Exhibit 1

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
CLARKSBURG DIVISION

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **JURY TRIAL DEMANDED** **HIGHLY CONFIDENTIAL — OUTSIDE COUNSEL'S EYES ONLY**

OPENING EXPERT REPORT AND DECLARATION OF DR. FRANKLIN SWARTZWELDER REGARDING MYLAN'S INFRINGINGMENT OF U.S. PATENT NO. 11,104,715

TABLE OF CONTENTS

I. INTRODUCTION AND SUMMARY OF OPINIONS

1. I have been retained on behalf of Plaintiff Regeneron Pharmaceuticals, Inc. ("Plaintiff" or "Regeneron") as an independent expert witness in this case. This expert report and declaration sets forth my analyses and opinions based on my knowledge, experience, and the materials I have considered.

2. In this report and declaration, I offer opinions concerning the process employed by Mylan to manufacture its aflibercept product, M710. I have compared that process to the processes of claims 2-3, 6, 12-14, and 16 of Regeneron's U.S. Patent No. 11,104,715 ("the '715 patent"). Based on my analysis, Mylan's manufacturing process satisfies each and every element of these claims. I provide a brief summary of my infringement opinions below.

3. As part of its cell culture process, Mylan uses host cells that have been genetically engineered to express aflibercept. The particular host cells that Mylan uses are Chinese Hamster Ovary, or "CHO," cells.

4. [redacted]

5. [redacted]

6. [redacted]

7. Claims 2, 13, and 14 of the '715 patent recite color limitations of the harvest. [redacted]

[redacted]

Regeneron Protected Material

9. Claim 6 of the '715 patent requires a particular type of host cell. [redacted]

[redacted]

10. Based on my analysis of Mylan's manufacturing and formulation processes, it is my opinion that the aflibercept produced by the patented processes is not materially changed by any subsequent process. None of Mylan's purification or formulation steps are intended to modify the aflibercept protein itself. Moreover, the aflibercept produced by the patented process does not become a trivial or nonessential component of another product; rather, aflibercept is the active ingredient in Mylan's M710 drug product.

II. BACKGROUND AND QUALIFICATIONS

11. My qualifications are described in detail in my *curriculum vitae*, which is attached as Appendix A.

12. I have more than 30 years of experience in developing cell culture technology and processes. Much of my work and research has focused specifically on investigating and improving on mammalian cell culture products for use in biopharmaceutical manufacturing.

13. I received my Ph.D. in 1986 in Microbiology/Immunology from SUNY Buffalo, School of Medicine and Biomedical Sciences. The topic of my thesis was "The Mechanism of Activation of Murine B Lymphocytes by Lipopolysaccharide."

14. From 1989 through 1999, I worked at GIBCO Life Technologies, which I now understand to be part of ThermoFisher Scientific. At GIBCO, my early work focused on optimization of serum-free media for the culture of various cell lines, including those for Madin-Darby bovine kidney (or "MDBK") cells, Madin-Darby canine kidney (or "MDCK") cells, and fibroblast cells (*i.e.*, cells that contribute to the formation of connective tissue). During the last five years of my tenure at GIBCO, I led a Regenerative Medicine Media Development Group in the development of novel products for hematopoietic stem cells for analysis and the growth/expansion of human stem cells for clinical applications.

15. In 1999, I joined Gencyte, LLC, where I established a stem cell product development laboratory and Current Good Manufacturing Practice (or "cGMP") production capabilities within the company, as required by the U.S. Food & Drug Administration ("FDA"). Generally, cGMP regulations require systems that properly design, monitor, and control manufacturing processes and facilities.

16. In 2002, I co-founded Stemgenix, LLC—a spin-off of Gencyte—to focus on the development and commercialization of media products related to human stem cell research and clinical work. There, my team and I designed and commercialized a platform of over twenty media and cell culture products for stem cell research and clinical stem cell transplantation markets.

17. In 2003, I joined Sigma-Aldrich Corporation/SAFC, which subsequently became MilliporeSigma in 2015, where I remained until my retirement from industry in December 2021.

Throughout my tenure at MilliporeSigma, I focused on the design, development, and manufacture of catalog cell culture products and new custom Chinese Hamster Ovary (or "CHO") cell culture media products for several large biotherapeutic manufacturers.

18. Throughout my career, I frequently worked as a consultant with pharmaceutical companies to assist them with their development of cell culture products and processes. As part of that work, I routinely assessed existing cell culture processes—and accompanying data—to recommend improvements in media compositions or other aspects of their cell culture processes.

19. In 2016, I established an upstream processing Scientific Advisory Board ("SAB"), an expert network of scientists immersed in biological research, drug discovery, and biopharmaceutical production. In this role, I organized and led two SAB events for MilliporeSigma's BioProcessing Business. The outputs for these events were then integrated into the company's future strategic plans for the business.

20. In 2017, I became one of the original members of the Advanced Mammalian Biomanufacturing Innovation Center ("AMBIC"), which is a consortium of leading academic and industrial biotechnology experts focused on mammalian cell culture manufacturing at a precompetitive research level. In 2018, I was selected as the first AMBIC Mentor of the Year in recognition of outstanding project leadership and student mentorship.

21. In 2020, I was elected as the Chair-Elect and 2021 Chair of the AMBIC Industrial Advisory Board ("IAB"). During that time, I led a 30-member board of biotherapeutic manufacturers and suppliers in determining organizational research direction and funding for the consortium. As AMBIC IAB chair, I also worked with the AMBIC Center Director at Johns Hopkins University and academic leadership at each of the other four member universities

(Clemson University, University of Delaware, University of Massachusetts Lowell, and the University of Maryland) to ensure funding and implementation of industry research initiatives.

22. Most recently, in 2021, I organized and led the Innovation Summit for MilliporeSigma Process Solutions Division, which had over one hundred members.

23. I am being compensated for my work in this case at a rate of $350 per hour plus expenses. My compensation is in no way tied to the outcome of this case or the content of my testimony. I have not testified as an expert at trial or by deposition in the last four years.

III. ASSIGNMENT AND LEGAL STANDARDS

24. It is my understanding that Mylan has submitted Biologics License Application ("BLA") No. 761274 to the FDA requesting permission to market a biosimilar version of Regeneron's EYLEA (aflibercept) product in the United States, which Mylan refers to as M710. *See* MYL-AFL-BLA0001752 at 1754 ("This application is being submitted for Viatris' and Janssen Pharmaceuticals' codeveloped product, M710, a proposed biosimilar to Eylea® (Regeneron Pharmaceuticals Inc., United States and Bayer Healthcare Pharmaceuticals Inc., Germany).").

25. I have been asked to compare Mylan's process for manufacturing its biosimilar M710 product to claims 2-3, 6, 12-14, and 16 of the '715 patent (the "Asserted Claims") using the claim constructions discussed in Section IV, *infra*. I understand that this comparison is called an infringement analysis and that for Mylan to infringe a particular claim of the '715 patent, Mylan's biosimilar product—or the process used to manufacture Mylan's biosimilar product—must meet or satisfy all the limitations recited in the claim, literally or under the doctrine of equivalents.

26. In the absence of an express claim construction from the Court, I have been informed that in performing an infringement analysis, I am to use the ordinary and customary

meaning that the claim terms would have had to the hypothetical Person of Ordinary Skill in the Art ("POSA") as of the relevant date. My opinions with respect to the qualifications of the POSA as of the dates relevant to the '715 patent are discussed in Section IV, *infra*.

27. I have been informed that to literally infringe a patent claim, an accused product or process must have or perform each and every limitation of the claim exactly as recited. However, even in the absence of literal infringement, I have been informed that an accused product or process may nonetheless infringe under the doctrine of equivalents if the differences between the accused product or process and the claimed invention would have been insubstantial to the hypothetical person of ordinary skill in the art. The difference between an accused product or process and a claimed invention can be considered insubstantial if the missing element or step in the accused product or process performs substantially the same function in substantially the same way to achieve substantially the same result as the claimed invention.[1]

28. I have been informed that a biosimilar manufacturer who seeks FDA approval to market a biosimilar product that falls within the scope of a claim infringes that claim as a matter of law. Thus, if a BLA specification overlaps the scope of a given claim limitation, the biosimilar has infringed that limitation. For example, it is my understanding that if a biosimilar applicant seeks approval to manufacture and sell a product containing anywhere between 0.0–0.6% of a particular substance, then that proposed product would infringe a claim requiring that the composition contain less than 0.25% of the substance. I have been informed that for purposes of this inquiry, it does not matter whether the product as ultimately manufactured, or every batch of the product as ultimately manufactured, meets the limitations of the claim. The

[1] As discussed below, it is my opinion that Mylan literally infringes all of the Asserted Claims. I reserve the right in the future to offer an opinion regarding Mylan's infringement under the doctrine of equivalents.

relevant question is whether the BLA requests permission from the FDA to market a product that, based on the BLA specification, may fall within the scope of a patent claim.

29. I have been informed that infringement of a process patent can be found on the act of selling or offering to sell—or seeking approval from the FDA to sell—within the United States a product which is made outside the United States by a process patented in the United States. I understand that this act constitutes infringement unless the product made by the patented process has been "materially changed" by subsequent processes or the product is a trivial or nonessential component of another product. I understand that this means a product will be considered to have been made by a patented process if the additional processing steps which are not covered by the patent do not change the physical or chemical properties of the product in a manner which changes the basic utility of the product produced by the patented process.

30. I have been informed that, in actions alleging infringement of a process patent based on the importation, sale, offer for sale, or use—or where an applicant is seeking approval from the FDA for the sale—of a product which is made from a process patented in the United States, the product is presumed to have been made by the patented process if (1) a substantial likelihood exists that the product was made by the patented process, and (2) the plaintiff has made a reasonable effort to determine the process actually used in the production of the product and was unable to do so. I have further been informed that, for the purposes of this test, a "substantial likelihood" is less than a preponderance of the evidence (*i.e.*, more likely than not) but more than a slight possibility.

31. In arriving at my opinions contained in this report and declaration, I have considered my training, knowledge, basic texts and scientific principles, experience in the

relevant scientific disciplines, as well as the materials cited herein. A list of materials that I considered is set forth in Appendix B.

32. In addition to the opinions discussed in this report and declaration, I will be prepared to address, if asked, additional background information concerning the scientific principles underlying my expert opinions. If asked, I will be prepared to present a basic tutorial to explain the terms and concepts related to my opinions set forth in this report and declaration, the state of the art, the level of ordinary skill in the art, and the patent at issue. This tutorial may include demonstrative exhibits. In addition to the opinions expressed in this report and declaration, my testimony may include responses to facts, arguments, allegations, or references raised by other parties or experts in this litigation. I also reserve the right to supplement my conclusions if additional information is provided or if additional research leads me to conclude that supplementation is necessary.

IV. THE PERSON OF ORDINARY SKILL IN THE ART

33. I have been asked to provide my opinion as to the qualifications of the hypothetical person of ordinary skill in the art ("POSA") to whom the inventions disclosed and claimed in the '715 patent were directed. I have been informed that factors for determining ordinary skill in the art may include one or more of the following: (1) the educational level of the inventors; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the relevant technology; and (6) the educational level of workers active in the field. I have considered these factors in my analysis. I have also been informed that the POSA may possess the skills, education, and experience of multiple individuals working together as a team.

34. For the purposes of this report, I have been asked to assume the relevant date for the '715 patent to be December 6, 2019, which I understand to be the filing date of one of the U.S. provisional applications to which the '715 patent claims benefit.

35. I have been informed that there are potentially other relevant dates for the '715 patent, including August 13, 2020 and August 18, 2020. The opinions I express in this report would not change were I to consider any of these other dates to be the relevant date of the '715 patent. I reserve the right to supplement my opinions concerning the relevant date of the '715 patent based on additional information provided to me.

36. In my opinion, the POSA for the '715 patent would have had a doctoral degree in chemical engineering, molecular biology, or a related discipline and experience in the process development and manufacture of recombinant proteins in mammalian cell lines for therapeutic use. Alternatively, the person of ordinary skill could have less formal education (*i.e.*, a B.S. or M.S.), with a commensurate increase in their years of post-graduate experience. The POSA would also have been familiar with a variety of issues relevant to the manufacturing of pharmaceutical proteins, including, among other things, cell culture media and analytical characterization techniques. This level of skill is consistent with the backgrounds of the individuals I have interacted with in this field over my career.

V. SCIENTIFIC AND TECHNICAL BACKGROUND

37. I have been asked to provide a brief technical background, which is set forth below.

38. Proteins can recognize and bind specifically to other molecules. Protein-based biopharmaceutical compositions can treat, among others, ophthalmological diseases, cancer, autoimmune disease, and infections. '715 patent, 1:31-34.

39. Over the past few decades, scientists have identified particular proteins that bind specifically to targets of therapeutic interest. For example, aflibercept is an engineered protein capable of binding to a protein known as Vascular Endothelial Growth Factor ("VEGF") and neutralizing it, thereby helping to treat various eye disorders caused by the overproduction of VEGF in the eye. '715 patent, 1:31-67.

40. Therapeutic proteins can be made in so-called "recombinant" cell lines that have been genetically engineered to produce the protein. Birch 2006 at 672.[2] These recombinant cell lines are often mammalian. *Id.* One such mammalian cell line is a Chinese Hamster Ovary (or "CHO") cell line. *Id.* It is necessary to cultivate large quantities of such cells to manufacture commercial quantities of a therapeutic protein. The cell culture field is concerned with the processes and technologies for doing so.

A. Cell Culture and the Cell Culture Medium

41. Cell culture, as a noun, in its most general sense refers to the act of growing cells in an artificial environment. Cell Culture Basics at 2.[3] "[T]he artificial environment in which the cells are cultured invariably consists of a suitable vessel containing a substrate or medium that supplies the essential nutrients (amino acids, carbohydrates, vitamins, minerals), growth factors, hormones, and gases (O_2, CO_2), and regulates the physiochemical milieu (pH, osmotic pressure, temperature)." *Id.*

42. While many cells must be anchored to a solid support to grow in culture, the cells typically used in the industrial manufacture of proteins have been adapted to be "grown floating

[2] The Birch 2006 review is a general overview of protein production.

[3] This handbook is distributed by ThermoFisher Scientific and Gibco, two vendors of reagents and supplies for culturing cells. The handbook is intended to assist their customers with using their products to culture cells successfully, and it provides a useful introduction to cell culture.

in the culture medium." *Id.* Such cultures are known as "suspension cultures." *Id.* Because suspension cultures can be grown at larger scales, they are the preferred type of culture used for the industrial manufacture of proteins. Birch 2006 at 675 ("The preferred culture format for large-scale (substantially greater than 10 L) is single cell suspension.").

43. The liquid in which a cultured cell floats is referred to as the "culture medium" or cell culture media. Cell Culture Basics at 2. As the Handbook explains, "[t]he culture medium is the most important component of the culture environment, because it provides the necessary nutrients, growth factors, and hormones for cell growth, as well as regulating the pH and the osmotic pressure of the culture." *Id.* at 21.

44. There are different types of cell culture media. Some cell culture media components are derived from tissue extraction or animal body fluids, such as plasma, lymph, and serum. One example is fetal calf serum.

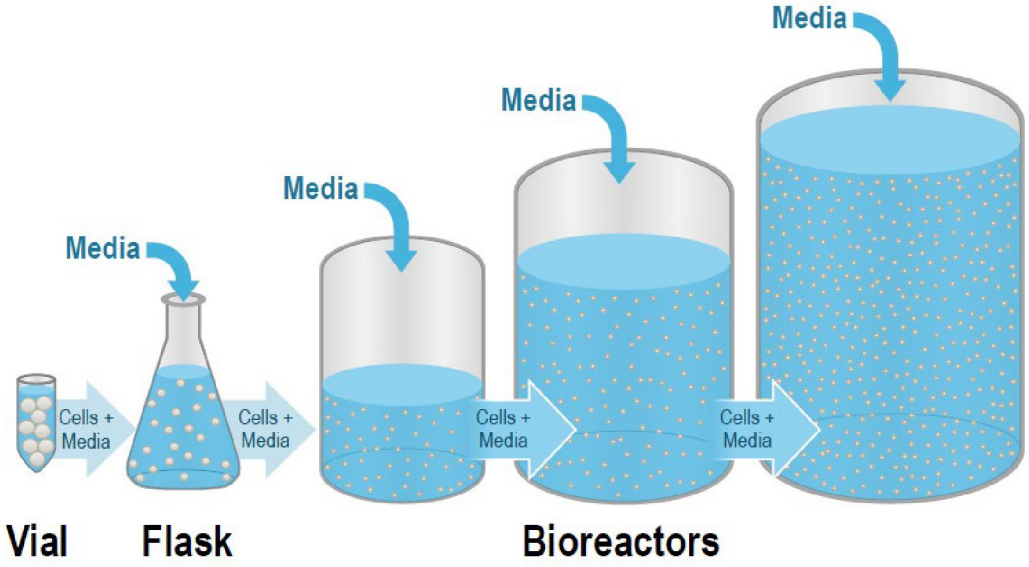
45. "Chemically defined" media is a type of media that, as the '715 patent explains, is a "synthetic growth medium in which the identity and concentration of all the ingredients are defined." '715 patent, 30:44-47. In the context of the '715 patent, "[c]hemically defined media do not contain bacterial, yeast, animal, or plant extracts, animal serum, or plasma, although individual plant or animal-derived components (e.g., proteins, polypeptides, etc.) may be added." *Id.*, 30:47-51.

46. The culture medium's composition depends upon the composition of its component parts. The solution introduced to the bioreactor—an apparatus designed to grow mammalian cells under controlled conditions—is typically referred to as the "basal cell culture medium" or "base cell culture medium." The "inoculum" typically refers to the cells (and any culture medium in which the cells were grown that is carried over in the transfer) that is used to

"seed" or initiate a subsequent stage of the cell culture process. In "fed-batch" cell culture processes, nutrients continue to be added to the culture medium over the course of production. The solutions added to the culture medium are referred to as "feeds." All of these components affect the culture medium's composition at a given point in time.

B. Large-Scale Cell Culture Operations

47. The industrial manufacture of proteins happens on a massive scale. Typical cell culture processes culminate in culturing the cells in bioreactors that can be as large as 20,000 liters.[4] Birch 2006 at 678, 680. The below illustration sets forth the stages of a typical cell culture process.

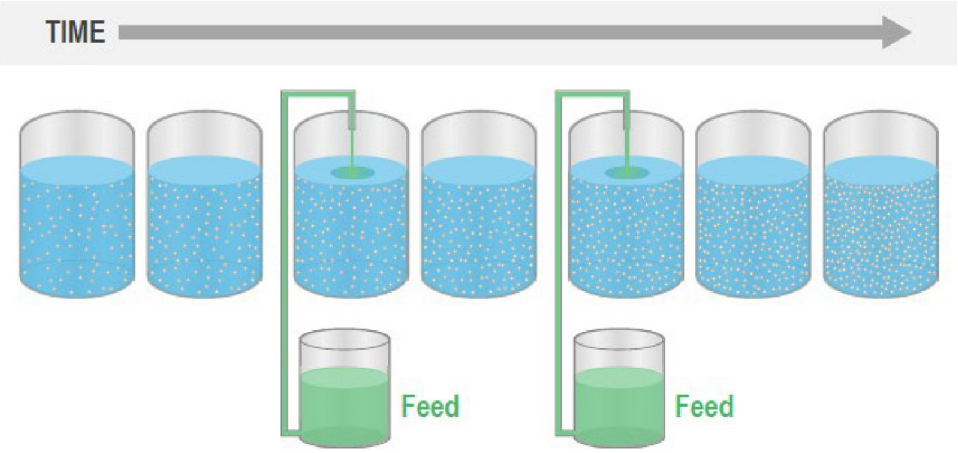


48. The cell culture process is initiated with a single vial of frozen cells taken from a "working cell bank." Those cells, sometimes referred to as an "inoculum," are transferred to a larger flask. After the cell number has expanded sufficiently, the cells are transferred to

[4] A bioreactor typically allows a manufacturer to manage specific characteristics of the cell culture like temperature, pH, gas (*e.g.*, oxygen, carbon dioxide), and agitation controls to support cell growth and production.

successively larger bioreactors. At each stage, media is added that contacts the cells and supplies nutrients. That added media is combined with the cells and media from the previous stage of the process. The above description is an example of how a large-scale process may be implemented. In practice the number of expansion steps from vial thaw to the final bioreactor will vary depending on process requirements.

49. One type of cell culture process is known as a "fed-batch" process because the "basal" cell culture medium is supplemented with "feeds." Birch 2006 at 678. Those feeds are typically solutions added to replenish the supply of nutrients in the cell culture medium during production. I have illustrated the addition of feeds to a bioreactor below.



50. In the typical protein manufacturing process using CHO cells, the protein is secreted by the cells into the culture medium. The protein that has been secreted by the cells throughout the process is then "harvested." '715 patent, 55:49-52. As the '715 patent explains, "[w]here the protein of interest is secreted into the medium, supernatants from such expression systems can be first concentrated using a commercially available protein concentration filter, for example, using an Amicon™ or Millipore Pellicon™ ultrafiltration unit. In one aspect, the

protein of interest may be harvested by centrifugation followed by depth filtration and then affinity capture chromatography." *Id.*, 55:45-52.

VI. THE '715 PATENT

51. In this section of my report, I analyze the '715 patent. I first discuss aspects of the patent's disclosure in its "specification," *i.e.* the text and figures of the patent. I then discuss aspects of the claims of the '715 patent, which are at the end of the specification. Finally, I discuss the instructions I have received about how to interpret those claims.

A. Specification

52. The '715 patent is titled "Methods for Producing Aflibercept in Chemically Defined Media Having Reduced Aflibercept Variants." It states on the first page that it is assigned to Regeneron Pharmaceuticals, Inc.

53. The '715 patent defines "cumulative amount" as "the total amount of a particular component added to a bioreactor over the course of the cell culture to form the CDM, including amounts added at the beginning of the culture (CDM at day 0) and subsequently added amounts of the component. Amounts of a component added to a seed-train culture or inoculum prior to the bioreactor production (i.e., prior to the CDM at day 0) are also included when calculating the cumulative amount of the component. A cumulative amount is unaffected by the loss of a component over time during the culture (for example, through metabolism or chemical degradation). Thus, two cultures with the same cumulative amounts of a component may nonetheless have different absolute levels, for example, if the component is added to the two cultures at different times (e.g., if in one culture all of the component is added at the outset, and in another culture the component is added over time). A cumulative amount is also unaffected by in situ synthesis of a component over time during the culture (for example, via metabolism or chemical conversion). Thus, two cultures with the same cumulative amounts of a given

component may nonetheless have different absolute levels, for example, if the component is synthesized in situ in one of the two cultures by way of a bioconversion process. A cumulative amount may be expressed in units such as, for example, grams or moles of the component." '715 patent, 31:7-31.

54. The '715 patent defines "cumulative concentration" as "the cumulative amount of a component divided by the volume of liquid in the bioreactor at the beginning of the production batch, including the contribution to the starting volume from any inoculum used in the culture." *Id.*, 31:33-36.

55. The '715 patent provides the following exemplary cumulative concentration calculation, *see id.*, 31:37-48:

> if a bioreactor contains 2 liters of cell culture medium at the beginning of the production batch, and one gram of component X is added at days 0, 1, 2, and 3, then the cumulative concentration after day 3 is 2 g/L (i.e., 4 grams divided by 2 liters). If, on day 4, an additional one liter of liquid not containing component X were added to the bioreactor, the cumulative concentration would remain 2 g/L. If, on day 5, some quantity of liquid were lost from the bioreactor (for example, through evaporation), the cumulative concentration would remain 2 g/L. A cumulative concentration may be expressed in units such as, for example, grams per liter or moles per liter.

56. The '715 patent defines "chemically defined medium" or "chemically defined media" as "a synthetic growth medium in which the identity and concentration of all the ingredients are defined. Chemically defined media do not contain bacterial, yeast, animal, or plant extracts, animal serum, or plasma, although individual plant or animal-derived components (e.g., proteins, polypeptides, etc.) may be added." *Id.*, 30:44-51.

57. The '715 patent explains that "color observed during the production of a recombinant protein, specifically, an anti-VEGF protein, can be measured by various methods."

Id., 56:50-52. Two of the non-limiting examples listed in the patent are the European pharmacopoeia color number and CIE L*, a*, b* (or "CIELAB"). *Id.*, 56:52-57:9. The European pharmacopoeia method uses a visual color matching standard with thirty-seven color reference solutions. *Id.*, 57:7-10. It has "three parent solutions for red (cobaltous (II) chloride), yellow (ferrous (III) chloride) and blue colors (cuprous (II) sulphate) and 1% hydrochloric acid, five color reference solutions for yellow (Y), greenish-yellow (GY), brownish-yellow (BY), brown (B) and red (R) hues." *Id.*, 57:2-7. "Each reference solution is clearly defined in the CIE-Lab color space, for example, by lightness, hue and chroma." *Id.*, 57:10-12. The brownish-yellow standard scale runs from BY1-BY7. *Id.*, 57:9. "Of the seven yellow-brown standards (BY standards), BY1 is the darkest standard and BY7 is the least dark." *Id.*, 57:12-13.

58. To test the color of liquids under the European pharmacopoeia procedure, a test solution is compared with a standard color solution. *Id.*, 57:35-36. "The composition of the standard color solution is selected depending on the hue and intensity of the color of the test solution." *Id.*, 57:36-38. The '715 patent further explains that it is typical for the comparison to be "carried out in flat-bottomed tubes of colorless, transparent, neutral glass that are matched as closely as possible in internal diameter and in all other respects (e.g., tubes of about 12, 15, 16, or 25 mm diameter)." *Id.*, 57:39-42. "The color assigned to the test solution should not be more intense than that of the standard color. Color comparisons are typically carried out in diffused light (e.g., daylight) against a white background. Colors can be compared down the vertical axis or horizontal axis of the tubes." *Id.*, 57:45-50.

59. Alternatively, CIE L*, a*, b* (or "CIELAB") color measurements, one of the other non-limiting methods for color observation in the patent, quantifies colors with twenty color reference solutions (identified sequentially by the letters A to T). *Id.*, 57:51-56. The '715

patent explains that the "color of the measured sample is automatically correlated to the color reference solutions. This means that the color reference solution that is closest to the sample (i.e., the reference solution with the smallest color difference ΔE* to the color of the sample) is displayed. The ΔL*, Δa* and Δb* values give the quantitative differences between the L*, a* and b* values of the sample and those of the displayed USP solutions." *Id.*, 57:56-62.

60. For the CIELAB color measurements "L* represents the degree of lightness of a color on a scale of 0-100, with 0 being the darkest and 100 the lightest, a* represents the redness or greenness of a color (positive values of a* represent red, whereas negative values of a* represent green), and b* represents the yellowness or blueness of a sample, with positive values of b* representing yellow and negative values of b* representing blue. Color difference from a standard, or from an initial sample in an evaluation, can be represented by a change in the individual color components ΔL*, Δa*, and Δb*." *Id.*, 57:64-58:7. "The composite change, or difference in color, can be calculated as a Euclidian distance in space using the formula: dE*= $\sqrt{(\Delta L*)^2 + (\Delta a*)^2 + (\Delta b*)^2}$." *Id.*, 58:7-10.

61. The '715 patent explains that the color of the BY standards can also be expressed under the CIELAB color space. *Id.*, 58:24-27. Below is a table reproduced from the patent, which demonstrates the characterization of the European Brown-Yellow color standards in the CIELAB color space.

TABLE 2

Characterization of European Brown-Yellow Color Standards in the CIE L*, a*, b* Color Space

Std.	L*^	a*^	b*^	L*⁻	a*⁻	b*⁻
BY1	93.95	−2.76	28.55	92.84	−3.16	31.15
BY2	94.76	−2.96	22.69	94.25	−3.77	26.28
BY3	96.47	−2.84	16.41	95.92	−3.44	18.52
BY4	97.17	−1.94	9.07	97.67	−2.63	10.70
BY5	98.91	−1.19	4.73	98.75	−1.61	5.77
BY6	99.47	−0.59	2.09	99.47	−0.71	2.38
BY7	99.37	−0.31	1.13	99.71	−0.37	1.17

^Reported by Pack et al.
⁻Measured experimentally herein-the L* and b* values, for each BY color standard

Id., 58:27-41.

B. Claims

62. The claims of the '715 patent cover, among other things, a method for producing aflibercept using particular cell culture conditions.

63. Specifically, claim 1 recites:

> A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:
> (a) providing a host cell genetically engineered to express aflibercept;
> (b) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM and one or more of the following:
> i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM;
> ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM;
> iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM;
> iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM, and
> v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and
> (c) harvesting aflibercept produced by said host cell.

64. Claim 2 adds a further requirement to claim 1. It recites:

> The method of claim 1, wherein said harvest has a color no more yellow-brown than European Color Standard BY2, wherein the aflibercept concentration is 5.0 g/L.

65. Claim 3 adds a further requirement to claim 2. It recites:

> The method of claim 2, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.

66. Claim 6 adds a further requirement to claim 1. It recites:

> The method of claim 1, wherein said host cell is selected from the group consisting of CHO, NS0, Sp2/0, 40 embryonic kidney cell and BHK.

67. Claim 12 adds a further requirement to claim 1. It recites:

> The method of claim 1, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.

68. Claim 13 adds a further requirement to claim 1. It recites:

> The method of claim 1, wherein the harvest has a color that is:
>
> a. no more yellow-brown than European Color Standard BY2;
> b. no more yellow-brown than European Color Standard BY3;
> c. no more yellow-brown than European Color Standard BY4;
> d. no more yellow-brown than European Color Standard BY5;
> e. between European Color Standard BY2 and BY3; or
> f. between European Color Standard BY2 and BY4, and wherein the aflibercept concentration in the harvest is 5.0 g/L.

69. Claim 14 adds a further requirement to claim 13. It recites:

> The method of claim 13, wherein the color of harvest is characterized in the CIE L*, a*, b* color space, where L* is about 70 to about 99, a* is about 0 and b* is about 20 or less than 20 when the concentration of aflibercept is 5.0 g/L.

70. Claim 16 recites:

> A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:
> (a) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM and one or more of the following:
> i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM;
> ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM;
> iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM;
> iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM, and
> v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and
> (b) harvesting aflibercept produced by said host cell.

C. Claim Construction

71. I understand that the parties have stipulated to the following claim construction regarding the '715 patent.

Claim Term	**Agreed-Upon Construction**
Cumulative Concentration	the cumulative amount of a component divided by the volume of liquid in the bioreactor at the beginning of the production batch, including the contribution to the starting volume from any inoculum used in the culture

72. In offering the opinions expressed herein, I have applied the above construction.

73. I also understand that the Court has not yet ruled on the following claim constructions regarding the '715 patent and therefore they remain in dispute:

Claim Term	**Regeneron's Proposed Construction**	**Mylan's Proposed Construction**
Anti-oxidants	Plain and ordinary meaning in view of the claims and specification; to the	limited to "taurine, hypotaurine, glycine, thioctic acid, glutathione,

	extent there is a dispute as to claim scope, this term is not limited to "taurine, hypotaurine, glycine, thioctic acid, glutathione, choline chloride, hydrocortisone, Vitamin C, Vitamin E and combinations thereof"	choline chloride, hydrocortisone, Vitamin C, Vitamin E and combinations thereof"
Chemically Defined Medium (CDM)	a synthetic growth medium in which the identity and concentration of all the ingredients are defined	a synthetic growth medium in which the identity and concentration of all the ingredients are defined *and does not contain bacterial, yeast, animal, or plant extracts or hydrolysates, animal serum, or plasma*
Cell(s) Cultured in a Chemically Defined Medium (CDM)	Plain and ordinary meaning in view of the claims and specification; to the extent there is a dispute as to claim scope, this limitation does not exclude methods where the cell is subsequently cultured in a non-chemically defined medium	Plain and ordinary meaning: harvested from a clarified harvest made using CDM (i.e., a synthetic growth medium in which the identity and concentration of all the ingredients are defined and does not contain bacterial, yeast, animal, or plant extracts or hydrolysates, animal serum, or plasma)

74. In offering the opinions expressed herein, I have applied both constructions of "anti-oxidants" and "chemically defined medium." I have applied Regeneron's proposed construction of "cell(s) cultured in a chemically defined medium." I have not analyzed whether Mylan's process is covered by claim 1 were Mylan's construction of "cell(s) cultured in a chemically defined medium" to be applied.

VII. MYLAN'S MANUFACTURING PROCESS

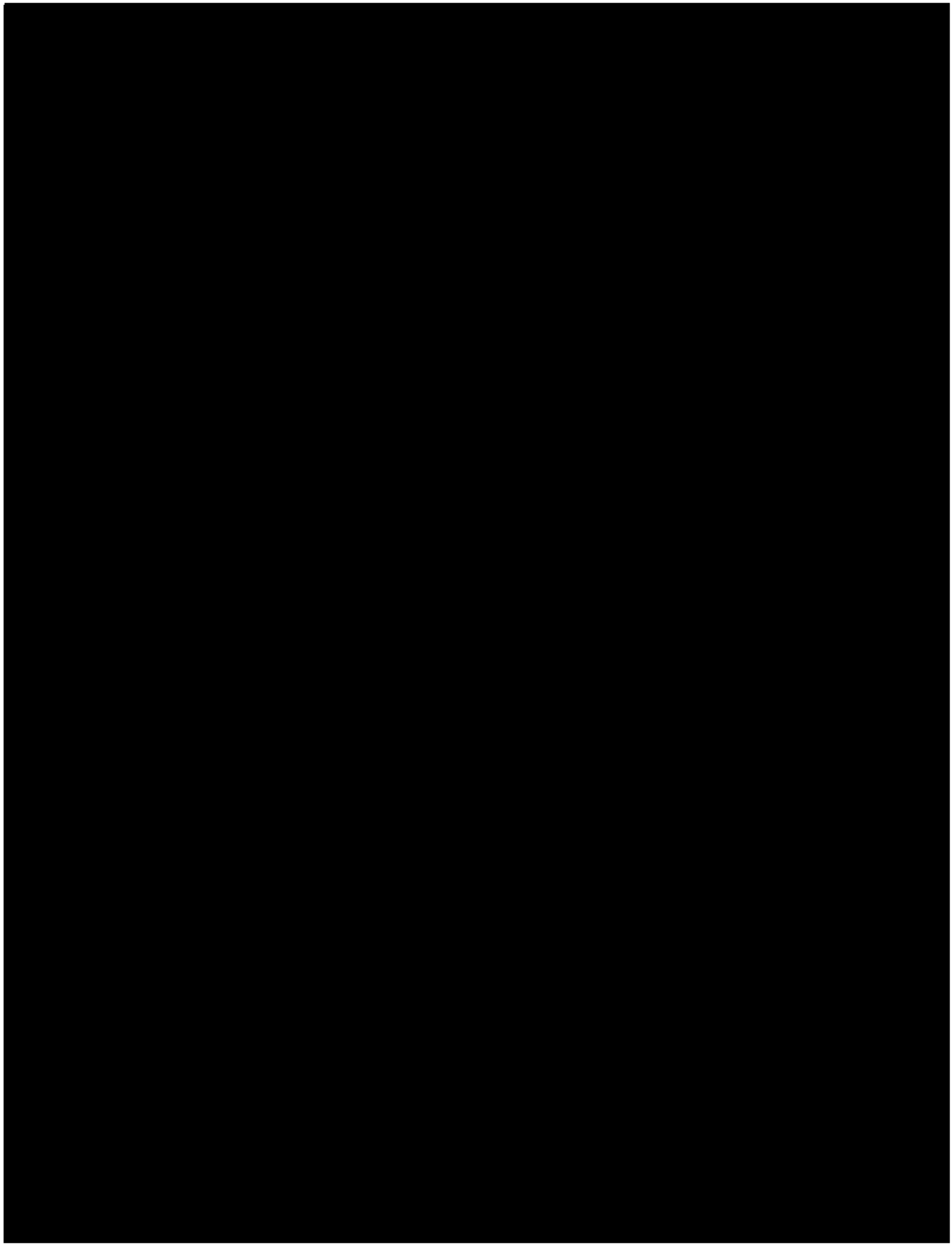
75. [redacted]

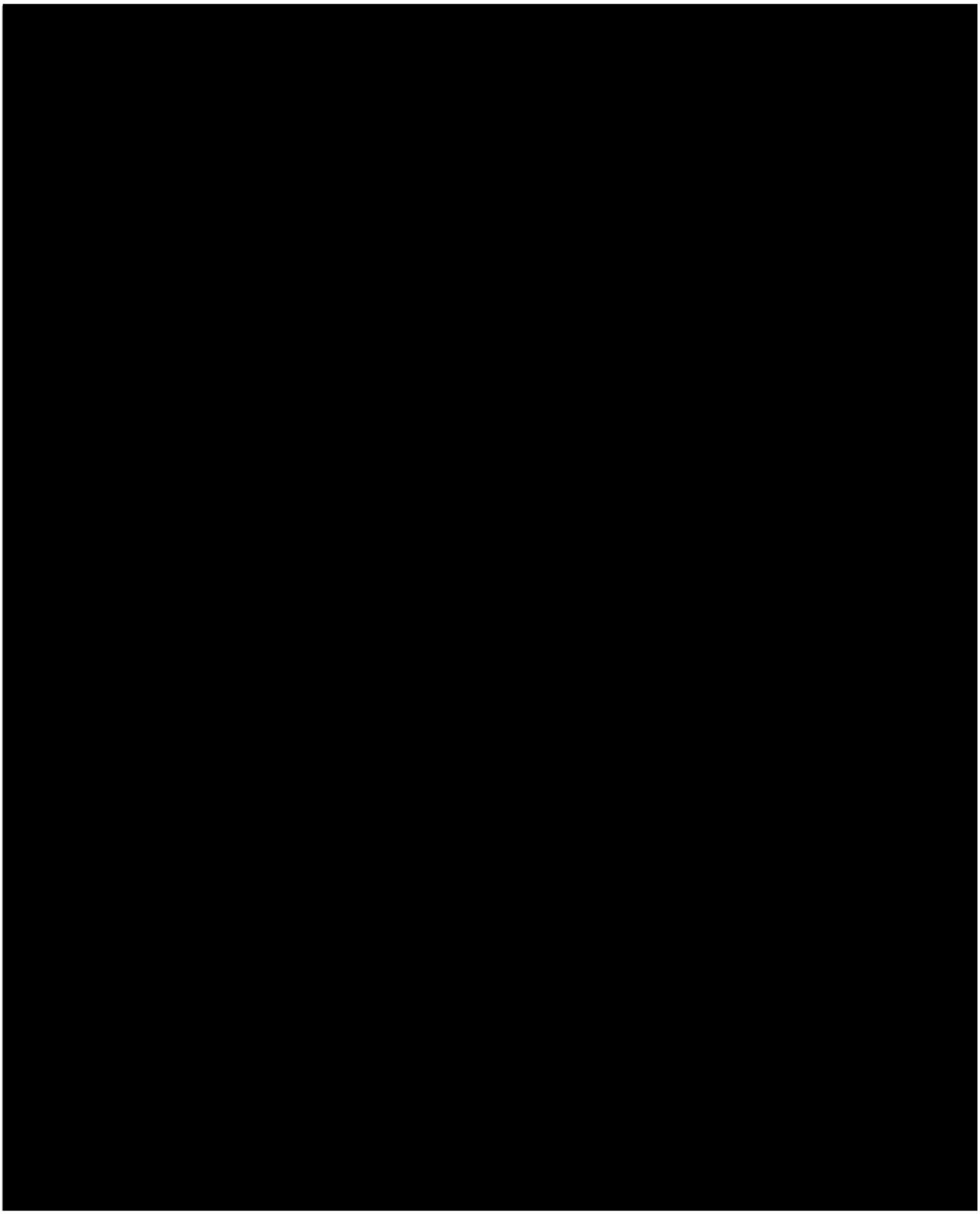
76. [redacted]

77. [redacted]

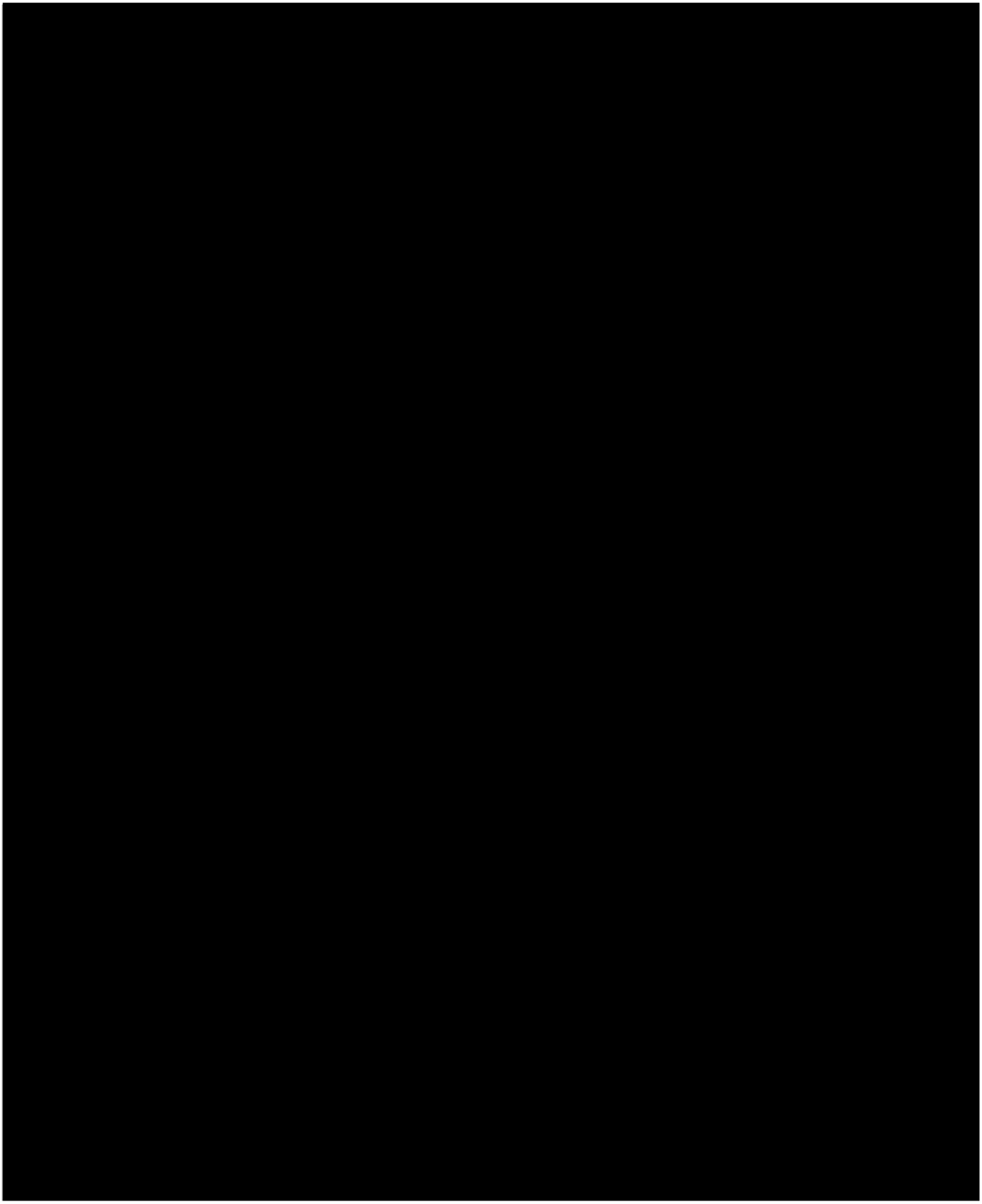
A. The Basal Media in Mylan's Manufacturing Process is Chemically Defined.

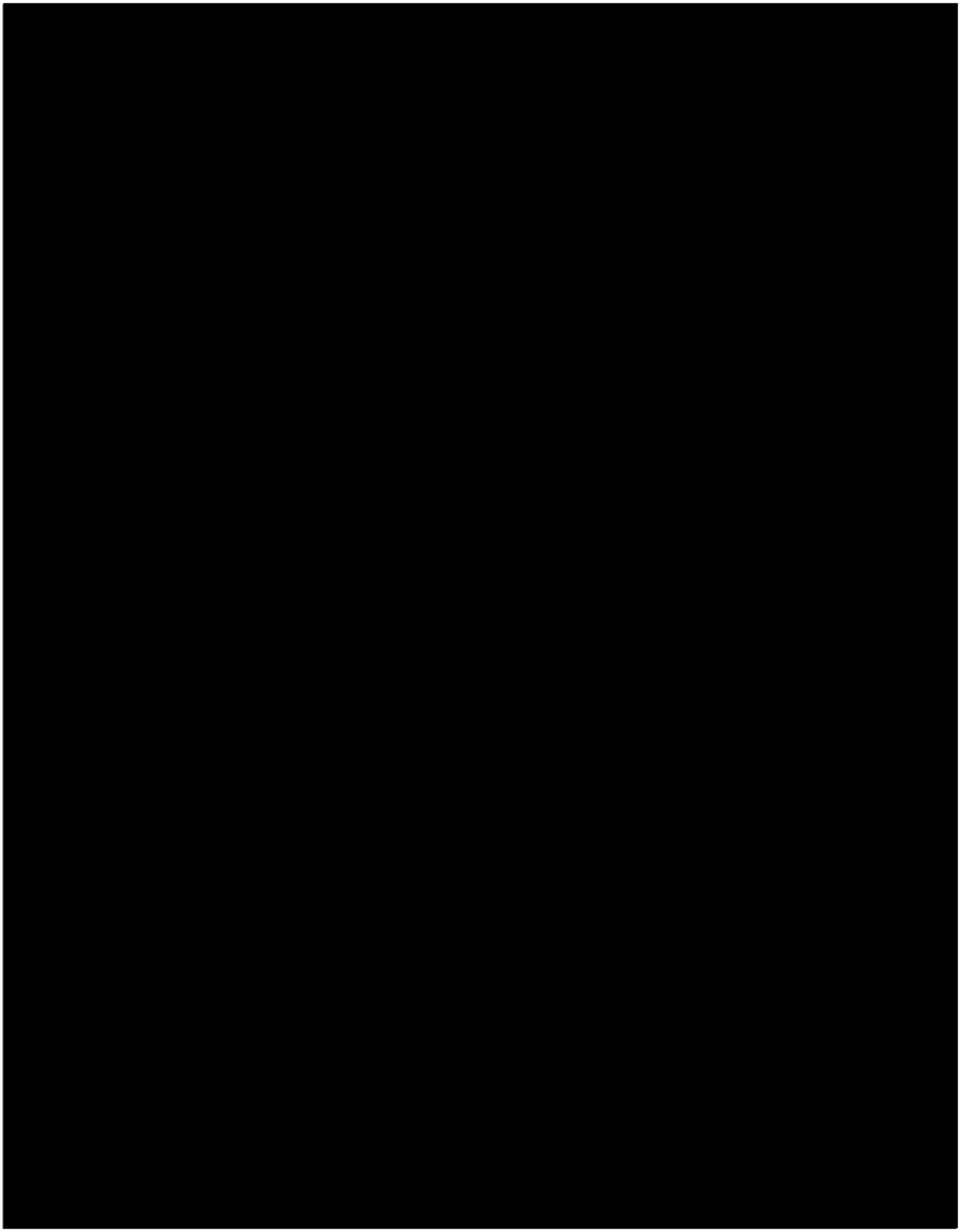
78. [redacted]

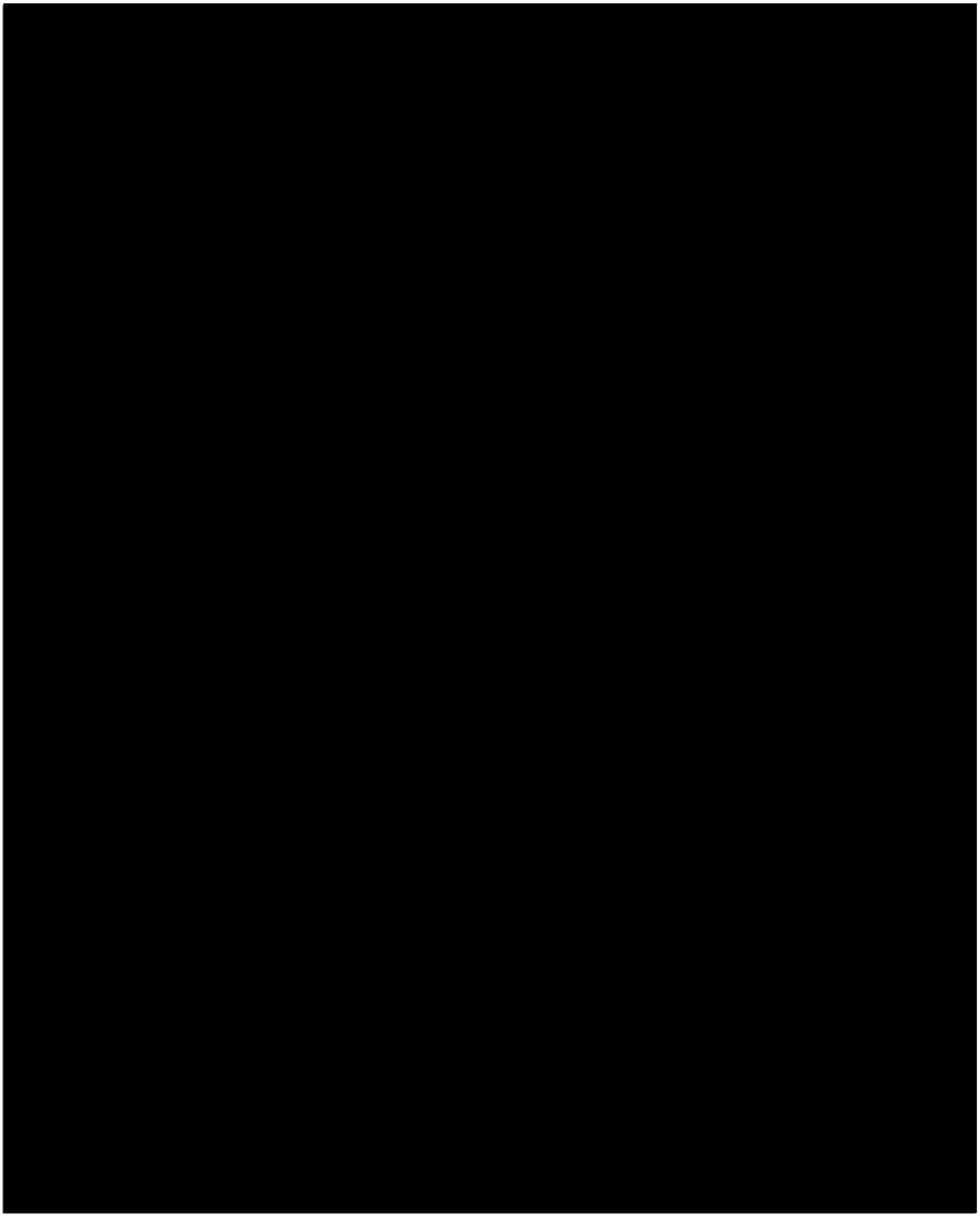


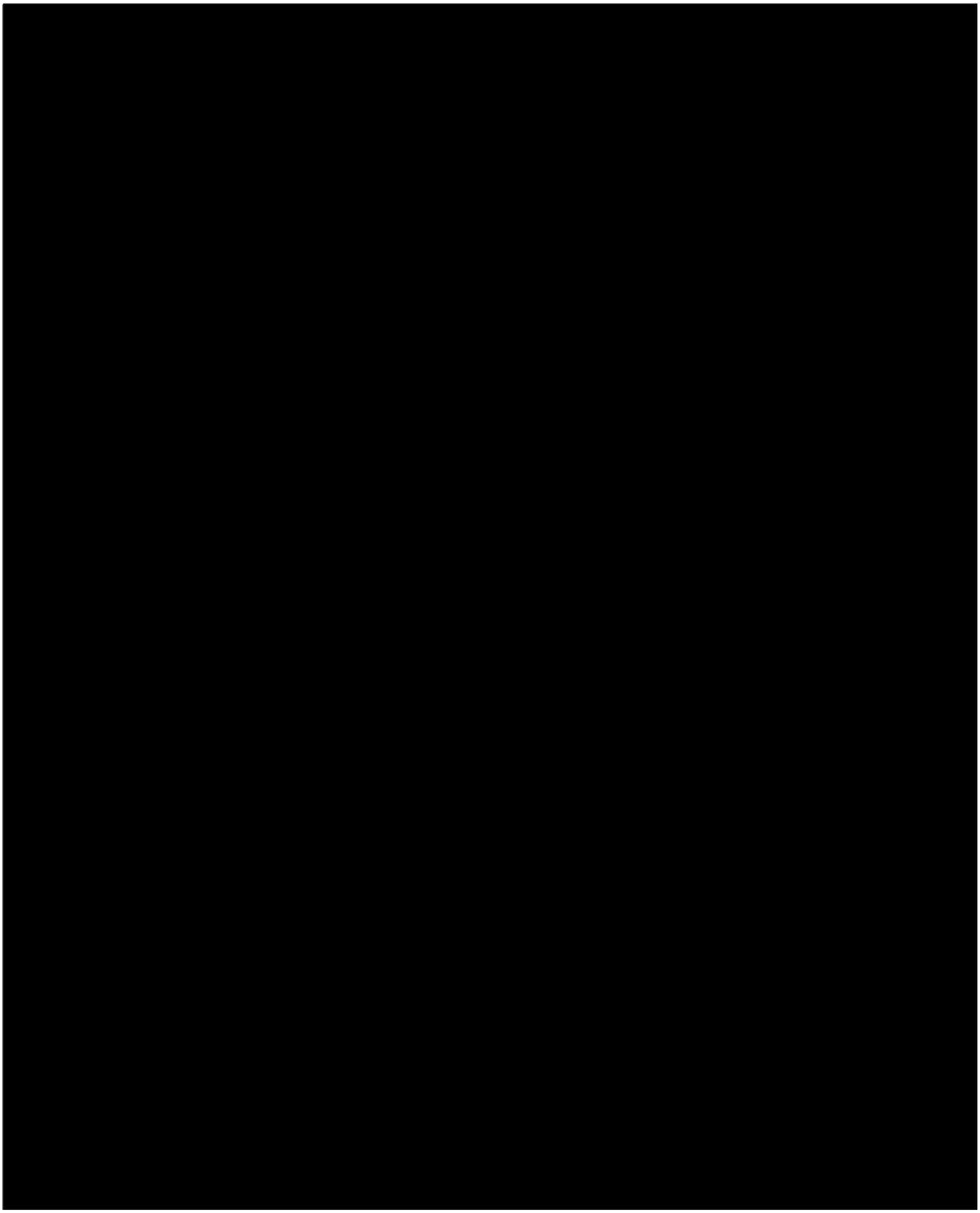


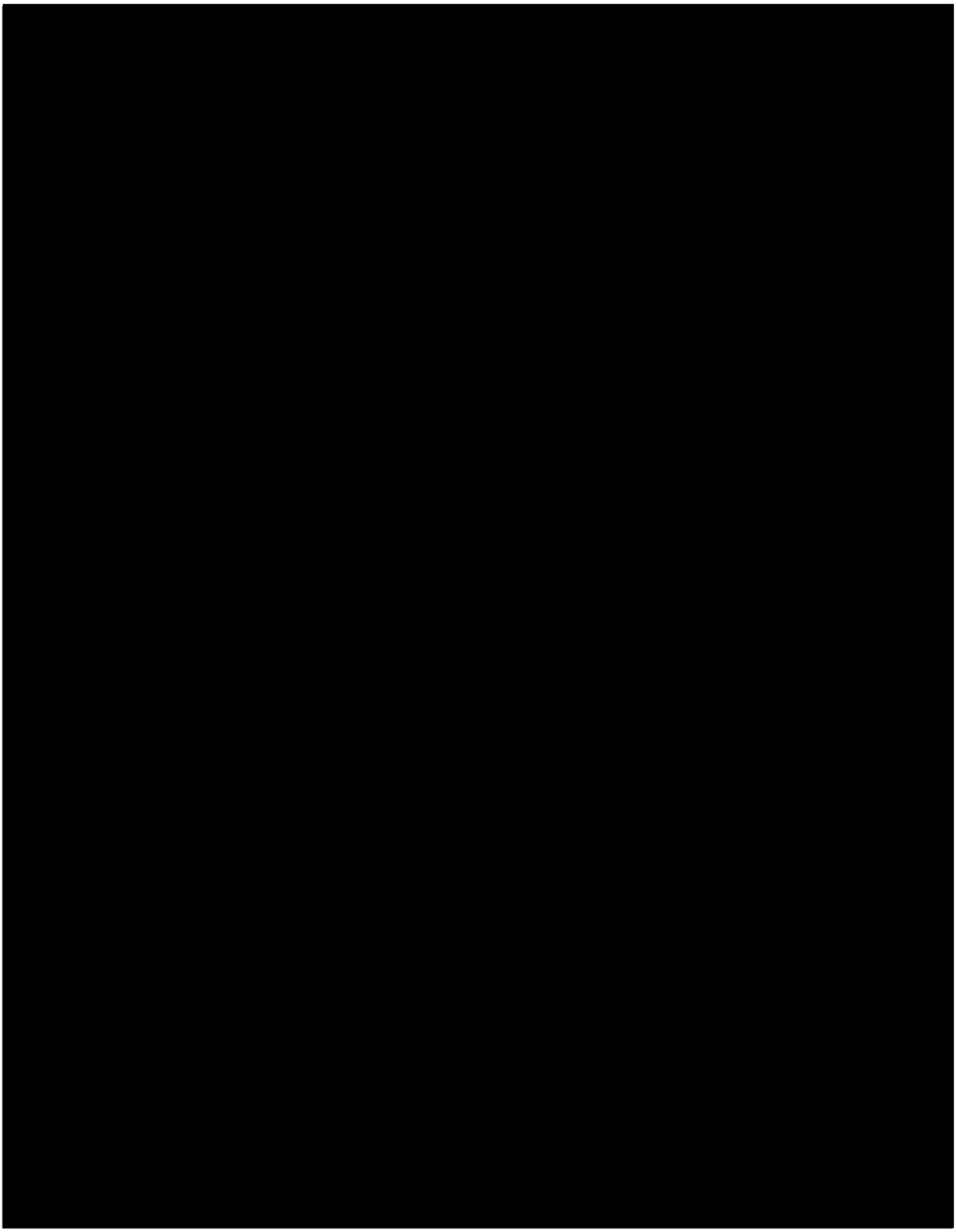
B. Stages of Mylan's Manufacturing Process

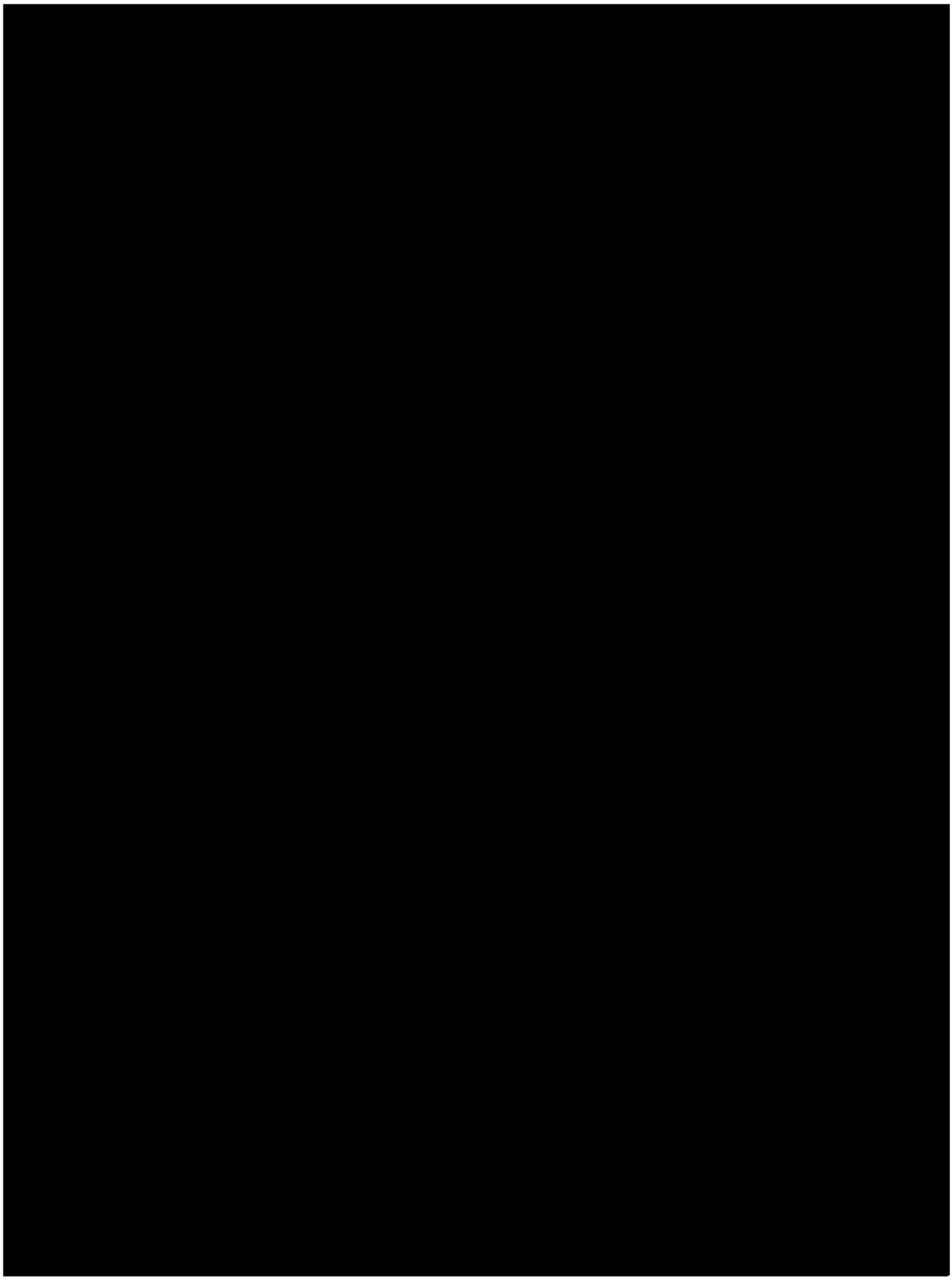


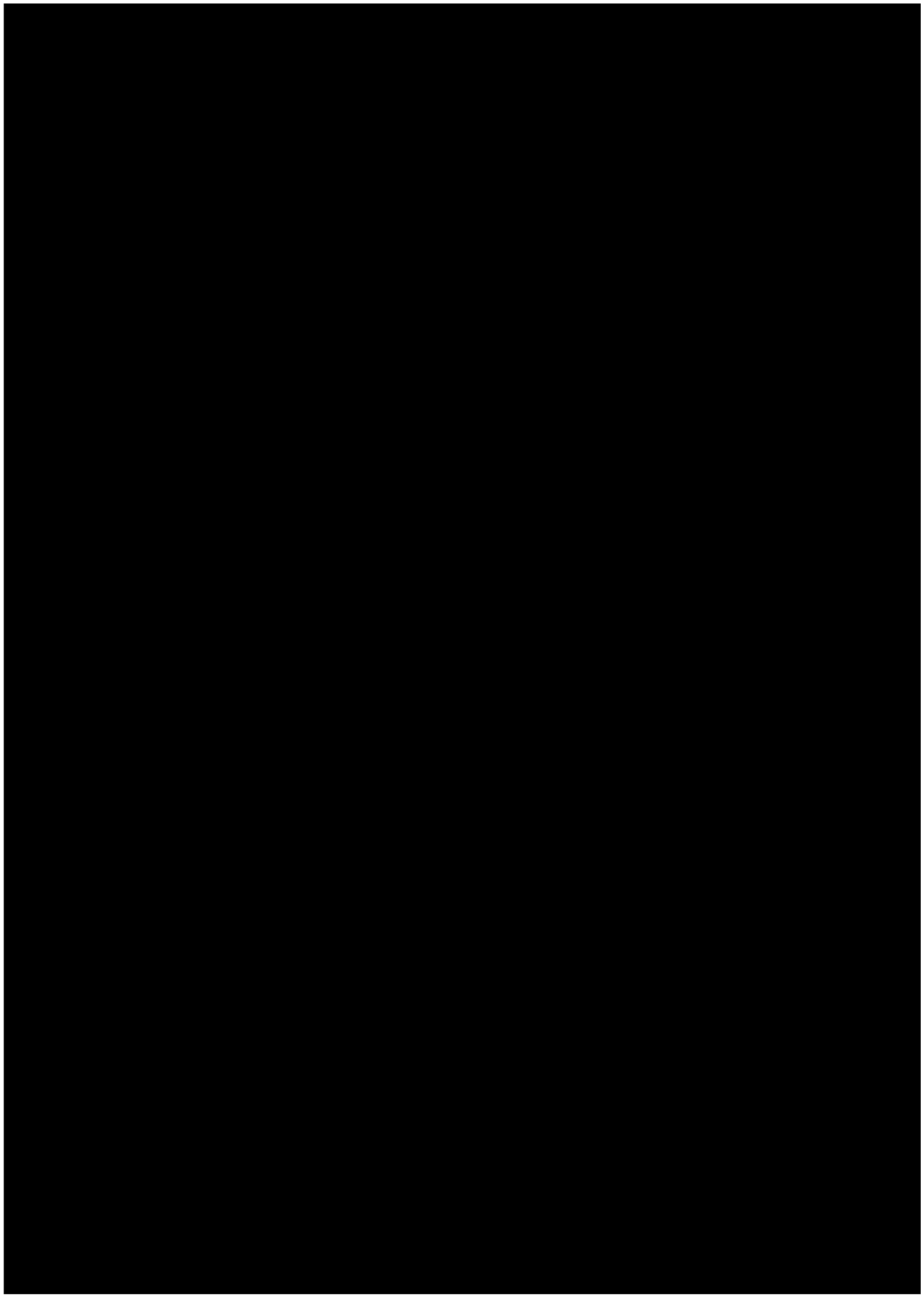


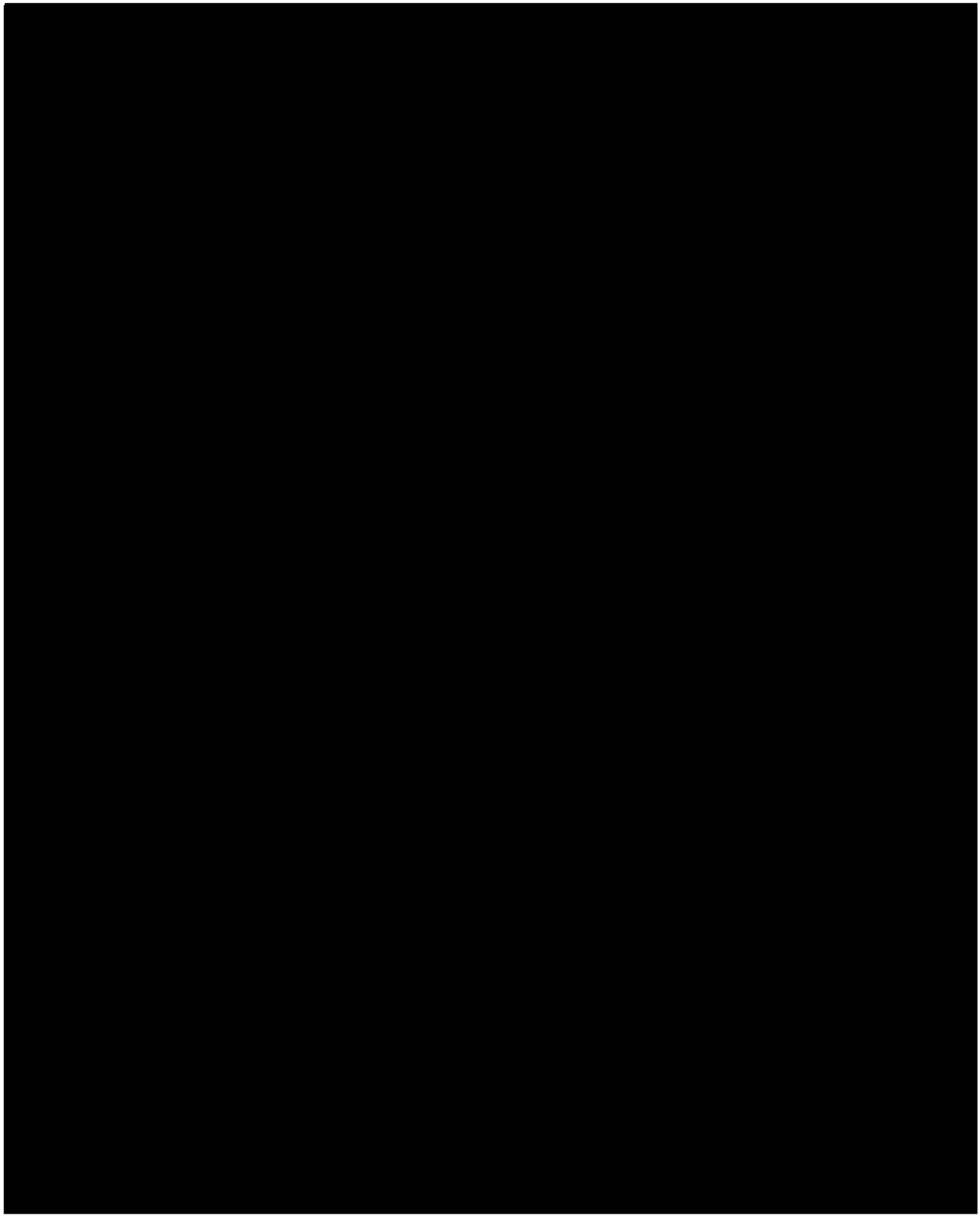


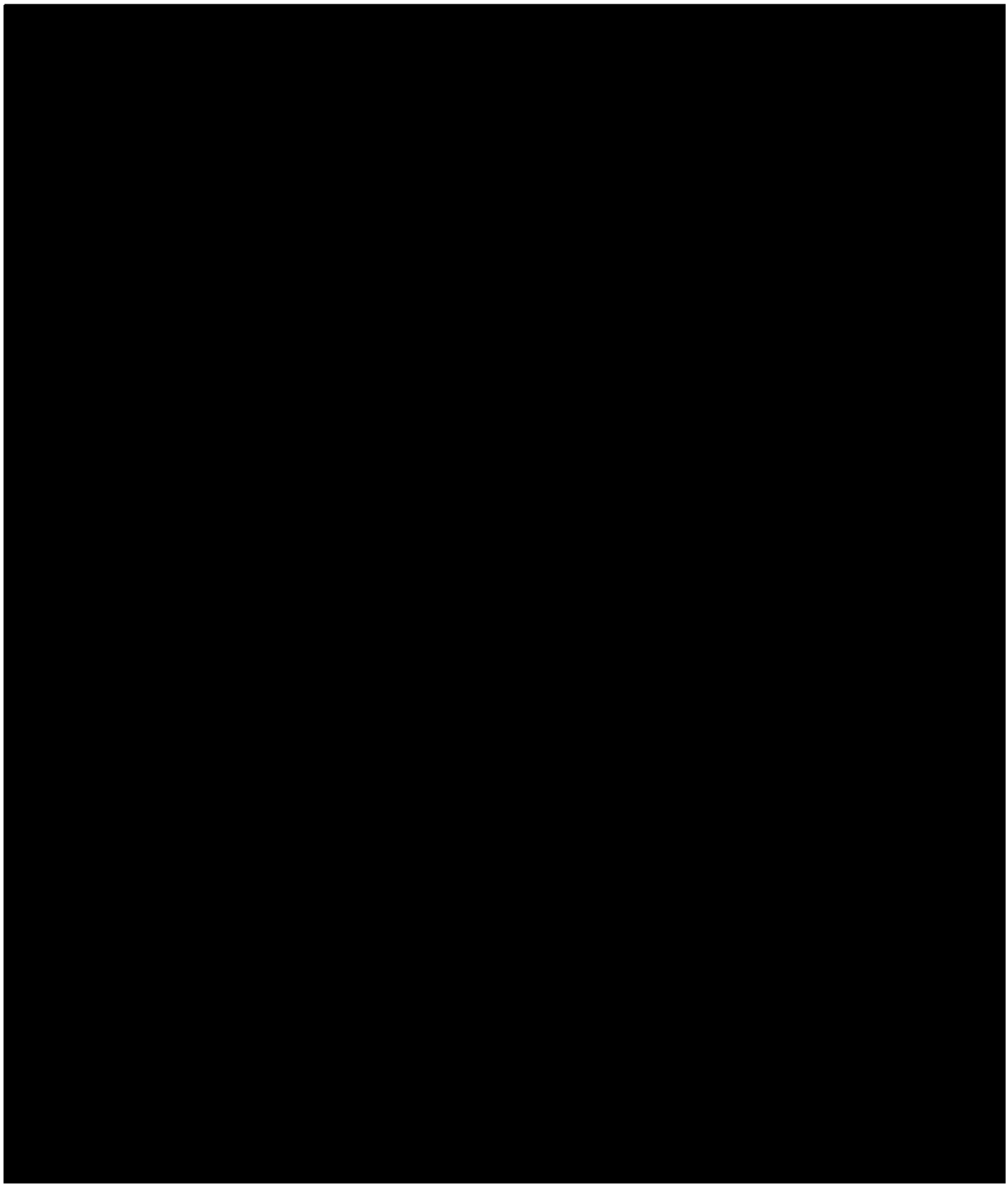












[redacted]

VIII. MYLAN'S INFRINGEMENT OF THE ASSERTED CLAIMS OF THE '715 PATENT

110. In this Section, I discuss Mylan's infringement of particular limitations in the Asserted Claims of the '715 patent.

A. "A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM)" (Claims 1, 16)

111. [redacted]

[14] I understand that claim 1 is not one of the Asserted Claims. I include it here because several of the Asserted Claims depend from claim 1.

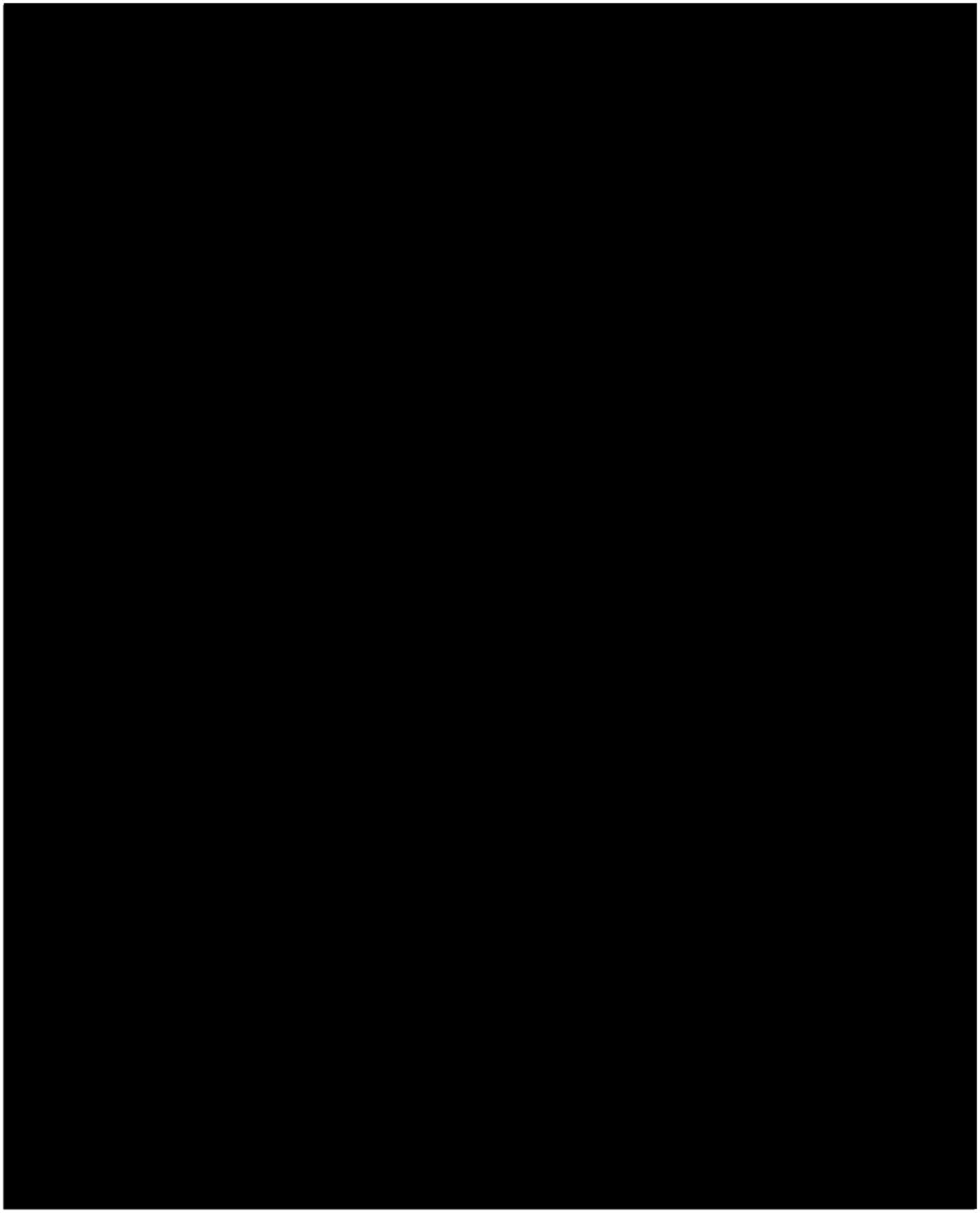
[redacted]

B. "providing a host cell genetically engineered to express aflibercept" (Claim 1)

117. [redacted]

118. [redacted]

C. "culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept" (Claims 1, 16)



D. Cumulative Concentration Limitations (Claims 1, 16)

127. As part of the culturing step discussed in the previous Section, claims 1 and 16 also recite particular requirements for the ingredients in the CDM. In particular, the "cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM."

128. In addition to the nickel requirement, the CDM must also satisfy one or more of the following requirements:

i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM;
ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM;
iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM;
iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM, and
v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant.

Regeneron Protected Material

[redacted]

E. "harvesting aflibercept produced by said host cell" (Claims 1, 16)

131. Claims 1 and 16 require a step of harvesting aflibercept produced by said host cell.

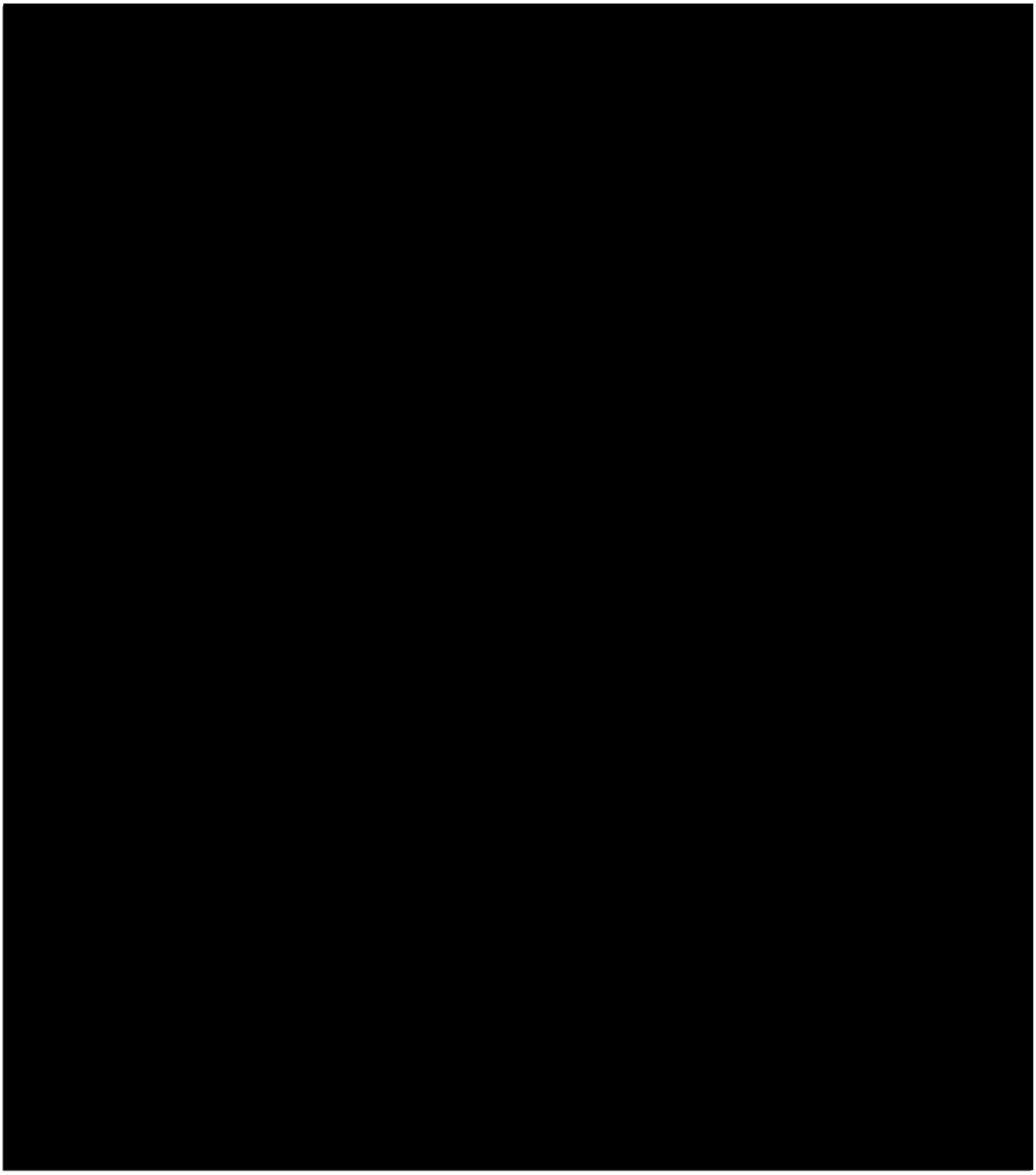
[15] I understand that certain of the information related to the components in Mylan's media is highly sensitive. To help preserve the confidentiality of that material, I have separated my opinions about those components in Appendices C and D.

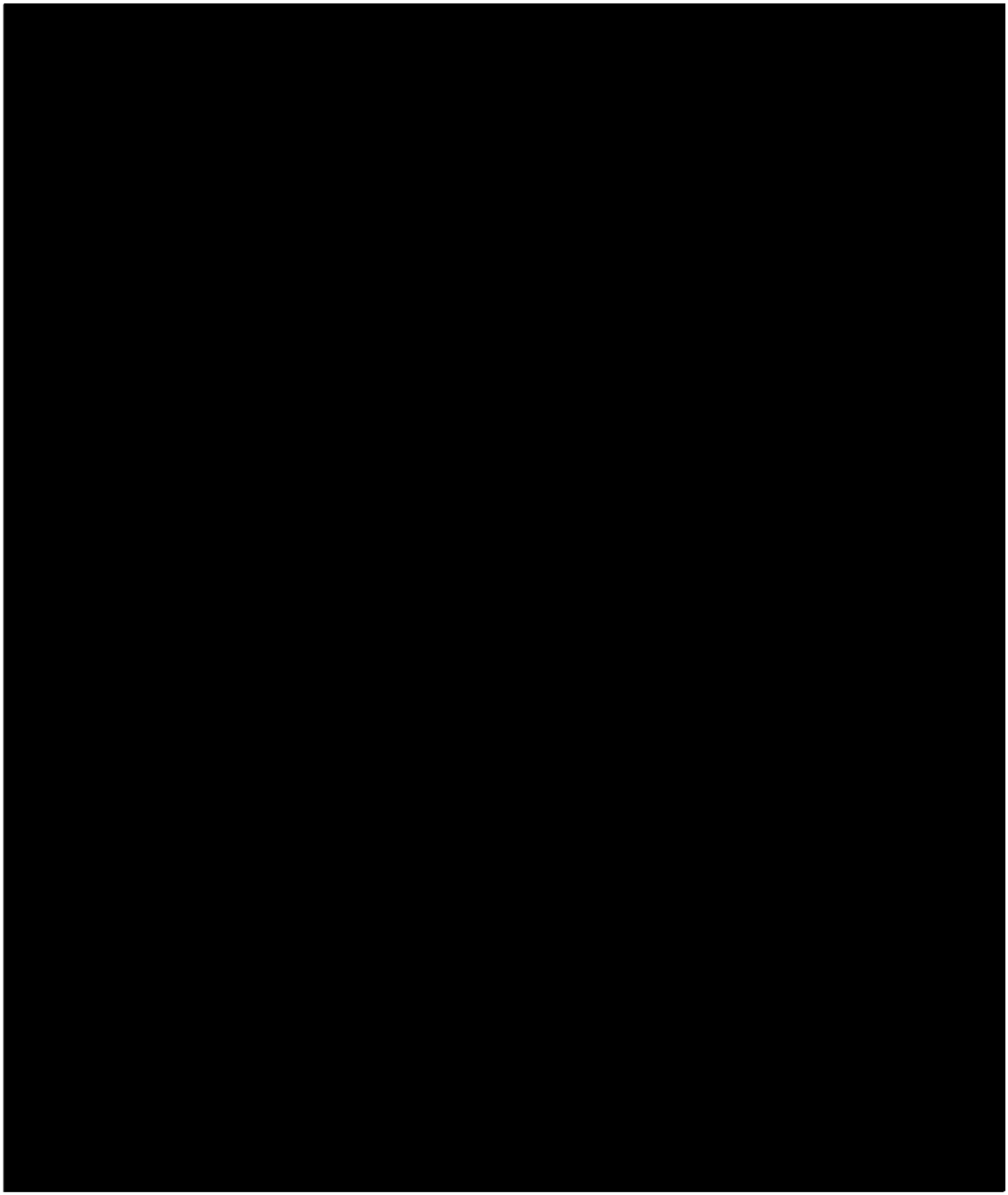
F. Color Limitations (Claims 2, 13, 14)

136. Several of the Asserted Claims recite limitations related to color, including claims 2, 13, and 14. For example, claim 2 states the following: "The method of claim 1, wherein said harvest has a color no more yellow-brown than European Color Standard BY2, wherein the aflibercept concentration is 5.0 g/L."

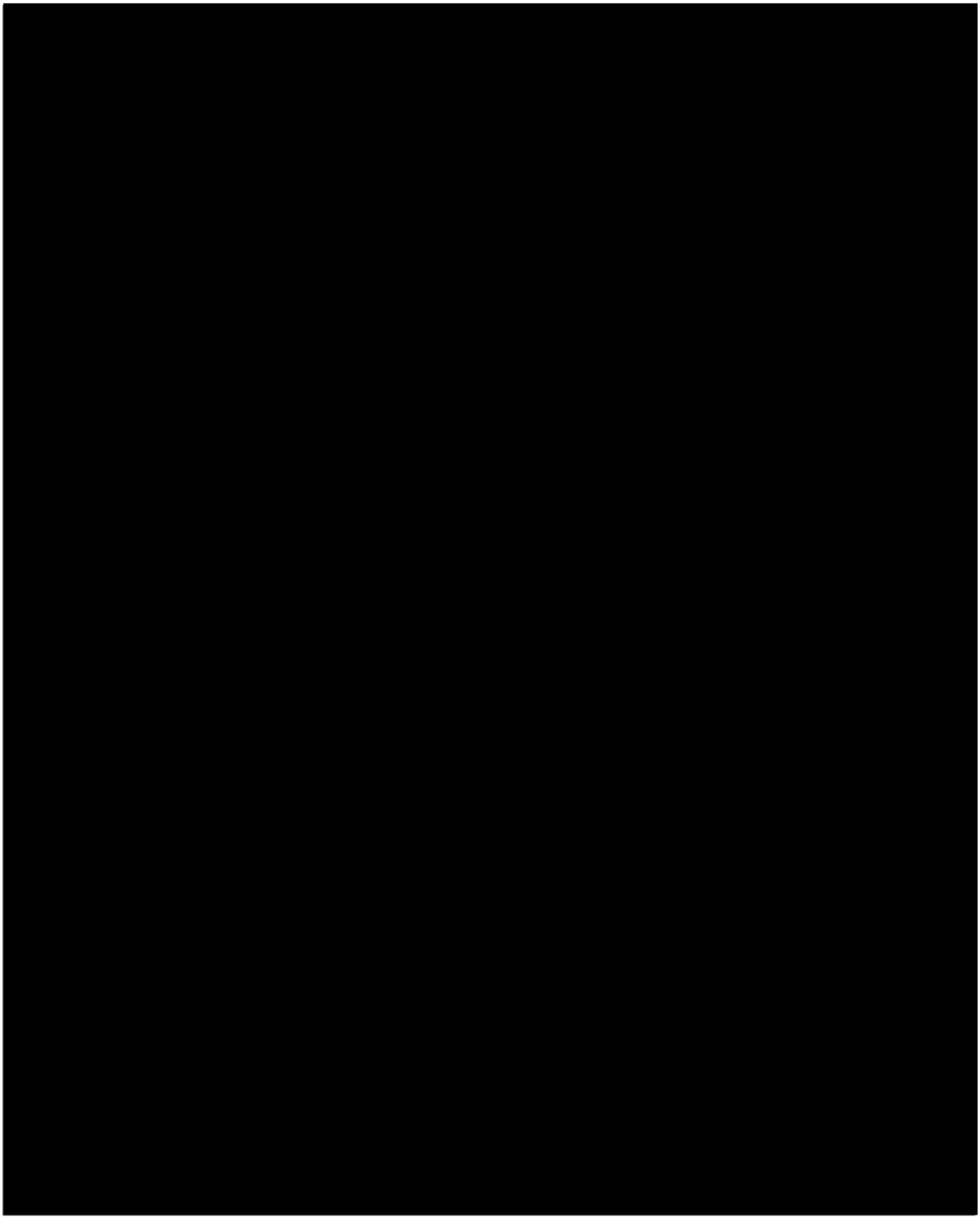
137. Claim 13 recites a number of different possible colors for the harvest, one of which requires that the harvest has a color that is no more yellow-brown than European Color Standard BY2 wherein the aflibercept concentration in the harvest is 5.0 g/L.

138. I understand that claims 2 and 13 both depend from claim 1, and I incorporate my infringement analysis of claim 1 into my analysis of claims 2 and 13.





[redacted]



G. Anti-oxidant Limitation (Claims 3 and 12)

152. Claim 3 of the '715 patent states, "The method of claim 2, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof."

153. Claim 12 recites, "The method of claim 1, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof."

[redacted]

H. Host Cell Limitation (Claim 6)

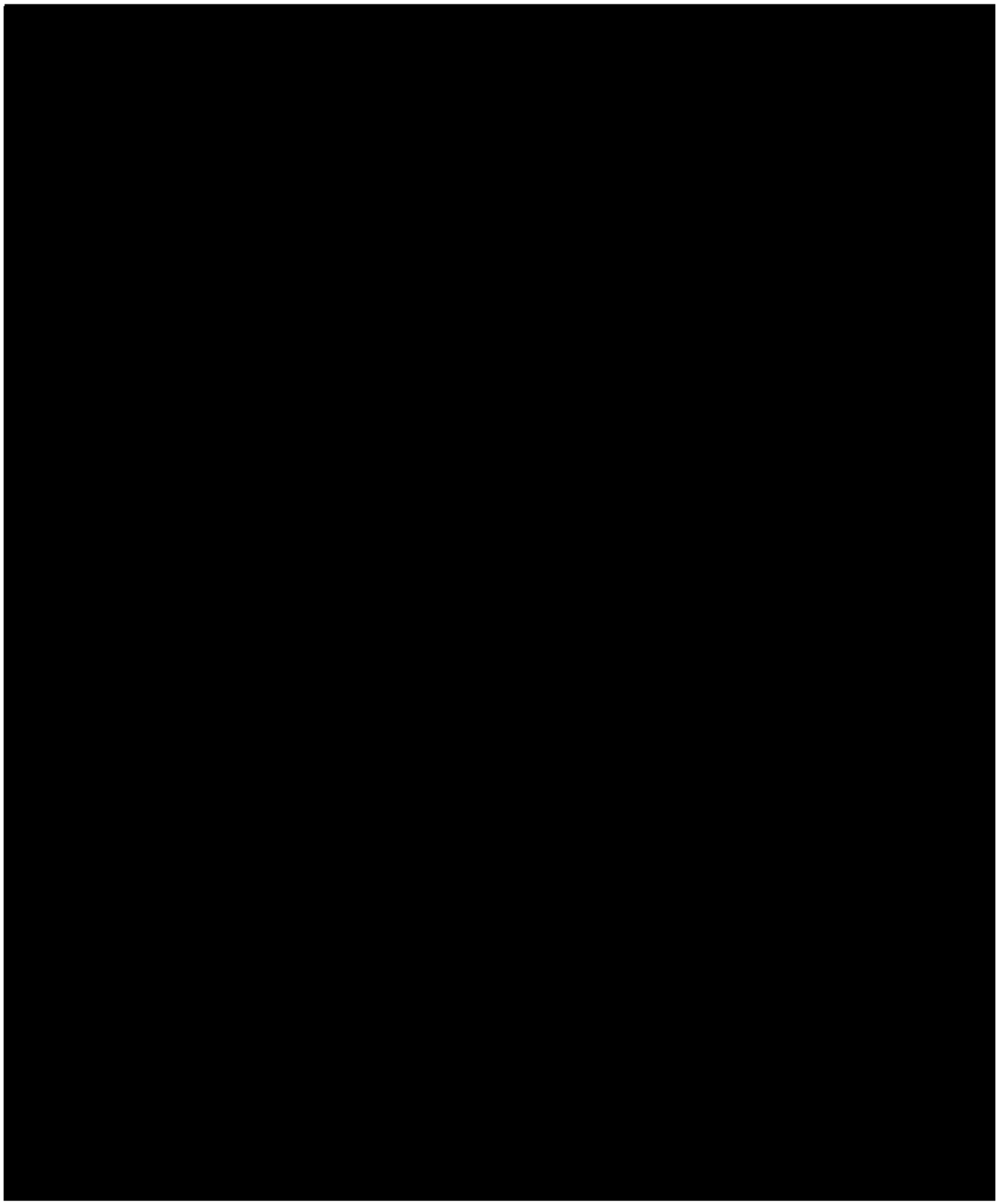
157. Claim 6 of the '715 patent states, "The method of claim 1, wherein said host cell is selected from the group consisting of CHO, NS0, Sp2/0, 40 embryonic kidney cell and BHK." I understand that claim 6 depends from claim 1, and I incorporate my analysis of claim 1 into my analysis of claim 6.

[redacted]

I. Material Change and Trivial or Nonessential Component

160. For the reasons set forth above, it is my opinion that Mylan's manufacturing process literally infringes the Asserted Claims of the '715 patent.

[redacted]



[redacted]

IX. CLAIM CHART

168. In this section, I set forth a claim chart comparing Mylan's process with the claim limitations of the '715 patent.

'715 Patent Claim	Mylan's Process
1. A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:	[redacted]
(a) providing a host cell genetically engineered to express aflibercept;	
(b) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept	

'715 Patent Claim	Mylan's Process
wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 µM or about 0.4 µM and one or more of the following: i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 µM; ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 µM; iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 µM; iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM, and v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and	[redacted]
(c) harvesting aflibercept produced by said host cell.	
2. The method of claim 1, wherein said harvest has a color no more yellow-brown than European Color Standard BY2, wherein the aflibercept concentration is 5.0 g/L.	

'715 Patent Claim	Mylan's Process
3. The method of claim 2, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.	[redacted]
6. The method of claim 1, wherein said host cell is selected from the group consisting of CHO, NS0, Sp2/0, embryonic kidney cell and BHK.	
12. The method of claim 1, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.	

13. The method of claim 1, wherein the harvest has a color that is: a. no more yellow-brown than European Color Standard BY2; b. no more yellow-brown than European Color Standard BY3; c. no more yellow-brown than European Color Standard BY4; d. no more yellow-brown than European Color Standard BY5; e. between European Color Standard BY2 and BY3; or f. between European Color Standard BY2 and BY4, and wherein the aflibercept concentration in the harvest is 5.0 g/L.	[redacted]
14. The method of claim 13, wherein the color of harvest is characterized in the CIE L*, a*, b* color space, where L* is about 70 to about 99, a* is about 0 and b* is about 20 or less than 20 when the concentration of aflibercept is 5.0 g/L.	

16. A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:	[redacted]
(a) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept	
wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 µM or about 0.4 µM and one or more of the following: i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 µM; ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 µM; iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 µM; iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and	
(b) harvesting aflibercept produced by said host cell.	

I declare that the foregoing is, to the best of my knowledge and belief, true and correct.

Dated: 2/2/2023

Franklin J. Swartzwelder Ph.D.

Franklin Swartzwelder, Ph.D.