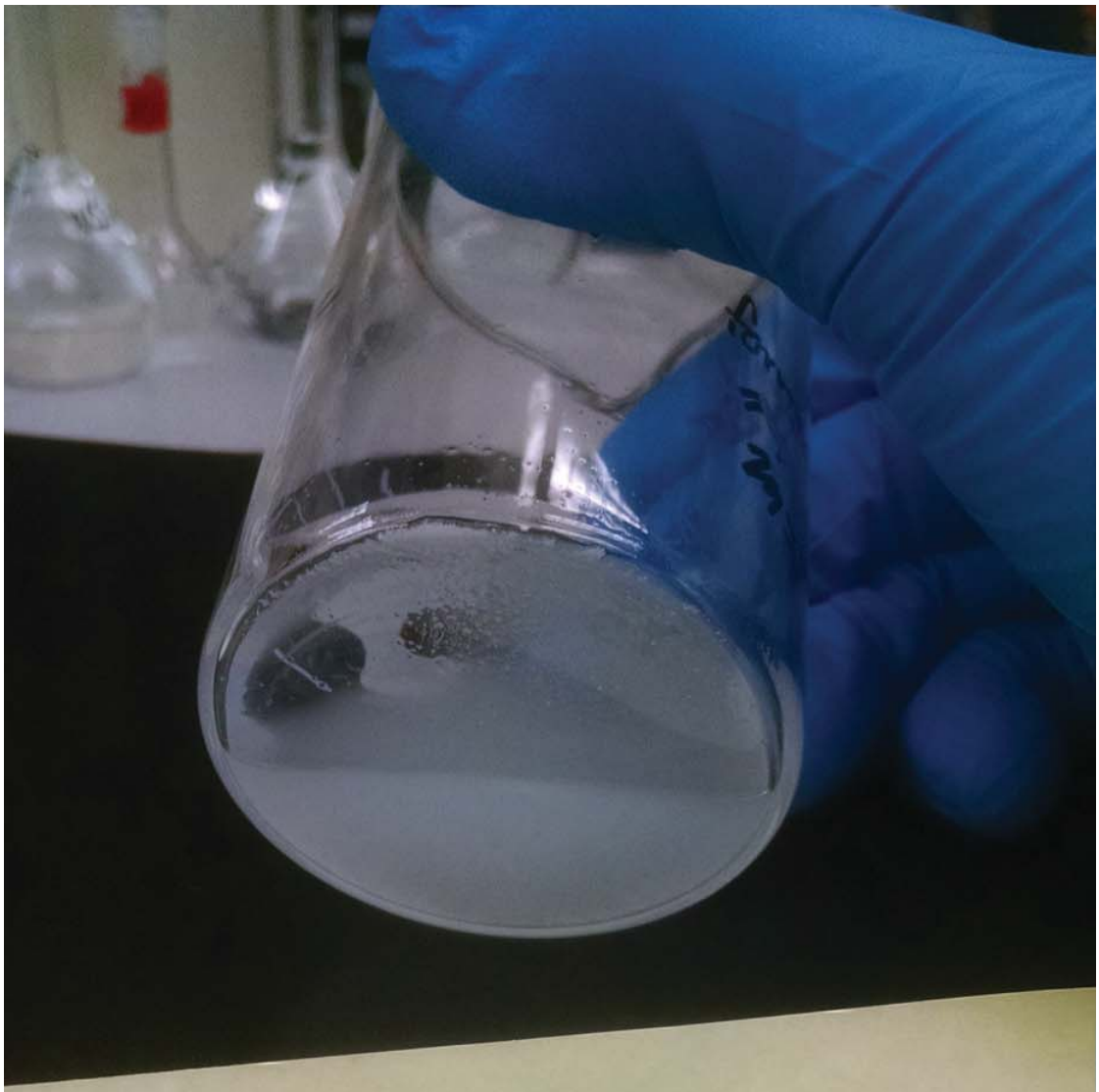

14 day Stability
after mixing


14 day Stabilit

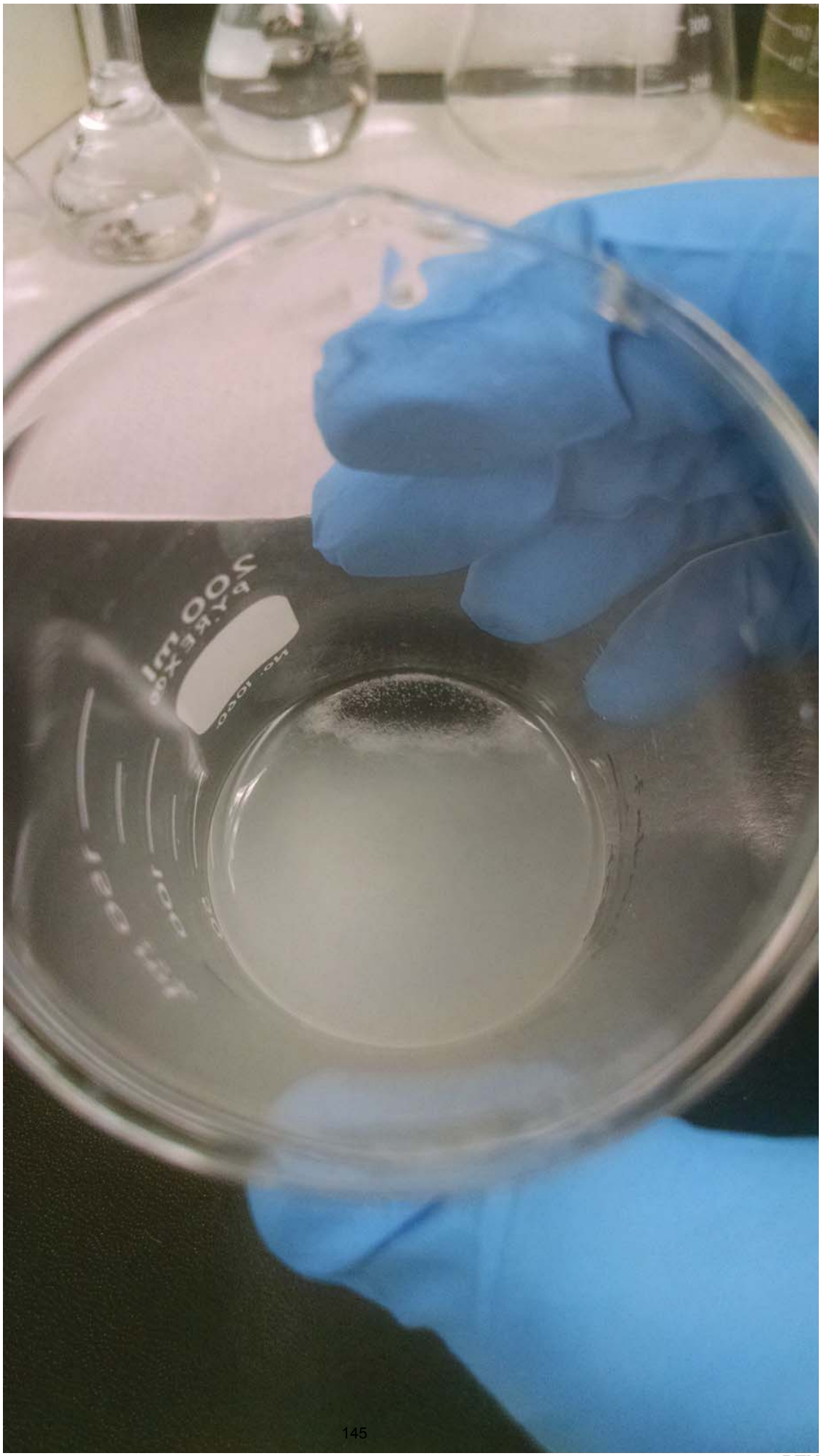

Hal-C
MJH
7/13/2016
14 day Stability

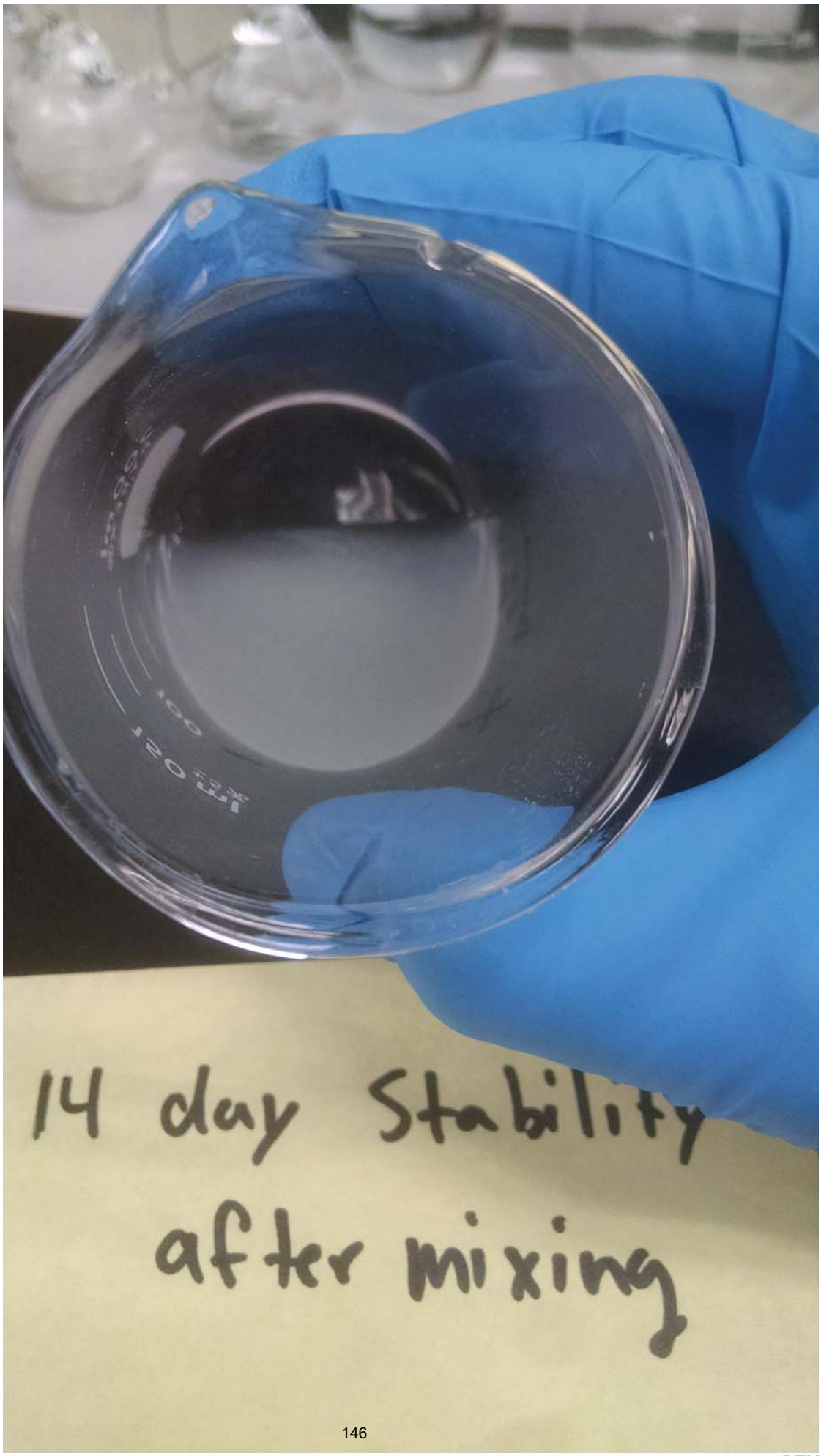


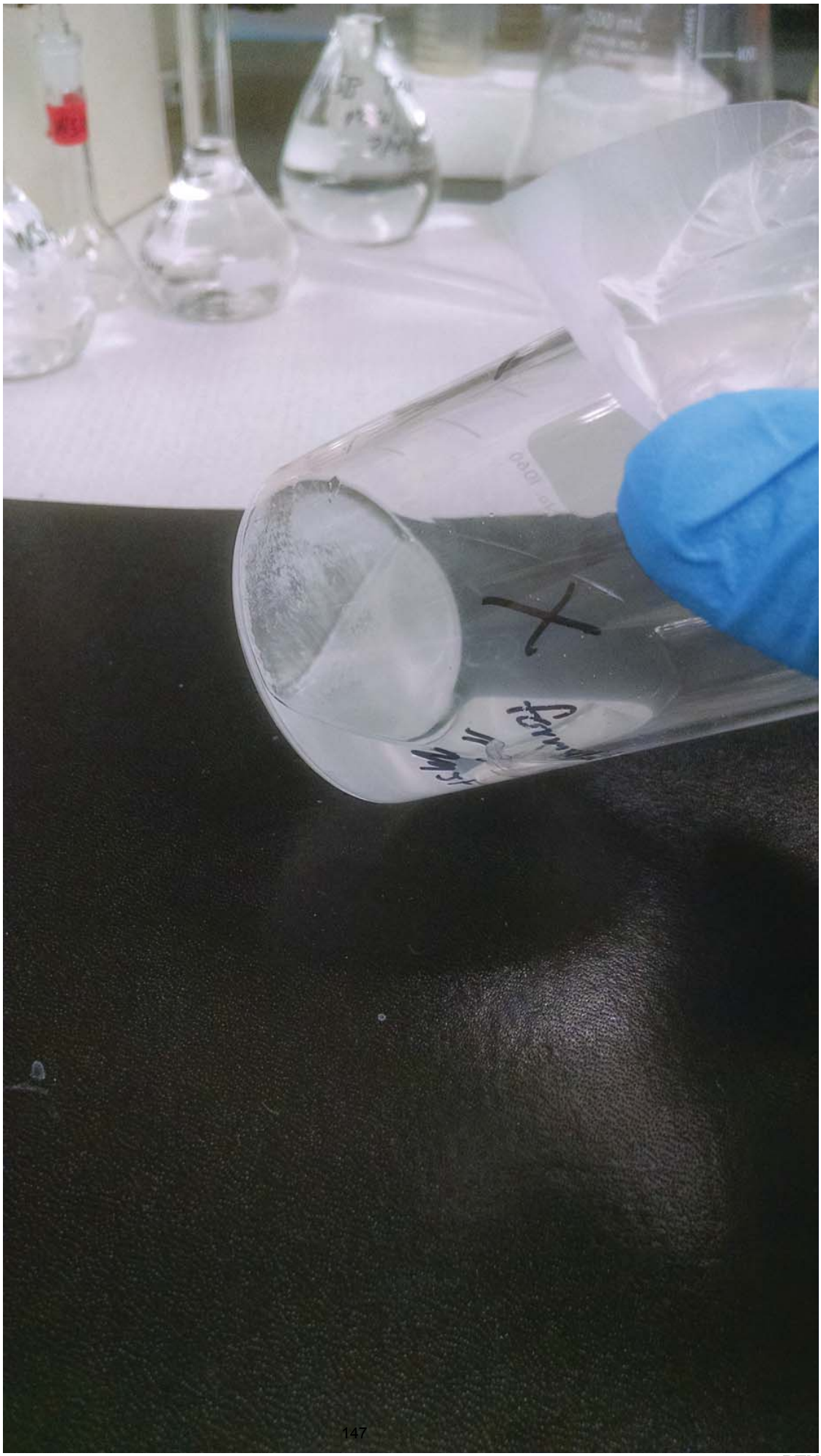
14 day Stability

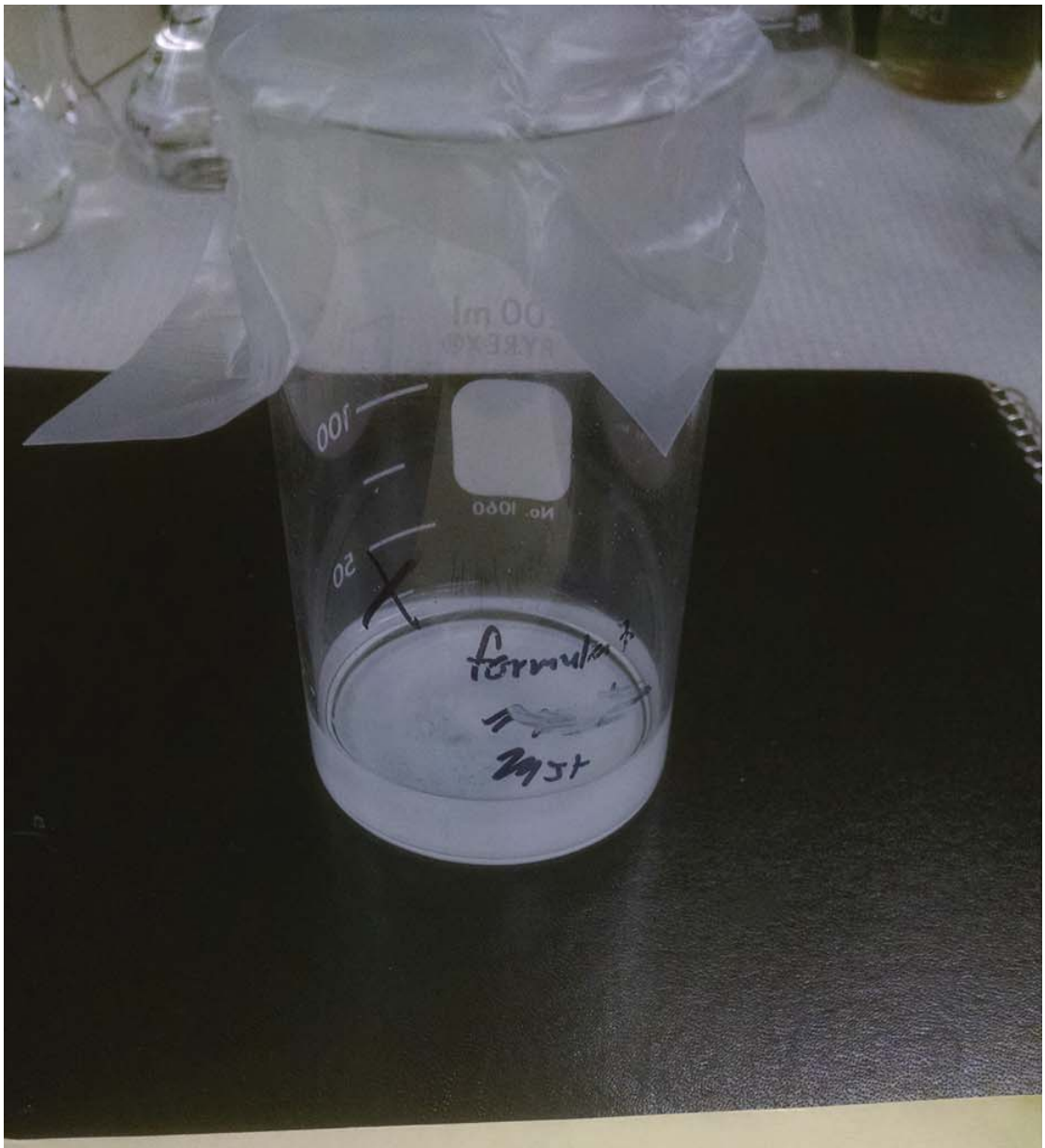


14 day Stability after mixing


PYREX
500 ml


14 day Stability
after mixing





14 day Stability

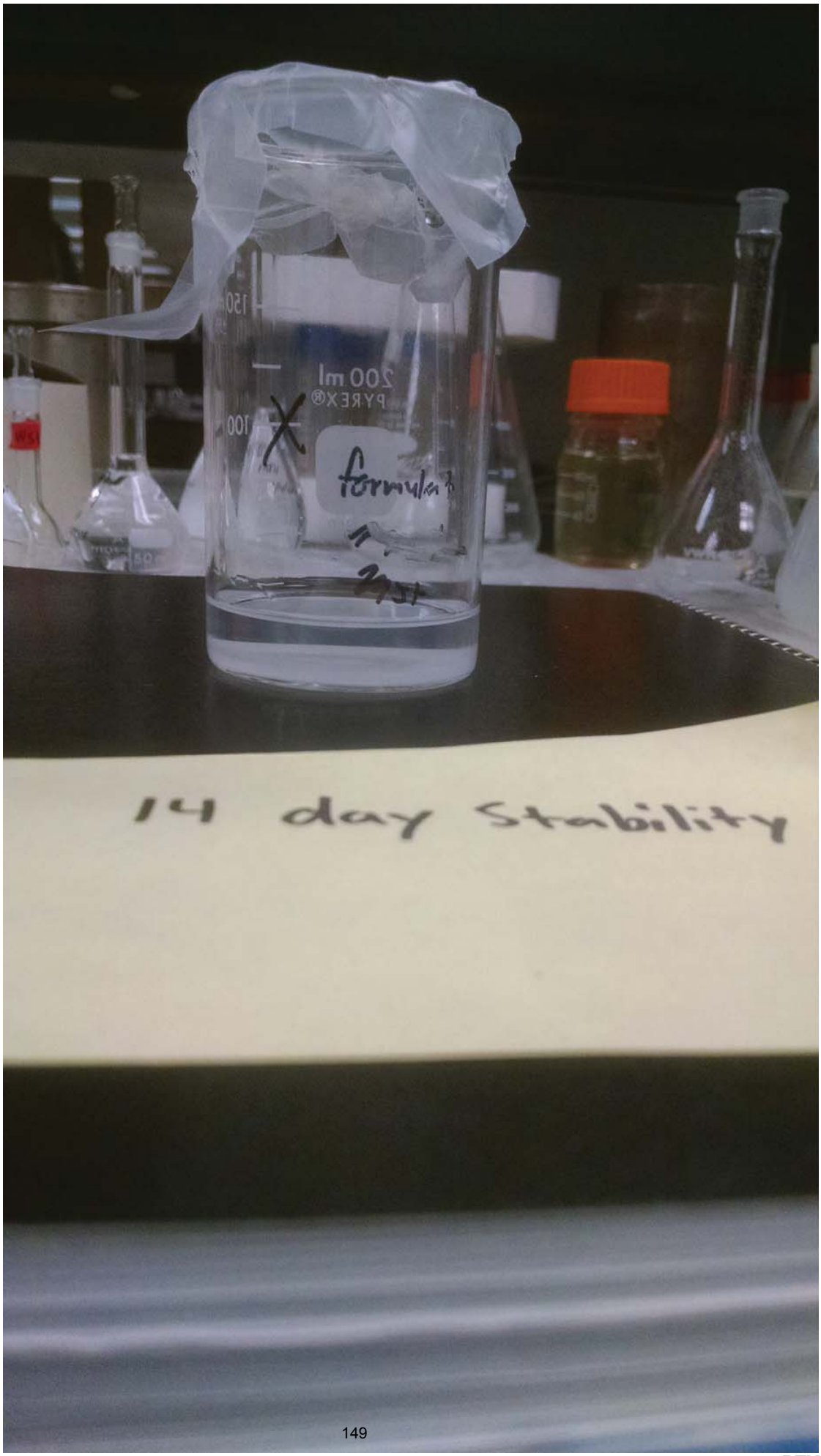

200 ml
PYREX®
formula
14 day Stability

Exhibit T - 14 Day Stability Appearance Notebook pages

14 day Appearance

Mal-A : Clearly visible settling w/ cloudy faint aqueous phase. Majority of particulates were settled in the center of the flask.

Mal-B : Visible particle settling over the bottom of the flask and the aqueous phase is more cloudy than in a other observation

Mal-C : Clearly visible settling over the bottom of the flask and there is a faint, cloudy aqueous phase.

Mal-D : Visible particle settling at the bottom of the flask with a cloudy white aqueous phase

HSD : Visible particle settling at the bottom of the flask with a cloudy white aqueous phase

X-form : Nearly transparent aqueous phase with nearly all particles deposited over the bottom of the flask.

Witnessed & Understood by me,	Date	Invented by:	Date
MJH	7/28/2016	Recorded by:	

Project No. _____

TLE _____ Book No. _____

m Page No. ____

14 day Redispersability Observations

Mal-A: Upon mixing particles began to disperse but a portion remained adhered to the center of the flask.

Mal-B: upon mixing noticeable energy was needed to disperse the particles and a small amount remained at the bottom of the flask

Mal-C: upon mixing some of the particulates began to disperse however a large portion remained stuck or caked on the bottom of the flask.

Mal-D: upon mixing there was obvious difficulty in dispersing the particles but nearly all of them eventually detached.

HSD: upon mixing there was obvious difficulty in dispersing the particles but a majority of them eventually were dispersed.

X-form: upon mixing particles were easily dispersed however large particles or agglomerates quickly settled to the bottom within a few seconds.

To Page No. ____

essed & Understood by me,	Date	Invented by:	Date
MTH	7/28/2016	Recorded by:	

Appendix A

MATTHEW J. HERPIN, Ph.D

601 Hearn Street #202 • Austin, Texas 78703 • 512.947.8626
matt.herpin@.utexas.edu

I. Personal

Born October 31st 1981 in Corpus Christi, Texas. United States Citizen.

II. Education

Ph.D., Pharmaceutics, December 2015
Advisor: Dr. Hugh D.C. Smyth
The University of Texas, Austin, TX

Bachelor of Science, Biochemistry, May 2005
The University of Texas, Austin, TX

III. Positions Held

January 2016 to Current
Postdoctoral Research Fellow- University of Texas at Austin, College of Pharmacy

May 2015 to January 2016
Graduate Research Assistant- University of Texas at Austin, College of Pharmacy

January 2012 to January 2014
PhRMA Foundation Pre-Doctoral Fellow- University of Texas at Austin, College of Pharmacy

January 2011 to May 2015
Teaching Assistant- University of Texas at Austin, College of Pharmacy
Courses:

- Physical and Chemical Principles of Drugs & Laboratory, Fall: 2011
- Pharmaceutical Compounding Laboratory, Spring: 2011, 2014, 2015

2008 to July 2010
Research Associate
Appian Labs, LLC, Austin, TX
Aeonclad Biomedical, LLC, Austin, TX
Enavail, LLC, Austin, TX

- Responsible for leading a product development group with the overall responsibility of developing solid dosage forms. The development group is comprised of formulation development and analytical team members. Reports directly to the Director of Research and Development and company President.

- Responsible for the development of solid dosage forms with a strong emphasis on products utilizing diffusion based hydrogel controlled release systems, plasma enhanced chemical vapor deposition/polymer based controlled release coatings and particle engineering technologies to drug absorption profiles and improve bioavailability.
- Provide strategic, scientific and managerial leadership to the formulation and analytical teams to solve complex drug development issues
- Develop experimental plans based on client needs and overall project goals
- Coordinate the production and analytical testing of pharmaceutical formulations
- Interpret experimental observations according to sound scientific principles
- Interact with clients and consultants to provide project updates verbally and in the form of technical reports
- Work closely with the Operations group to coordinate the transfer of technology from R&D to cGMP manufacturing
- Prepare and review batch records and standard operating procedures
- Provide and submit intellectual property ideas relating to novel pharmaceutical formulations, processing techniques or analytical methods.

2006 to October 2008
Analytical Chemist, Quality Control
Inhalation Chemist, Platform Development, and Quality Control
Pharmaform, LLC, Austin, TX

- Responsible for the USP testing of pharmaceutical dosage forms in Research and Development and in Phase I to III clinical trials. Reported to the Vice President of Quality Control
  - Interacted with clients to determine project goals and to provide project updates
  - Planned, designed, and performed experiments relating to the development of as standard method of analysis for solid dosage forms and dry powder inhalers.
  - Conducted testing on physical and chemical properties pertaining to product purity potency and performance. Including: High Performance Liquid Chromatography, USP Dissolution Testing,
  - Worked closely with method development chemists and manufacturing to solve problems associated with production.
  - Provide manufacturing analytical support.
  - Coordinated product analytical testing
  - Wrote and reviewed technical reports submitted to clients

August 2003 to 2006
Compounding Pharmacy Technician (CPhT)
Peoples Pharmacy, Austin, TX

- Responsible for compounding preparation of various pharmaceutical dosage forms including: capsules, gels, lotions, creams, suppositories, rapid-disintegrating tablets, medicated lollipops and others.
    - Assists pharmacist in the dispensing of medication to patients
    - Managing inventory and ordering supplies

IV. Relevant Training Completed

- Inhalation Aerosol Technology Workshop: University of Maryland, Baltimore.
- Waters HPLC Operation and Utilization Course
- cGMP Certification Training: Compliance LLC

V. Relevant Coursework Completed

Biopolymers: Drug and Gene Delivery
Biopharmaceutics and Pharmacokinetics
Physical and Chemical Principles of Drugs
Pharmaceutics
Pharmaceutical Compounding
Modern Advances in Pharmaceutics
Advanced Manufacturing Pharmacy
Product Development
Statistics for Translational Scientists

VI. Professional Memberships

American Association of Pharmaceutical Scientists	2011 – present
American Chemical Society	2011 – present
American Association of Advancing Science	2012 – present

VII. Current Research Interests

- Precision ophthalmic drug delivery via tunable aerosol dynamics
- Drug particle engineering by way of super-heated processing and high pressure homogenization
- Ophthalmic and pulmonary drug delivery device design and development
- Enhanced aerodynamics and performance of inhalation powders
- Preformulation, formulation, and characterization of novel delivery systems.

VIII. Formulation Development Proficiencies

- Inhalation Aerosol Based Systems- Including various nebulizers, pMDI and evaporation/condensation aerosols
- Topical Ophthalmic drug delivery systems/vehicles-
- Diffusion Based Controlled Release Tablets (direct compression)
- Various Particle Engineering Technologies: High Pressure Homogenization, Solvent Precipitation/Evaporation, Spray Drying, Super-Heated Aqueous Particle Engineering
- Solubilization/Complexation with Cyclodextrins
- Dry Powder Inhalation formulations
- Powder Encapsulation

- Preparation of Emulsions, Creams, Lotions, Gels, Suspensions
- Excipient Uses and Functionality

IX . Technical Proficiencies and Research Experience

Analytical Instrumentation and Methodology:

- UV-Vis/Fluorescence Spectrophotometers
- Fourier Transform Infrared Spectroscopy
- Laser Diffraction Particle Sizing (Sympatec-Helos)
- High Performance Liquid Chromatography-Method Development/Qualification
- Inverse Gas Chromatography
- Dynamic Light Scattering
- Atomic Absorption
- Differential Scanning Calorimetry
- Faraday Cage for Electrostatic Analysis
- Powder X-Ray Diffraction

Physical Testing

- United States Pharmacopoeia (USP) Dissolution Tests
- Angle of Repose
- Moisture Analyzer
- Next Generation Impactor (aerodynamic assessment of fine particles)
- Anderson Cascade Impactor/ Twin Stage Impactor
- Instron Compression and Elongation Analysis
- Tablet Hardness
- Tablet Friability

Biochemical Techniques

- Polymerase Chain Reaction(PCR)
- Western Blotting
- PAGE/Agarose Gel Electrophoresis
- Various enzyme activity assays

Microscopy

- Atomic Force Microscopy (AFM)
- High Performance Liquid Chromatography-Method Development/Qualification
- Two Photon Microscopy
- Scanning Electron Microscopy
- Raman Microscopy

X. Awards and Honors

- PhRMA Foundation Pre-Doctoral Fellowship (2012 - 2014)
- Teaching Excellence Award- Outstanding Teaching Assistant- 2014
- Student Entrepreneur Acceleration and Launch, Program Graduate- 2015
- Texas Venture Labs- Founding Company Participant

XI. Publications and Presentations

Herpin MJ, Raffa-Carvhalo S, Smyth HDC, McConville JT, Variable Flow Pattern Effects on Fine Particle Generation from a Dry Powder Inhaler, Littlefield Excellence in Research Poster Presentation, 2010

Bosselmann S, Owens III DE, Kennedy RL, **Herpin MJ**, Williams III RO. Plasma deposited stability enhancement coating for amorphous ketoprofen. European Journal of Pharmaceutics and Biopharmaceutics. 2011;78(1):67-74.

Donovan MJ, Gibbons A, **Herpin MJ**, Marek S, Mcgill S, Smyth HDC. Novel Dry Powder Inhaler Particle Dispersion Systems-A Review. Future Medicine. 2011

Herpin M.J, Smyth HDC, A Novel Ocular Soft Mist Aerosol Device for Tunable Drug Delivery, American Association of Pharmaceutical Scientists Conference, Poster Presentation, Oct. 2012

Herpin M.J, Smyth HDC, Non-Aqueous Aerosol Deposition for Ocular Drug Delivery, American Association of Pharmaceutical Scientists Conference, Poster Presentation, Oct. 2013

Moraga, D., Bahamondez, T., **Herpin, M.,** Maloney, A. Yazdi, A., Du, P., Du, J., Smyth, H., Hydrofluoroalkane Propellant Driven Metered Dose Inhaler Formulations. In Textbook of Aerosol Medicine.

Herpin M.J, Smyth HDC, Aqueous Based Aerosol Vehicles for Enhanced Ocular Drug Delivery, American Association of Pharmaceutical Scientists Conference, Poster Presentation, Oct. 2014

Herpin M.J., Ebi, Dominik, Clemens, N., Smyth H.D.C. Characterization of Toroidal Vortices Generated by a Novel Ocular Drug Delivery Device. *International Journal of Pharmaceutics*. 2016 (In Preparation)

Herpin M.J., Xinfei, X. Smyth, H.D.C., Super Heated Aqueous Particle Engineering for Poorly Water Soluble Drugs. International Journal of Pharmaceutics. 2016 (In Preparation)

Herpin M.J., Smyth, H.D.C. Precision Ocular Drug Delivery Via Aerosol Ring Vortices. *Drug Delivery in Translational Medicine*. 2016. (In Preparation)

Bandara, H. M. H. N., **Herpin M.J**, Kolaccny D., Harb A., Romanovicz D., Smyth H.D.C., . "Incorporation of farnesol significantly increases the efficacy of liposomal ciprofloxacin against Pseudomonas aeruginosa biofilms in vitro." *Molecular Pharmaceutics* (2016).

XI. Intellectual Property

1. Smyth, H.D.C., **Herpin M.J**., Toroidal Pharmaceutical Formulations, U.S. Patent No. 61/501,671
2. Smyth, H.D.C., **Herpin M.J.,** Method for Fine Particle Manufacture, U.S. Patent No. 14/458,818
3. Cannon C., Parth, S., Smolen, J., Smyth H., Yazdi A., **Herpin M.J**., Antimicrobial and Anti-Inflammatory Compositions. Provisional U.S. Patent Application. # 62/168,561

Appendix B

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing using E4MP HMPC and micronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the mixing techniques described in Cramer Example I.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	E4MP (4000 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E4MP will be tested
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			This drug will be in suspension and will therefore need to be procured in micronized form.
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Preparation according to Example I

Example III will be prepared by combining the following components utilizing "conventional mixing techniques similar to that described in Example 1":

> In an appropriately sized vessel, the dextrose, polysorbate 80 and benzalkonium chloride are added one at a time to water with mixing, allowing each to dissolve or completely disperse before adding the next. To this is added, with mixing, a premixed slurry of the avicel and water. Upon forming a uniform solution, the beclomethasone, loratadine and phenylethyl alcohol are added. After all the ingredients are added, purified water is used to bring the batch to the appropriate weight.

Accordingly 500 mL of Example III will be made using the procedure outlined below:

1. In an appropriately sized vessel to manufacture 500 mL of product,
    a. To 100 mL of distilled water
    b. Add polysorbate 80
    c. Mix step – Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
    d. Add benzalkonium chloride
    e. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
    f. Add glycerin

g. Mix- Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
h. Add EDTA
i. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed
j. Add NaCl
k. Mix - Approximately 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed

2. In a separate vessel the hydroxyl methylcellulose is prepared"
    a. As per the Handbook of Pharmaceutical Excipients (2^{nd} Edition, 1994) 20% of the required water is used to hydrate the HPMC (100 mL distilled water)
    b. The water is vigorously stirred at RPMs adequate to disperse the powder and heated to approximately 90 deg C
    c. While stirring, the HPMC is added, and mixing continues until all particles are thoroughly wetted
    d. Then to the dispersed HPMC, 200 mL of cold distilled water is added while mixing
    e. The mixture is then cooled to between 20 to 25°C (68 to 77°F) or below as according to the Methocel™ product guide ("How to Prepare Aqueous Solutions of METHOCEL™").
3. This premixed HPMC mixture is then added to the ingredients of step 1 to form a uniform solution.
    a. Note: Since Example III does not list the grade of HPMC used, this experiment will be replicated using grades AAA, BBB, and CCC. The manufacturer has stated that each grade is suitable for nasal administration.
4. To this solution Triamcinolone and Azelastine are added and mixed at 100-300 rpm with an overhead stirrer with a impeller stirring system, until visually mixed.
    a. Perform bulk product testing (top, middle, and bottom) to ensure stability over a period (2-3 or more hours) sufficient to demonstrate uniformity of the bulk following production.
5. The samples are then mixed using a high-speed homogenizer.
6. The formulations are then filled into nasal spray bottles (approximately 16.5 g per bottle) and spray pumps fitted to the bottles.
7. Filled bottles will be stored at room temperature and optionally additional bottles not stored at room temperature will be stored at accelerated stability conditions (40 deg C and 75% RH).
8. Bottles will be tested at time points indicated below using various performance assays.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual Inspection of spray quality	a. Visual observation of emission of formulation during actuation of pump	Observation of spray/jet/ failure to emit	Qualitatively assesses acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			

Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing Following Malhotra Method using E3 Prem HMPC and micronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	Low viscosity: E3 PREM LV (3 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E3 Prem will be tested
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			This drug will be in suspension and will therefore need to be procured in micronized form.
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Preparation by Method Detailed in Geena Malhotra's 2011 Declaration

The technique will use the ingredients and process described below:

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.

10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.

11) Volume was made-up with purified water.

12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual	a. Visual observation of emission of formulation	Observation	Qualitatively assesses

Inspection of spray quality	during actuation of pump	of spray/jet/ failure to emit	acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing Following Malhotra Method using E3 Prem HMPC and Unmicronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	Low viscosity: E3 PREM LV (3 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E3 Prem will be tested
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

A. Preparation by Method Detailed in Geena Malhotra's 2011 Declaration

The technique will use the ingredients and process described below:

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.

10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.

11) Volume was made-up with purified water.

12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual	a. Visual observation of emission of formulation	Observation	Qualitatively assesses

Inspection of spray quality	during actuation of pump	of spray/jet/ failure to emit	acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/7/16

Nasal Spray Manufacturing and Characterization Testing Following Malhotra's Method using E4MP HMPC and micronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	E4MP (4000 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E4MP will be tested.
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			This drug will be in suspension and will therefore need to be procured in micronized form.
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Preparation by Method Detailed in Geena Malhotra's 2011 Declaration

The technique will use the ingredients and process described below:

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.

10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.

11) Volume was made-up with purified water.

12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual	a. Visual observation of emission of formulation	Observation	Qualitatively assesses

Inspection of spray quality	during actuation of pump	of spray/jet/ failure to emit	acceptability of spray
Spray Content Uniformity	a. Dose collection tubes b. HPLC drug assay c. Actuation Station d. Analytical Balance	SMA-001-00	Quantitative assessment of the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
Droplet Size Analysis*	a. Sympatec Laser Diffraction	SMA-003-00	Assesses the spray quality.
Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
Solid Particle Size*	a. Light Microscopy	SMA-002-00	Assesses the stability of the suspended particles and can inform on particle aggregation/agglomeration.
Osmolality*	a. MicroOsmette- Freezing Point Depression Osmometer	SMA-008-00	
Plume Geometry*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.
Spray Pattern*	a. Spray View or Comparable Analysis Software b. Actuation Station	SMA-005-00	Quantifies spray characteristics.

Time points will be evaluated at 0, 7, and 14 days. The samples will be stored in ambient storage conditions. pH will be measured at all time points.

V. Report

A report detailing the preparation methods and results of the testing will be provided.

Final Protocol
7/716

Nasal Spray Manufacturing and Characterization Testing Following Malhotra's Method using E4MP HMPC and Unmicronized Triamcinolone

I. Purpose

The purpose of this experiment is to re-create and evaluate the disclosure in EP 0780127 ("Cramer") to determine whether it a nasal spray with properties that are suitable for nasal administration. Specifically, this experiment will recreate Example III for an intranasally administered composition comprising triamcinolone acetonide and azelastine HCL.

Example III from Cramer will be prepared following the method set forth in Geena Malhotra's declaration submitted to the U.S. Patent and Trademark Office on August 12, 2011.

Samples will be evaluated for appearance, spray content uniformity, spray pattern, droplet size, particle size, viscosity, stability, and osmolality, for example.

II. Materials

INGREDIENT	Grade	SUPPLIER	NOTES
Polysorbate 80			
Benzalkonium chloride			
Glycerin			
Hydroxypropyl methylcelluose (HPMC)	E4MP (4000 mPas)	Dow	HPMC is available in multiple grades (viscosities) and chemical substitution. Since this is not defined within the patent example, E4MP will be tested.
Sodium Chloride			
Ethylenediamine tetraacetic acid (EDTA)			
Distilled water -			
Triamcinolone acetonide			
Azelastine HCl			

III. Preparation of Cramer Example III

Cramer Example III is:

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine HCl was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.
10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.
11) Volume was made-up with purified water.
12) Stirring was done with a high-speed homogenizer and pH was checked.

IV. Product Performance Testing and Characterization

Typically several tests are performed for nasal products as part of standard characterization testing protocols to determine pharmaceutical acceptability. For the current testing the selected methods to characterize the product in terms of formulation appearance, spray characterization, uniformity of dosing, viscosity, osmolarity, and physical stability of the suspension.

TEST	EQUIPMENT	Protocol #	Notes
Appearance	a. Visual Inspection	SMA-007-00	Qualitative assessment of homogeneity and pharmaceutical acceptability . Looks at sedimentation, separation of suspended particles, agglomeration, redispersability of suspension upon shaking. This will be done on both formulation and the filled bottles.
Assay	a. HPLC Assay to assess the potency of Suspended Triamcinolone Acetonide	HPLC Method	10 mLs of sample will be drawn off the top, middle and bottom of formulated composition, and then again after 3 Hrs to determine blend uniformity/settling stability
Pump Delivery	a. Analytical Balance	SMA-009-00	Quantitative assessment of the variability of formulation dispensing from the nasal spray pump. A Valois Nasal Spray Pump from Aptar will be used. Pump: VP7
Visual Inspection of spray quality	a. Visual observation of emission of formulation during actuation of pump	Observation of spray/jet/ failure to emit	Qualitatively assesses acceptability of spray
Spray	a. Dose collection tubes	SMA-001-00	Quantitative assessment of

Content Uniformity	b. HPLC drug assay c. Actuation Station d. Analytical Balance		the variability of emitted dose from the nasal spray pump. Will be quantified using Triamcinolone acetonide assay.
*The Following Tests Only to be Conducted As Needed to Supplement Previous Findings			
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Viscosity*	a. Dynamic	SMA-004-00	Assesses the viscosity of the product and will assist in interpretation of product performance tests.
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