

HEMISPHERX BIOPHARMA INC
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Registration No. 333-205228

PROSPECTUS SUPPLEMENT

(To Prospectus Dated August 4, 2015)

3,333,334 Shares of Common Stock

HEMISPHERX BIOPHARMA, INC.

We are offering 3,333,334 shares of our common stock to institutional investors pursuant to this prospectus supplement and the accompanying prospectus and a stock purchase agreement with such investors. In a concurrent private placement, we are selling to such investors warrants to purchase 2,500,000 shares of our common stock purchased by such investors in this offering, or the Warrants. The Warrants and the shares of our common stock issuable upon the exercise of the Warrants are not being registered under the Securities Act of 1933, as amended, or the Securities Act, are not being offered pursuant to this prospectus supplement and the accompanying prospectus and are being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act and Rule 506(b) promulgated thereunder.

Our common stock is listed on the NYSE MKT under the symbol "HEB." The Warrants being issued in the concurrent private placement are not listed on any securities exchange and we do not expect to list the Warrants. The last reported sale price of our common stock on the NYSE MKT on August 31, 2016 was \$1.46 per share.

You should read "Risk Factors" beginning on page S-6 of this prospectus supplement and the risk factors described in other documents incorporated by reference herein before buying our securities.

We retained H.C. Wainwright & Co., LLC as our exclusive placement agent to use their reasonable best efforts to solicit offers to purchase the securities in this offering. The placement agent has no obligation to buy any of the

securities from us or to arrange for the purchase or sale of any specific number or dollar amount of the securities. We expect that delivery of the securities being offered pursuant to this prospectus supplement and the accompanying prospectus will be made on or about September 6, 2016.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement is truthful or complete. Any representation to the contrary is a criminal offense.

Common Stock	Per Share	Total
Public offering price(1)	\$ 1.50	\$5,000,000
Placement agents fees(2)	\$ 0.21	\$350,000
Proceeds, before expenses, to us(3)	\$ 1.29	\$4,650,000

(1) **Includes \$0.01 for each share as the purchase price for warrants to purchase 75% of the number of shares sold in this offering. The warrants are being sold in a concurrent private placement.**

(2) **We have also agreed to pay the placement agent a management fee of 1% and reimbursement it for legal fees and expenses of the placement agent in the amount of \$70,000 For additional information about the compensation paid to the placement agent, see "Plan of Distribution."**

(3) **The amount of the offering proceeds to us presented in this table does not give effect to any exercise of the Warrants being issued in this offering.**

Rodman & Renshaw

a unit of H.C. Wainwright & Co.

The date of this prospectus supplement is September 1, 2016.

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ABOUT THIS PROSPECTUS SUPPLEMENT

References in this prospectus supplement to “Hemispherx,” the “Company,” “we,” “our” or “us” refer to Hemispherx Biopharma, Inc. and its subsidiaries on a consolidated basis.

This prospectus supplement and the accompanying prospectus dated August 4, 2015 are part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. This prospectus supplement and the accompanying prospectus relate to the offer by us of shares of our common stock to certain investors. We provide information to you about this offering of shares of our common stock in two separate documents that are bound together: (1) this prospectus supplement, which describes the specific details regarding this offering; and (2) the accompanying prospectus, which provides general information, some of which may not apply to this offering. Generally, when we refer to this “prospectus,” we are referring to both documents combined. If information in this prospectus supplement is inconsistent with the accompanying prospectus, you should rely on this prospectus supplement. However, if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in this prospectus supplement or the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement as our business, financial condition, results of operations and prospects may have changed since the earlier dates. You should read this prospectus supplement, the accompanying prospectus and the documents and information incorporated by reference in this prospectus supplement and the accompanying prospectus when making your investment decision. You should also read and consider the information in the documents we have referred you to under the headings “*Where You Can Find More Information; Information Incorporated by Reference.*”

You should rely only on information contained in or incorporated by reference into this prospectus supplement and the accompanying prospectus. We have not, and the placement agent has not, authorized anyone to provide you with information that is different. We are offering to sell and seeking offers to buy shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus supplement, the accompanying prospectus and the documents and information incorporated by reference in this prospectus supplement and the accompanying prospectus are accurate only as of their respective dates, regardless of the time of delivery of this prospectus supplement or of any sale of our common stock.

PROSPECTUS SUPPLEMENT SUMMARY

The items in the following summary are described in more detail later in this prospectus supplement and in the accompanying prospectus. This summary provides an overview of selected information and does not contain all the information you should consider before investing in our common stock. Therefore, you should read the entire prospectus supplement and the accompanying prospectus carefully, including the “Risk Factors” section, and other documents or information included or incorporated by reference in this prospectus supplement and the accompanying

prospectus before making any investment decision.

Our Business

We are a specialty pharmaceutical company headquartered in Philadelphia, Pennsylvania and engaged in the clinical development of new drug therapies based on natural immune system enhancing technologies for the treatment of viral and immune based disorders. We were founded in the early 1970s doing contract research for the National Institutes of Health. Since that time, we have established a strong foundation of laboratory, pre-clinical and clinical data with respect to the development of natural interferon and nucleic acids to enhance the natural antiviral defense system of the human body and to aid the development of therapeutic products for the treatment of certain chronic diseases.

Our flagship products include Alferon N Injection® and the experimental therapeutic Ampligen®. Alferon N Injection® is approved for a category of STD infection, and Ampligen® represents an experimental RNA being developed for globally important viral diseases and disorders of the immune system. Hemispherx' platform technology includes components for potential treatment of various severely debilitating and life threatening diseases. Alferon® LDO (Low Dose Oral) is a formulation under development targeting influenza.

The below chart provides a summary of the clinical indications for both Ampligen® and Alferon® currently under development.

Recent Developments

On August 18, 2016, we received approval of our New Drug Application (“NDA”) from Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica (“ANMAT”) for commercial sale of rintatolimod (U.S. tradename: Ampligen®) in the Argentine Republic for the treatment of severe myalgic encephalomyelitis/chronic fatigue syndrome (“ME/CFS”). The product will be marketed by GP Pharm, our commercial partner in Latin America. We believe that rintatolimod is the first drug to receive approval for this indication anywhere in the world.

We believe that this approval provides a platform for potential commercial sales in certain countries within the European Union under regulations that support cross-border pharmaceutical sales of licensed drugs. We and GP Pharm are now working to expand the approval of rintatolimod to additional countries with a focus on Latin America. In Europe, approval in a country with a stringent regulatory process in place, such as Argentina, should add further validation for the product as the Early Access Program is launched in Europe. ANMAT approval is only an initial, but important, step in the overall successful commercialization of our product. There are a number of actions that must occur before we could be able to commence commercial sales in Argentina. Commercialization in Argentina will require, among other things, an appropriate reimbursement level, appropriate marketing strategies, completion of manufacturing preparations for launch (including possible requirements for approval of final manufacturing), and there are no assurances as to whether or when such multiple subsequent steps will be successfully performed to result in an overall successful commercialization and product launch.

Current Non-Compliance with NYSE MKT Continued Listing Requirements

On March 15, 2016, we received written notice from the NYSE MKT LLC that we were not in compliance with its continued listing standards because our common stock had been selling for a low price per share for a substantial period of time. The NYSE MKT determined that the continued listing of our common stock was predicated on our effecting a reverse stock split of our common stock. Our stockholders approved a reverse stock split, our Board effected a 12-to-1 reverse stock split effective August 26, 2016 and our reverse split shares started trading on August 29, 2016. The NYSE MKT will assess whether we continue to be below continued listing standards in mid-September 2016. As a result of the reverse stock split we believe, but cannot assure, that we will be in compliance with the continued listing standards.

Our Corporate Information

Our principal executive offices are located at One Penn Center, 1617 JFK Boulevard, Suite 500, Philadelphia, Pennsylvania 19103, and our telephone number is 215-988-0080. We maintain a website at "<http://www.hemispherx.net>". Information contained on our website is not considered to be a part of, nor incorporated by reference in, this prospectus.

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THE OFFERING

Common Stock offered by us: 3,333,334 shares

Public offering price: \$1.50

Common Stock to be outstanding immediately after the offering: 24,077,686 shares

Use of Proceeds: We plan to allocate the net proceeds from the offering for preparation for technology transfer opportunities, expenses related to Ampligen® manufacturing, working capital and general corporate purposes. See “*Use of Proceeds*”.

Risk Factors: This investment involves a high degree of risk. You should read the “Risk Factors” section of this prospectus supplement and in the documents included in or incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of risks to consider before deciding to purchase shares of our common stock.

NYSE MKT trading symbol: HEB

Concurrent offering: In a concurrent private placement, we are selling to the purchasers of shares of our common stock in this offering warrants to purchase 75% of the number of shares of our common stock purchased by such investors in this offering, or up to 2,500,000 warrants. We will receive gross proceeds from the concurrent private placement transaction solely to the extent such warrants are exercised for cash. The warrants will be exercisable six months after issuance at an exercise price of \$2.00 per share and will expire five years from the date on which first exercisable. The warrants and the shares of our common stock issuable upon the exercise of the warrants are not being offered pursuant to this prospectus supplement and the accompanying prospectus and are being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act and Rule 506(b) promulgated thereunder. See “*Private Placement of Warrants*” below.

RISK FACTORS

Investment in our common stock involves a high degree of risk. In addition to the other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus, you should carefully consider the risks described below and in the section entitled “Risk Factors” in our Annual Report on Form 10-K for our most recent fiscal year filed with the Securities and Exchange Commission, subsequent Quarterly Reports on Form 10-Q, and in other reports we file with the Securities and Exchange Commission that are incorporated by reference herein, before making an investment decision. The following risks are presented as of the date of this prospectus supplement and we expect that these will be updated from time to time in our periodic and current reports filed with the Securities and Exchange Commission, which will be incorporated herein by reference. Please refer to these subsequent reports for additional information relating to the risks associated with investing in our common stock. The risks and uncertainties described therein and below could materially adversely affect our business, operating results and financial condition, as well as cause the value of our common stock to decline. You may lose all or part of your investment as a result. You should also refer to the other information contained in this prospectus supplement and the accompanying prospectus, or incorporated by reference, including our financial statements and the notes to those statements, and the information set forth under the caption “Special Note Regarding Forward-Looking Statements.” Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks mentioned below. Forward-looking statements included in this prospectus supplement are based on information available to us on the date hereof, and all forward-looking statements in documents incorporated by reference are based on information available to us as of the date of such documents. We disclaim any intent to update any forward-looking statements. The risks described below and contained in our Annual Report on Form 10-K, Form 10-Q and in our other periodic reports are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business operations.

Risks Related to this Offering

Investors in this offering will suffer immediate and substantial dilution in the net tangible book value per share of our common stock.

The offering price per share of common stock in this offering is considerably more than the net tangible book value per share of our outstanding common stock. As a result, investors purchasing shares of common stock in this offering will pay a price per share that substantially exceeds the value of our tangible assets after subtracting liabilities. Investors will incur immediate dilution of \$0.63 per share, based on the public offering price of \$1.50 per share and the net tangible book value as of June 30, 2016. For a more detailed discussion of the foregoing, see the section entitled “Dilution” below. In addition, the investors in this offering will receive unregistered warrants to purchase 2,500,000 shares of our common stock purchased by such investors in this offering and the placement agent will receive unregistered warrants to purchase up to 5% of the aggregate number of shares of common stock sold in this offering. To the extent outstanding stock options or warrants are exercised, there will be further dilution to new

investors. Furthermore, to the extent we need to raise additional capital in the future and we issue additional equity or convertible debt securities, our then existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

We will have broad discretion in how we use the proceeds, and we may use the proceeds in ways in which you and other stockholders may disagree.

We plan to use the net proceeds from the offering towards activities listed in “*Use of Proceeds*”. Pending these uses, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade and interest-bearing instruments. Our Management will have broad discretion in the application of the proceeds from this offering and could spend the proceeds in ways that do not necessarily improve our operating results or enhance the value of our common stock.

There is uncertainty regarding the application of the federal and state securities laws to our offering of common stock and warrants, and there is a corresponding risk that we could be required to refund the purchase price of securities offered to purchasers who so elect.

We are conducting an offering under a registration statement filed with the SEC and a concurrent private placement intended to comply with the requirements of Section 4(a)(2) under the Securities Act and Rule 506(b) promulgated thereunder. See “*Private Placement of Warrants*” below. Shares of common stock and warrants are being offered and sold in combination. The shares of common stock are intended to be offered and sold in a transaction registered under the Securities Act, while the warrants and shares of common stock issuable thereunder are intended to be offered and sold in a private placement exempt from the registration requirements of the Securities Act.

While we are aware of other transactions using a concurrent public/private offering approach, the SEC has not addressed whether concurrent public and private offerings and sales to the same prospective investors could adversely impact the public offering or preclude the private offering from satisfying the requirements of Rule 506(b). If the securities offered in our concurrent private placement do not satisfy the conditions of Rule 506(b), the offering could be a violation of Section 5 of the Securities Act and each purchaser could have the right to rescind its purchase of the securities, meaning that we could be required to refund the purchase price of the securities to each purchaser electing rescission. If that were to occur, we could face severe financial demands and reputational harm that could adversely affect our business and operations. Additionally, if we did not in fact qualify for the exemptions upon which it has relied, we may become subject to significant fines and penalties imposed by the SEC. It is also possible that additional remedies may be available to purchasers under applicable state law.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

The statements in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements reflect our current views with respect to future events are based on assumptions and are subject to risks, uncertainties and other important factors. We discuss many of these risks, uncertainties and other important factors in greater detail under the heading “Risk Factors” in this prospectus supplement. Because the risk factors referred to above, in the Prospectus, in our Annual Report on Form 10-K for our most recent fiscal year filed with the Securities and Exchange Commission, subsequent Quarterly Reports on Form 10-Q, and in other reports we file with the Securities and Exchange Commission that are incorporated by reference herein, could cause actual results or outcomes to differ materially from those expressed in any forward-looking statements made by us, you should not place undue reliance on any such forward-looking statements.

Further, these forward-looking statements represent our estimates and assumptions only as of the date such forward-looking statements are made. You should carefully read this prospectus supplement and the accompanying prospectus, together with the information incorporated by reference, completely and with the understanding that our actual future results may be materially different from what we expect. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our business, results of operations and financial condition. Any forward-looking statement speaks only as of the date on which it is made and we undertake no obligation to update any forward-looking statement or statements to reflect events or circumstances after the date on which such statement is made or reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which will arise. We cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. Any statements in this prospectus and the information incorporated herein by reference about our expectations, beliefs, plans, objectives, assumptions or future events or performance that are not historical facts are forward-looking statements. You can

identify these forward-looking statements by the use of words or phrases such as “believe”, “may”, “could”, “will”, “estimate”, “continue”, “anticipate”, “intend”, “seek”, “plan”, “expect”, “should”, or “would,” and similar expressions intended to identify forward-looking statements.

Among the factors that could cause actual results to differ materially from those indicated in the forward-looking statements are risks and uncertainties inherent in our business including, without limitation: the potential therapeutic effect of our products, general industry conditions and competition; general economic factors; the Company’s ability to adequately fund its projects; the impact of pharmaceutical industry regulation and healthcare legislation in the United States and internationally; trends toward healthcare cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the Company’s ability to accurately predict the future market conditions; manufacturing difficulties or delays; dependence on the effectiveness of the Company’s patents and other protections for products; and the exposure to litigation, including patent litigation, and/or regulatory actions

We have disclosed that in February 2013, we received a Complete Response from the FDA declining to approve our Ampligen® New Drug Application (“NDA”) for Chronic Fatigue Syndrome Treatment (“CFS”) stating that we should conduct at least one additional clinical trial, complete various nonclinical studies and perform a number of data analyses. Accordingly, the remaining steps to potentially gain FDA approval of the Ampligen® NDA, the final results of these and other ongoing activities could vary materially from our expectations and could adversely affect the chances for approval of the Ampligen® NDA. These activities and the ultimate outcomes are subject to a variety of risks and uncertainties, including but not limited to risks that (i) the FDA may ask for additional data, information or studies to be completed or provided; and (ii) the FDA may require additional work related to the commercial manufacturing process to be completed or may, in the course of the inspection of manufacturing facilities, identify issues to be resolved. With regard to our NDA for Ampligen® to treat CFS, we note that there are additional steps which the FDA has advised Hemispherx to take in our seeking approval. The final results of these and other ongoing activities, and of the FDA review, could vary materially from Hemispherx’ expectations and could adversely affect the chances for approval of the Ampligen® NDA. Any failure to satisfy the FDA’s requirements could significantly delay, or preclude outright, approval of our drugs for commercial sale.

We completed the construction of the \$8 million our facility enhancement project in 2015 which, upon FDA approval, should provide for a higher capacity and more cost effective manufacturing process for the production of Alferon N Injection®. Commercial sales of Alferon and Alferon API internationally are projected to begin as soon as the necessary regulatory approvals are obtained. However, commercial sales of Alferon® in the USA will not resume until new batches of commercial filled and finished product are produced and released by the FDA. We are continuing the validation of Alferon® production and production of new Alferon® API inventory commenced in February 2015. While the facility is approved by the FDA under the Biological License Application (“BLA”) for Alferon®, this status will need to be reaffirmed by an FDA pre-approval inspection. We will also need the FDA’s approval to release commercial product once we have submitted satisfactory stability and quality release data. We had anticipated that it would take approximately until at least the 2nd half of 2015 before we would have Alferon® approved for commercial sales; however, during the final stage of the manufacturing process we encountered issues regarding a change in both the contract supplier of leukocytes and the long term supply availability related to a reagent used in the formulation of Alferon®. We have substantially resolved these issues through engaging in multiple agreements with suppliers of leukocytes as well as entering into a licensing agreement with a foreign multinational chemicals and biotechnology company that has been in business for over a century for the sourcing of the primary reagent allowing us to manufacture Alferon®. However, due to the interruption of the required flow of leukocytes, production ceased, causing parts to malfunction in the upstream process when the system was restarted for testing. We were working diligently to make the necessary repairs to be able to restart the validation process; however, in the process of obtaining time estimates for the repairs we experienced a flood within portions of our manufacturing facility. As a result, we will be constrained in our ability to manufacture product in the near future due to this flood in the upstream processing cleanroom that contains the bioreactor. The flood occurred on the afternoon of January 5, 2016, caused by a malfunctioning water supply pipe for the sprinkler system covering a large amount of the cleanroom in stagnant water and silt from the sprinkler system. Our facility insurer has been proactive in addressing and covering the loss. While repairs have required preapproval by our insurer, activity has moved forward quickly. The repairs noted below required special action because of the need to keep this critical manufacturing room within International Organization for Standardization (ISO) classifications and the need to certify that all the equipment that was exposed, or submerged, is in proper condition and operating effectively following the corrective actions. All HEPA filters affected by the flood were tested by an outside contractor and have passed all required tests. The flooring that was damaged has been repaired using a special epoxy that is used in cleanrooms. A large portion of the walls in the ISO classified area were damaged. We had a damage mitigation company come in to stop any moisture from seeping further into the ISO classified areas. Subsequently, all damaged walls and ceilings have been replaced with cleanroom grade materials and need no further work. Six pumps that were affected by the flood were sent back to the manufacturer for inspection and repair. Repairs that were required have been completed on the pumps and they were reinstalled in the Alferon manufacturing facility after the floor repair work was completed. All pumps will need to be qualified for use in the manufacturing process prior to the validation process for a Pre-Approval Inspection. All air ducts supplying the Alferon manufacturing area needed to be cleaned and insulation replaced along with ceiling tiles. The duct insulation and ceiling tile replacement will be performed after the duct cleaning work is completed. All smaller pieces of machinery and equipment that could not be salvaged have been replaced. The final repair step required to be performed will be HVAC air balancing and qualification.

Currently, the manufacturing process is on hold and there is no definitive timetable to have the facility back online. In addition, due to the repair issues mentioned above and the high cost estimates to bring the facility back online, we most likely will need additional funds to finance the revalidation process in our facility to initiate commercial manufacturing, thereby readying ourselves for an FDA Pre-Approval Inspection. If we are unable to gain the necessary FDA approvals related to the manufacturing process and/or final product of new Alferon® inventory, our

operations most likely will be materially and/or adversely affected. In light of these contingencies, there can be no assurances that the approved Alferon N Injection® product will be returned to production on a timely basis, if at all, or that if and when it is again made commercially available, it will return to prior sales levels.

Approval of Ampligen® for CFS in the Argentine Republic does not in any way suggest that the Ampligen® NDA in the United States will obtain commercial approval. Also, it is noted that ANMAT approval is only an initial, but important, step in the overall successful commercialization. Commercialization in Argentina will require, among other things, an appropriate reimbursement level, appropriate marketing strategies, completion of manufacturing preparations for launch (including possible requirements for approval of final manufacturing), and there are no assurances as to whether or when such multiple subsequent steps will be successfully performed to result in an overall successful commercialization and product launch.

USE OF PROCEEDS

We estimate that the net proceeds to us from this offering, after deducting placement agent fees but before paying offering expenses, will be approximately \$4,650,000 assuming all offered shares are sold.

We plan to allocate the net proceeds from the offering for preparation for technology transfer opportunities, expenses related to Ampligen® manufacturing, working capital and general corporate purposes.

We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds from this offering. Pending application of the net proceeds as described above, we intend to invest the net proceeds to us from this offering in a variety of capital preservation investments, including short-term, investment-grade and interest-bearing instruments.

PRIVATE PLACEMENT OF WARRANTS

Concurrently with the closing of the sale of shares of common stock in this offering, we also expect to issue and sell to the investors warrants to purchase an aggregate of 2,500,000 shares of our common stock, at an initial exercise price equal to \$2.00 per share, or the Warrants.

Each Warrant shall be exercisable six months after issuance and have a term of exercise equal to five years from the date on which first exercisable. Subject to limited exceptions, a holder of Warrants will not have the right to exercise any portion of its warrants if the holder, together with its affiliates, would beneficially own in excess of 4.99% of the number of shares of our common stock outstanding immediately after giving effect to such exercise.

Such securities will be issued and sold without registration under the Securities Act, or state securities laws, in reliance on the exemptions provided by Section 4(a)(2) of the Act and/or Regulation D promulgated thereunder and in reliance on similar exemptions under applicable state laws. Accordingly, the investors may exercise those Warrants and sell the underlying shares only pursuant to an effective registration statement under the Securities Act covering the resale of those shares, an exemption under Rule 144 under the Securities Act, or another applicable exemption under the Securities Act.

DILUTION

If you invest in our common stock in this offering, your interest will be diluted to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock after this offering. As of June 30, 2016, giving retroactive effect to the recent 12-to-1 reverse stock split, our historical net tangible book value was \$16,590,000, or \$0.80 per share, based on 20,735,810 shares of our common stock outstanding as of June 30, 2016. Our historical net tangible book value per share represents the amount of our total tangible assets reduced by the amount of our total liabilities, divided by the total number of shares of our common stock outstanding as of June 30, 2016. After giving effect to our sale in this offering of 3,333,334 shares of common stock at the public offering price of \$1.50 per share, and after deducting placement agent fees and estimated offering costs payable by us, our net tangible book value as of June 30, 2016 would have been \$21,040,001, or \$0.87 per share. This represents an immediate increase of net tangible book value of \$0.07 per share to our existing stockholders and an immediate dilution of \$0.63 per share to investors purchasing shares in this offering. The following table illustrates this per share dilution.

Public offering price per share	\$1.50
Historical net tangible book value per share at June 30, 2016	\$0.80
Increase per share attributable to investors purchasing shares in this offering	0.07
Pro forma net tangible book value per share, as adjusted to give effect to this offering	0.87
Dilution to investors in this offering	\$0.63

The above discussion and table are based on 20,735,810 shares outstanding as of June 30, 2016 and exclude:

- 163,850 shares of common stock issuable upon the exercise of warrants outstanding as of June 30, 2016, at a weighted average exercise price of \$4.91 per share;
- 1,297,633 shares of common stock issuable upon the exercise of options outstanding as of June 30, 2016, at a weighted average exercise price of \$13.19 per share;

355,589 shares of common stock reserved for future issuance under our equity incentive plans;
2,500,000 shares of common stock issuable upon exercise of warrants to be issued in a private placement, as described above under “*Private Placement of Warrants*”; and
166,667 shares of common stock issuable upon exercise of warrants to be issued to the placement agent, as described in “*Plan of Distribution*.”

To the extent that outstanding exercisable options or warrants are exercised, you may experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital by issuing equity or convertible debt securities, your ownership will be further diluted.

PLAN OF DISTRIBUTION

Pursuant to an engagement agreement dated July 26, 2016, we have engaged H.C. Wainwright & Co., LLC, or the placement agent, to act as our exclusive placement agent in connection with this offering of our shares of common stock pursuant to this prospectus supplement and accompanying prospectus. Under the terms of the engagement agreement, the placement agent has agreed to be our exclusive placement agent, on a reasonable best efforts basis, in connection with the issuance and sale by us of our shares of common stock in this takedown from our shelf registration statement. The terms of this offering were subject to market conditions and negotiations between us, the placement agent and prospective investors. The engagement agreement does not give rise to any commitment by the placement agent to purchase any of our shares of common stock or the private placement warrants, and the placement agent will have no authority to bind us by virtue of the engagement agreement. Further, the placement agent does not guarantee that it will be able to raise new capital in any prospective offering. The placement agent may engage sub-agents or selected dealers to assist with the offering.

We will enter into securities purchase agreements directly with investors in connection with this offering, and we will only sell to investors who have entered into securities purchase agreements.

We will deliver the shares of common stock being issued to the investors electronically upon receipt of investor funds for the purchase of the shares of our common stock offered pursuant to this prospectus supplement. We expect to deliver the shares of our common stock being offered pursuant to this prospectus supplement on or about September 6, 2016.

We have agreed to pay the placement agent a total cash fee equal to 7% of the gross proceeds of this offering. In addition, we have agreed to pay the placement agent a management fee equal to 1.0% of the gross proceeds of this offering, \$20,000 for its expenses in connection with confidentially marketing the transaction and to reimburse agent

the placement agent's legal fees and expenses in the amount of \$50,000. In addition, we have agreed to issue to the placement agent warrants to purchase up to 5% of the aggregate number of shares of common stock sold in this offering. The placement agent warrants will have substantially the same terms as the private placement warrants being sold concurrently to the investors in this offering, except that the placement agent warrant shall have an exercise price equal to 125% of the public offering price. Pursuant to FINRA Rule 5110(g), the placement agent warrants and any shares issued upon exercise of the placement agent warrants shall not be sold, transferred, assigned, pledged, or hypothecated, or be the subject of any hedging, short sale, derivative, put or call transaction that would result in the effective economic disposition of the securities by any person for a period of 180 days immediately following the date of effectiveness or commencement of sales of this offering, except the transfer of any security: (i) by operation of law or by reason of our reorganization; (ii) to any FINRA member firm participating in the offering and the officers or partners thereof, if all securities so transferred remain subject to the lock-up restriction set forth above for the remainder of the time period; (iii) if the aggregate amount of our securities held by the placement agent or related persons do not exceed 1% of the securities being offered; (iv) that is beneficially owned on a pro-rata basis by all equity owners of an investment fund, provided that no participating member manages or otherwise directs investments by the fund and the participating members in the aggregate do not own more than 10% of the equity in the fund; or (v) the exercise or conversion of any security, if all securities remain subject to the lock-up restriction set forth above for the remainder of the time period.

We have also agreed to give the placement agent a one year right of first refusal to act as our lead underwriter or placement agent for any further capital raising transactions undertaken by us; and a one year tail fee equal to the cash and warrant compensation in this offering, if any investor with which we have had substantive discussions with respect to this offering, provides us with further capital during such one year period following termination of our engagement (45 days after July 26, 2016).

We have agreed to indemnify the placement agent and specified other persons against some civil liabilities, including liabilities under the Securities Act and the Exchange Act, and to contribute to payments that the placement agent may be required to make in respect of such liabilities.

The placement agent may be deemed to be an underwriter within the meaning of Section 2(a)(11) of the Securities Act, and any commissions received by it and any profit realized on the resale of the securities sold by it while acting as principal might be deemed to be underwriting discounts or commissions under the Securities Act. As an underwriter, the placement agent would be required to comply with the requirements of the Securities Act and the Exchange Act, including, without limitation, Rule 415(a)(4) under the Securities Act and Rule 10b-5 and Regulation M under the Exchange Act. These rules and regulations may limit the timing of purchases and sales of shares of common stock and warrants by the placement agent acting as principal. Under these rules and regulations, the placement agent:

- may not engage in any stabilization activity in connection with our securities; and
- may not bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities, other than as permitted under the Exchange Act, until it has completed its participation in the distribution.

Our common stock is listed on the NYSE MKT under the symbol “HEB.”

LEGAL MATTERS

The validity of the issuance of the securities offered hereby will be passed upon by our counsel, Silverman Shin & Byrne PLLC. The placement agent has been represented in connection with this offering by Ellenoff Grossman & Schole LLP.

EXPERTS

The financial statements incorporated in this prospectus supplement by reference from the Company's Annual Report on Form 10-K for the year ended December 31, 2016 have been audited by RSM LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 that we filed with the SEC. This prospectus does not contain all of the information included in the registration statement. The registration statement that contains this prospectus supplement, including the exhibits to the registration statement, contains additional information about us and the securities offered by this prospectus supplement. For further information about us and our securities covered by this prospectus supplement and the accompanying prospectus, you should refer to the registration statement and the exhibits filed with the registration statement. We are subject to the information requirements of the Securities Exchange Act of 1934 and file annual, quarterly and current reports, proxy statements and other information with the SEC. You can read our SEC filings, including the registration statement, over the Internet at the SEC's website at www.sec.gov or through our website at www.hemispherx.net. Information contained on our website is not considered to be a part of, nor incorporated by reference in, this prospectus. You may also read and obtain copies any document we file with the SEC at its Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

IMPORTANT INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to “incorporate by reference” the information that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be an important part of this prospectus, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference the following documents and any future filing made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934 prior to the termination of the offering:

- our annual report on Form 10-K for the year ended December 31, 2015;
- our quarterly reports on Form 10-Q for the quarters ended March 31, 2016 and June 30, 2016;
- our current reports on Form 8-K filed with the Commission on August 15, 2016, August 17, 2016, August 19, 2016 and August 24, 2016;
- our proxy statement on Schedule 14A filed on June 27, 2016; and
- A description of our common stock contained in our registration statement on Form S-1, SEC File No. 333-117178, and any amendment or report filed for the purpose of updating this description.

We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed above or filed in the future, that are not deemed “filed” with the SEC, including our Compensation Committee report or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

You may request a copy of these filings (other than exhibits, unless they are specifically incorporated by reference in the documents), at no cost, by writing or telephoning us at the following address:

Investor Relations

One Penn Center, 1617 JFK Blvd., Suite 500

Philadelphia, PA 19103

Phone: 215-988-0080

Fax: 215-988-1739

Email: ir@hemispherx.net

S-12

PROSPECTUS

HEMISPHERX BIOPHARMA, INC.

\$77,849,014

Debt Securities

Preferred Stock

Common Stock

Debt Warrants

Equity Warrants

Units

We may from time to time offer to sell any combination of debt securities, preferred stock, common stock, debt warrants, equity warrants and units described in this prospectus in one or more offerings. The aggregate initial offering price of all securities sold under this prospectus will not exceed \$77,849,014.

This prospectus provides a general description of the securities we may offer. Each time we sell securities, we will provide specific terms of the securities offered in a supplement to this prospectus. The prospectus supplement may also add, update or change information contained in this prospectus. You should read this prospectus and the applicable prospectus supplement carefully before you invest in any securities. This prospectus may not be used to consummate a sale of securities unless accompanied by the applicable prospectus supplement.

We will sell these securities directly to our stockholders or to purchasers or through agents on our behalf or through underwriters or dealers as designated from time to time. If any agents or underwriters are involved in the sale of any of these securities, the applicable prospectus supplement will provide the names of the agents or underwriters and any applicable fees, commissions or discounts.

Our common stock is traded on the NYSE MKT under the symbol “HEB.” On June 1, 2015, the last reported sale price for our common stock on the NYSE MKT was \$0.23 per share. The aggregate market value of the outstanding shares of our common stock held by non-affiliates was \$54,904,932, based on 242,554,673 shares of common stock outstanding, of which 238,717,096 are held by non-affiliates, and a closing sale price on NYSE MKT of \$0.23 on June 1, 2015. Pursuant to General Instruction I.B.6 of Form S-3, in no event will we sell securities in a public primary offering with a value exceeding more than one-third of our “public float” (the market value of our common stock held by our non-affiliates) in any 12-month period so long as our public float remains below \$75,000,000. We have sold 16,677,755 shares of our common stock pursuant to General Instruction I.B.6. of Form S-3 during the twelve calendar months prior to and including the date of this prospectus.

Investing in our securities involves risks. See “Risk Factors” on page 3.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is August 4, 2015

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ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement that we filed with the Securities and Exchange Commission, or the Commission, utilizing a “shelf” registration process. Under this shelf registration process, we may offer to sell any combination of the securities described in this prospectus in one or more offerings up to a total dollar amount of \$77,849,014. This prospectus provides you with a general description of the securities we may offer. Each time we sell securities under this shelf registration, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus. To the extent that any statement that we make in a prospectus supplement is inconsistent with statements made in this prospectus, the statements made in this prospectus will be deemed modified or superseded by those made in the prospectus supplement. You should read both this prospectus and any prospectus supplement, including all documents incorporated herein or therein by reference, together with additional information described under “Where You Can Find More Information” and “Information Incorporated by Reference.” We may only use this prospectus to sell the securities if it is accompanied by a prospectus supplement.

We have not authorized any dealer, salesman or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus and the accompanying prospectus supplement. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or the accompanying prospectus supplement. This prospectus and the accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and the accompanying prospectus supplement constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus and the accompanying prospectus supplement is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus and any accompanying prospectus supplement is delivered or securities are sold on a later date.

ABOUT HEMISPHERX

Hemispherx Biopharma, Inc. and its subsidiaries (collectively, “Hemispherx”, “Company”, “we” or “us”) are a specialty pharmaceutical company headquartered in Philadelphia, Pennsylvania and engaged in the clinical development of new drug therapies based on natural immune system enhancing technologies for the treatment of viral and immune based disorders. We were founded in the early 1970s doing contract research for the National Institutes of Health. Since that time, we have established a strong foundation of laboratory, pre-clinical and clinical data with respect to the development of natural interferon and nucleic acids to enhance the natural antiviral defense system of the human body and to aid the development of therapeutic products for the treatment of certain chronic diseases. We have three domestic subsidiaries BioPro Corp., BioAegean Corp., and Core BioTech Corp., all of which are incorporated in Delaware and are dormant. Our foreign subsidiary is Hemispherx Biopharma Europe N.V./S.A. which was established

in Belgium in 1998.

Our flagship products include Alferon N Injection® and the experimental therapeutic Ampligen®. Alferon N Injection® is approved for a category of STD infection, and Ampligen® represents an experimental RNA being developed for globally important viral diseases and disorders of the immune system. Hemispherx' platform technology includes components for potential treatment of various severely debilitating and life threatening diseases. Alferon® LDO (Low Dose Oral) is a formulation under development targeting influenza. We own and operate a 43,000 sq. ft. FDA approved facility in New Brunswick, NJ.

Our principal executive offices are located at One Penn Center, 1617 JFK Boulevard, Suite 500, Philadelphia, Pennsylvania 19103, and our telephone number is 215-988-0080. We maintain a website at "<http://www.hemispherx.net>." Information contained on our website is not considered to be a part of, nor incorporated by reference in, this prospectus. Unless the context requires otherwise, references in this prospectus to "Hemispherx," the Company," "we," "us" and "our" refer to Hemispherx Biopharma, Inc.

RISK FACTORS

You should carefully consider the specific risks set forth under "Risk Factors" in the applicable prospectus supplement, under "Risk Factors" under Item 1A of Part I of our most recent annual report on Form 10-K, and under "Risk Factors" under Item 1A of Part II of our subsequent quarterly reports on Form 10-Q, as updated by our subsequent filings under the Securities Exchange Act of 1934, as amended, or the Exchange Act, each of which is incorporated by reference in this prospectus, before making an investment decision. For more information, see "Information Incorporated by Reference."

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

Any statements in this prospectus and the information incorporated herein by reference about our expectations, beliefs, plans, objectives, assumptions or future events or performance that are not historical facts are forward-looking statements. You can identify these forward-looking statements by the use of words or phrases such as “believe”, “may”, “could”, “will”, “estimate”, “continue”, “anticipate”, “intend”, “seek”, “plan”, “expect”, “should”, or “would”. Among the factors that may cause actual results to differ materially from those indicated in the forward-looking statements are risks and uncertainties inherent in our business including, without limitation: the potential therapeutic effect of our products, the possibility of obtaining regulatory approval, our ability to manufacture and sell any products, our ability to enter into arrangements with third party vendors, market acceptance of our products, our ability to earn a profit from sales or licenses of any drugs, our ability to discover new drugs in the future, changing market conditions, changes in laws and regulations affecting our industry, issues related to operations at our New Brunswick, New Jersey facility; and other risks detailed in the documents incorporated by reference in this prospectus. If any of these risks or uncertainties materializes or any of these assumptions proves incorrect, our results could differ materially from the expectations in these statements. The forward-looking statements included in this prospectus are made only as of the date of this prospectus, and we are not under any obligation to update our respective forward-looking statements and do not intend to do so.

USE OF PROCEEDS

Unless otherwise indicated in the applicable prospectus supplement, we plan to allocate the net proceeds from the offering towards research and development, operations and general and administrative purposes related to the commercialization of Ampligen® and Alferon® related products, including, but not limited to, the following: (1) costs associated with validation of Alferon® production and preparation for the FDA pre-approval inspections of the facility, (2) manufacture of commercial product, (3) potential new preclinical and/or clinical studies in order to gain commercial approval for Ampligen® and broader approvals for Alferon® and Alferon LDO®, (4) working capital to build and maintain sufficient inventory by procuring raw materials, supplies and other items for the New Brunswick manufacturing facility, as well as to remunerate outside contractors for necessary services, such as, final filling and finishing operations in order to meet any anticipated demand from normal operations as well as through the possible pursuit of other disease areas and/or geographic regions that may present themselves, (5) potential establishment of sales and marketing capabilities, as well as consideration towards the expansion of our manufacturing capacity, and (6) working capital for general and administrative expenses. We will set forth in the particular prospectus supplement our intended use for the net proceeds we receive from the sale of our securities under such prospectus supplement. Pending the uses described above, we plan to invest the net proceeds of this offering in short and medium-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

RATIO OF EARNINGS TO FIXED CHARGES

The following summary is qualified by the more detailed information appearing in the computation table found in Exhibit 12.1 to the registration statement of which this prospectus is part and the historical financial statements, including the notes to those financial statements, incorporated by reference in this prospectus. Our ratio of earnings to fixed charges for each of the years ended December 31, 2010 to 2014 and the three months ended March 31, 2015 was as follows:

	Year Ended December 31,					Three Months
	2010	2011	2012	2013	2014	Ended
						March 31,
						2015
Ratio of earnings to fixed charges(1)	—	—	—	—	—	—

- (1) For purposes of computing this ratio of earnings to fixed charges, fixed charges consist of interest expense and premiums, discounts and capital expenses related to debt (loss) before income taxes plus fixed charges. Earnings were insufficient to cover fixed charges by approximately \$13.1 million, \$9.0 million, \$17.3 million, \$16.2 million and \$17.5 million for the years ended December 31, 2010, 2011, 2012, 2013 and 2014 and \$3.4 million for the first three months of 2015. We have not included a ratio of earnings to combined fixed charges and preferred stock dividends because we do not have any preferred stock outstanding as of the date of this prospectus.

We have incurred approximately \$103,000 in fixed charges in the past five years. Fixed charges mainly represent interest expensed as well as amortized discounts related to indebtedness. We have incurred Net Losses totaling approximately \$13.1 million, \$9.0 million, \$17.4 million, \$16.2 million and \$17.5 million for the years ended December 31, 2010, 2011, 2012, 2013 and 2014, respectively, and \$3.4 million for the first three months of 2015. Until we achieve profitability, we will not be able to cover our fixed charges from earnings.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities separately or together:

through one or more underwriters or dealers in a public offering and sale by them;

through agents; and/or

directly to one or more purchasers.

We may distribute the securities from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

- at prices related to such prevailing market prices; or

at negotiated prices.

We may solicit directly offers to purchase the securities being offered by this prospectus. We may also designate agents to solicit offers to purchase the securities from time to time. We may sell the securities being offered by this prospectus by any method permitted by law, including sales deemed to be an “at the market” offering as defined in Rule 415(a)(4) of the Securities Act of 1933, as amended, or the Securities Act, including without limitation sales made directly on the NYSE MKT, on any other existing trading market for our securities or to or through a market maker. We will name in a prospectus supplement any agent involved in the offer or sale of our securities.

If we utilize a dealer in the sale of the securities being offered by this prospectus, we will sell the securities to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

If we utilize an underwriter in the sale of the securities being offered by this prospectus, we will execute an underwriting agreement with the underwriter at the time of sale and we will provide the name of any underwriter in the prospectus supplement that the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we or the purchasers of securities for whom the underwriter may act as agent may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and the underwriter may compensate those dealers in the form of discounts, concessions or commissions.

We will provide in the applicable prospectus supplement any compensation we will pay to underwriters, dealers or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof.

Unless otherwise specified in the prospectus supplement, each series of the securities will be a new issue with no established trading market, other than our common stock, which is currently listed on the NYSE MKT. We will apply to the NYSE MKT to list any additional shares of common stock that we offer and sell pursuant to a prospectus supplement. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involves the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

We may authorize underwriters, dealers or agents to solicit offers by certain purchasers to purchase the securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. The contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

We may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement so indicates, in connection with

any derivative transaction, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including in short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and may use securities received from us in settlement of those derivatives to close out any related open borrowings of stock. The third party in such sale transactions will be an underwriter and, if not identified in this prospectus, will be identified in the applicable prospectus supplement or a post-effective amendment to the registration statement of which this prospectus is a part. In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus. Such financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplement, summarizes certain general terms and provisions of the debt securities that we may offer under this prospectus. When we offer to sell a particular series of debt securities, we will describe the specific terms of the series in a supplement to this prospectus. We will also indicate in the prospectus supplement the extent to which the general terms and provisions described in this prospectus apply to a particular series of debt securities.

We may issue debt securities either separately, or together with, or upon the conversion or exercise of or in exchange for, other securities described in this prospectus. Debt securities may be our senior, senior subordinated or subordinated obligations and, unless otherwise specified in a supplement to this prospectus, the debt securities will be our direct, unsecured obligations and may be issued in one or more series.

The debt securities will be issued under an indenture between us and a trustee to be identified in the applicable prospectus supplement. We have summarized select portions of the indenture below. The summary is not complete. The form of the indenture has been filed as an exhibit to the registration statement of which this prospectus forms a part and you should read the indenture for provisions that may be important to you. In the summary below, we have included references to the section numbers of the indenture so that you can easily locate these provisions. Capitalized terms used in the summary and not defined herein have the meanings specified in the indenture.

As used in this section only, “Hemispherx,” “we,” “our” or “us” refer to Hemispherx Biopharma, Inc. excluding our subsidiaries, unless expressly stated or the context otherwise requires.

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in a resolution of our board of directors, in an officer’s certificate or by a supplemental indenture. (Section 2.2) The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series (including any pricing supplement or term sheet).

We can issue an unlimited amount of debt securities under the indenture that may be in one or more series with the same or various maturities, at par, at a premium, or at a discount. (Section 2.1) We will set forth in a prospectus supplement (including any pricing supplement or term sheet) relating to any series of debt securities being offered, the aggregate principal amount and the following terms of the debt securities, if applicable:

• the title and ranking of the debt securities (including the terms of any subordination provisions);

• the price or prices (expressed as a percentage of the principal amount) at which we will sell the debt securities;

• any limit on the aggregate principal amount of the debt securities;

• the date or dates on which the principal of the debt securities of the series is payable;

• the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence

and be payable and any regular record date for the interest payable on any interest payment date;

the place or places where principal of, and interest, if any, on the debt securities will be payable (and the method of such payment), where the securities of such series may be surrendered for registration of transfer or exchange, and where notices and demands to us in respect of the debt securities may be delivered;

the period or periods within which, the price or prices at which and the terms and conditions upon which we may redeem the debt securities;

any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities and the period or periods within which, the price or prices at which and in the terms and conditions upon which debt securities of the series shall be redeemed or purchased, in whole or in part, pursuant to such obligation;

the dates on which and the price or prices at which we will repurchase debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;

the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;

whether the debt securities will be issued in the form of certificated debt securities or global debt securities;

the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;

the currency of denomination of the debt securities, which may be United States Dollars or any foreign currency, and if such currency of denomination is a composite currency, the agency or organization, if any, responsible for overseeing such composite currency;

the designation of the currency, currencies or currency units in which payment of principal of, premium and interest on the debt securities will be made;

if payments of principal of, premium or interest on the debt securities will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;

the manner in which the amounts of payment of principal of, premium, if any, or interest on the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies other than that in which the debt securities are denominated or designated to be payable or by reference to a commodity, commodity index, stock exchange index or financial index;

any provisions relating to any security provided for the debt securities;

any addition to, deletion of or change in the Events of Default described in this prospectus or in the indenture with respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;

- any addition to, deletion of or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities;
- the provisions, if any, relating to conversion or exchange of any securities of such series, including if applicable, the conversion or exchange price and period, provisions as to whether conversion or exchange will be mandatory, the events requiring an adjustment of the conversion or exchange price and provisions affecting conversion or exchange; and

any other terms of the debt securities, which may supplement, modify or delete any provision of the indenture as it applies to that series, including any terms that may be required under applicable law or regulations or advisable in connection with the marketing of the securities. (Section 2.2)

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of and any premium and interest on any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you with information on the restrictions, elections, general tax considerations, specific terms and other information with respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Transfer and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, or the Depository, or a nominee of the Depository (we will refer to any debt security represented by a global debt security as a “book-entry debt security”), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a “certificated debt security”) as set forth in the applicable prospectus supplement. Except as set forth under the heading “Global Debt Securities and Book-Entry System” below, book-entry debt securities will not be issuable in certificated form.

Certificated Debt Securities. You may transfer or exchange certificated debt securities at any office we maintain for this purpose in accordance with the terms of the indenture. (Section 2.4) No service charge will be made for any transfer or exchange of certificated debt securities, but we may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection with a transfer or exchange. (Section 2.7)

You may effect the transfer of certificated debt securities and the right to receive the principal of, premium and interest on certificated debt securities only by surrendering the certificate representing those certificated debt securities and either reissuance by us or the trustee of the certificate to the new holder or the issuance by us or the trustee of a new certificate to the new holder.

Global Debt Securities and Book-Entry System. Each global debt security representing book-entry debt securities will be deposited with, or on behalf of, the Depositary, and registered in the name of the Depositary or a nominee of the Depositary. Please see “Global Securities.”

Covenants

We will set forth in the applicable prospectus supplement any restrictive covenants applicable to any issue of debt securities. (Article IV)

No Protection In the Event of a Change of Control

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions which may afford holders of the debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control) which could adversely affect holders of debt securities.

Consolidation, Merger and Sale of Assets

We may not consolidate with or merge with or into, or convey, transfer or lease all or substantially all of our properties and assets to any person (a “successor person”) unless:

we are the surviving corporation or the successor person (if other than us) is a corporation organized and validly existing under the laws of any U.S. domestic jurisdiction and expressly assumes our obligations on the debt securities and under the indenture; and

immediately after giving effect to the transaction, no Default or Event of Default, shall have occurred and be continuing.

Notwithstanding the above, any of our subsidiaries may consolidate with, merge into or transfer all or part of its properties to us. (Section 5.1)

Events of Default

“*Event of Default*” means with respect to any series of debt securities, any of the following:

default in the payment of any interest upon any debt security of that series when it becomes due and payable, and continuance of such default for a period of 30 days (unless the entire amount of the payment is deposited by us with the trustee or with a paying agent prior to the expiration of the 30-day period);

default in the payment of principal of any debt security of that series at its maturity;

default in the performance or breach of any other covenant or warranty by us in the indenture (other than a covenant or warranty that has been included in the indenture solely for the benefit of a series of debt securities other than that series), which default continues uncured for a period of 60 days after we receive written notice from the trustee or Hemispherx and the trustee receive written notice from the holders of not less than 25% in principal amount of the outstanding debt securities of that series as provided in the indenture;

certain voluntary or involuntary events of bankruptcy, insolvency or reorganization of Hemispherx; or

any other Event of Default provided with respect to debt securities of that series that is described in the applicable prospectus supplement. (Section 6.1)

No Event of Default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an Event of Default with respect to any other series of debt securities. (Section 6.1) The occurrence of certain Events of Default or an acceleration under the indenture may constitute an event of default under certain of our indebtedness or that of our subsidiaries outstanding from time to time.

If an Event of Default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than 25% in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal of (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) and accrued and unpaid interest, if any, on all debt securities of that series. In the case of an Event of Default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all Events of Default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture. (Section 6.2) We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an Event of Default.

The indenture provides that the trustee will be under no obligation to exercise any of its rights or powers under the indenture unless the trustee receives indemnity satisfactory to it against any cost, liability or expense which might be incurred by it in exercising such right of power. (Section 7.1(e)) Subject to certain rights of the trustee, the holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to the debt securities of that series. (Section 6.12)

No holder of any debt security of any series will have any right to institute any proceeding, judicial or otherwise, with respect to the indenture or for the appointment of a receiver or trustee, or for any remedy under the indenture, unless:

• that holder has previously given to the trustee written notice of a continuing Event of Default with respect to debt securities of that series; and

• the holders of not less than 25% in principal amount of the outstanding debt securities of that series have made written request, and offered reasonable indemnity or security, to the trustee to institute the proceeding as trustee, and the

trustee has not received from the holders of not less than a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request and has failed to institute the proceeding within 60 days. (Section 6.7)

Notwithstanding any other provision in the indenture, the holder of any debt security will have an absolute and unconditional right to receive payment of the principal of, premium and any interest on that debt security on or after the due dates expressed in that debt security and to institute suit for the enforcement of payment. (Section 6.8)

The indenture requires us, within 120 days after the end of our fiscal year, to furnish to the trustee a statement as to compliance with the indenture. (Section 4.3) If a Default or Event of Default occurs and is continuing with respect to the debt securities of any series and if it is known to a responsible officer of the trustee, the trustee shall mail to each Securityholder of the debt securities of that series notice of a Default or Event of Default within 90 days after it occurs. The indenture provides that the trustee may withhold notice to the holders of debt securities of any series of any Default or Event of Default (except in payment on any debt securities of that series) with respect to debt securities of that series if the trustee determines in good faith that withholding notice is in the interest of the holders of those debt securities. (Section 7.5)

Modification and Waiver

We and the trustee may modify and amend the indenture or the debt securities of any series without the consent of any holder of any debt security:

to cure any ambiguity, defect or inconsistency;

to comply with covenants in the indenture described above under the heading “Consolidation, Merger and Sale of Assets”;

to provide for uncertificated securities in addition to or in place of certificated securities;

to make any change that does not adversely affect the rights of any holder of debt securities;

to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;

to effect the appointment of a successor trustee with respect to the debt securities of any series and to add to or change any of the provisions of the indenture to provide for or facilitate administration by more than one trustee; or

to comply with requirements of the Commission in order to effect or maintain the qualification of the indenture under the Trust Indenture Act. (Section 9.1)

We may also modify and amend the indenture with the consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or amendments.

We may not make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

reduce the amount of debt securities whose holders must consent to an amendment, supplement or waiver;

reduce the rate of or extend the time for payment of interest (including default interest) on any debt security;

reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;

reduce the principal amount of discount securities payable upon acceleration of maturity;

•

waive a default in the payment of the principal of, premium or interest on any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);

• make the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security;

• make any change to certain provisions of the indenture relating to, among other things, the right of holders of debt securities to receive payment of the principal of, premium and interest on those debt securities and to institute suit for the enforcement of any such payment and to waivers or amendments; or

• waive a redemption payment with respect to any debt security. (Section 9.3)

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. (Section 9.2) The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration. (Section 6.13)

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

Legal Defeasance. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, we may be discharged from any and all obligations in respect of the debt securities of any series (subject to certain exceptions). We will be so discharged upon the deposit with the trustee, in trust, of money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities.

This discharge may occur only if, among other things, we have delivered to the trustee an opinion of counsel stating that we have received from, or there has been published by, the United States Internal Revenue Service a ruling or, since the date of execution of the indenture, there has been a change in the applicable United States federal income tax law, in either case to the effect that, and based thereon such opinion shall confirm that, the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit, defeasance and discharge and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit, defeasance and discharge had not occurred. (Section 8.3)

Defeasance of Certain Covenants. The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, upon compliance with certain conditions:

we may omit to comply with the covenant described under the heading “Consolidation, Merger and Sale of Assets” and certain other covenants set forth in the indenture, as well as any additional covenants which may be set forth in the applicable prospectus supplement; and

any omission to comply with those covenants will not constitute a Default or an Event of Default with respect to the debt securities of that series (“covenant defeasance”).

The conditions include:

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depositing with the trustee money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. Dollars, government obligations of the government that issued or caused to be issued such currency, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants or investment bank to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities; and

delivering to the trustee an opinion of counsel to the effect that the holders of the debt securities of that series will not recognize income, gain or loss for United States federal income tax purposes as a result of the deposit and related covenant defeasance and will be subject to United States federal income tax on the same amounts and in the same manner and at the same times as would have been the case if the deposit and related covenant defeasance had not occurred. (Section 8.4)

Covenant Defeasance and Events of Default. In the event we exercise our option to effect covenant defeasance with respect to any series of debt securities and the debt securities of that series are declared due and payable because of the occurrence of any Event of Default, the amount of money and/or U.S. government obligations or foreign government obligations on deposit with the trustee will be sufficient to pay amounts due on the debt securities of that series at the time of their stated maturity but may not be sufficient to pay amounts due on the debt securities of that series at the time of the acceleration resulting from the Event of Default. However, we shall remain liable for those payments. (Section 8.4).

Governing Law

The indenture and the debt securities, including any claim or controversy arising out of or relating to the indenture or the securities, will be governed by the laws of the State of New York without regard to conflict of law principles that would result in the application of any law other than the laws of the State of New York. (Section 10.10)

DESCRIPTION OF COMMON STOCK

The following summary of the terms of our common stock does not purport to be complete and is subject to and qualified in its entirety by reference to our Amended and Restated Certificate of Incorporation as subsequently amended, or certificate of incorporation, and Amended and Restated Bylaws, or bylaws, copies of which are on file with the Commission as exhibits to registration statements previously filed by us. See “Where You Can Find More Information.”

General

Our authorized capital stock currently consists of 350,000,000 shares of common stock, par value \$0.001 per share, and 5,000,000 shares of preferred stock, \$0.01 par value per share. As of June 1, 2015, we had 242,554,673 shares of common stock outstanding; an aggregate of 16,905,280 shares of common stock reserved for issuance upon exercise of outstanding stock options and warrants; and an aggregate of 687,543 shares of common stock reserved for issuance pursuant to future grants under our 2009 Equity Incentive Plan. As of June 1, 2015, we had approximately 660,684 shares of common stock that are not reserved for issuance or subject to restrictions (see “Limitations on Use” below).

The following summary of the rights of our common stock is not complete and is qualified in its entirety by reference to our amended and restated certificate of incorporation, as subsequently amended, and amended and restated bylaws, copies of which are filed as exhibits to the registration statement of which this prospectus is a part.

Limitations on Use

Pursuant to our Certificate of Incorporation, there are specific limitations and restrictions on our ability to issue 150,000,000 of the 350,000,000 authorized shares of common stock, unless such issuances are primarily in connection

with strategic transactions or other non-fundraising purpose that met certain significant criteria. If we want to issue any of these shares for other purposes, we must first seek stockholder approval. In September 2012, our stockholders authorized our Board to use 75,000,000 of the 150,000,000 shares for fundraising purposes.

Voting Rights

Holders of our common stock are entitled to one vote per share on all matters to be voted upon by the stockholders. The holders of common stock are not entitled to cumulate voting rights with respect to the election of directors, which means that the holders of a majority of the shares voted can elect all of the directors then standing for election.

Dividends

Subject to limitations under Delaware law and preferences that may apply to any outstanding shares of preferred stock, holders of our common stock are entitled to receive ratably such dividends or other distribution, if any, as may be declared by our board of directors out of funds legally available therefor.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities, subject to the liquidation preference of any outstanding preferred stock.

Rights and Preferences

The common stock has no preemptive, conversion or other rights to subscribe for additional securities. There are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Fully Paid and Nonassessable

All outstanding shares of our common stock are, and all shares of common stock to be outstanding upon completion of the offering will be, validly issued, fully paid and nonassessable.

Certificate of Incorporation and Bylaw Provisions

See “Certain Provisions of Delaware Law and of the Company’s Certificate of Incorporation and Bylaws” for a description of provisions of our certificate of incorporation and bylaws which may have the effect of delaying changes in our control or management.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Continental Stock Transfer & Trust Company.

DESCRIPTION OF PREFERRED STOCK

We currently have authorized 5,000,000 shares of preferred stock, \$0.01 par value per share. As of the date of this prospectus, we did not have any shares of preferred stock outstanding.

General

Prior to issuance of shares of each series of our undesignated preferred stock, our board of directors is required by the Delaware General Corporate Law, or DGCL, and our Amended and Restated Certificate of Incorporation as subsequently amended, or certificate of incorporation, to adopt resolutions and file a Certificate of Designations with the Secretary of State of the State of Delaware, fixing for each such series the designations, powers, preferences, rights, qualifications, limitations and restrictions of the shares of such series. Our board of directors could authorize the issuance of shares of preferred stock with terms and conditions which could have the effect of discouraging a takeover or other transaction which holders of some, or a majority, of such shares might believe to be in their best interests or in which holders of some, or a majority, of such shares might receive a premium for their shares over the then-market price of such shares.

Subject to limitations prescribed by the DGCL, our certificate of incorporation and our Amended and Restated Bylaws, or bylaws, our board of directors is authorized to fix the number of shares constituting each series of preferred stock and the designations, powers, preferences, rights, qualifications, limitations and restrictions of the shares of such series, including such provisions as may be desired concerning voting, redemption, dividends,

dissolution or the distribution of assets, conversion or exchange, and such other subjects or matters as may be fixed by resolution of the board of directors. Each series of preferred stock that we offer under this prospectus will, when issued, be fully paid and nonassessable and will not have, or be subject to, any preemptive or similar rights.

The applicable prospectus supplement(s) will describe the following terms of the series of preferred stock in respect of which this prospectus is being delivered:

• the title and stated value of the preferred stock;

• the number of shares of the preferred stock offered, the liquidation preference per share and the purchase price of the preferred stock;

• the dividend rate(s), period(s) and/or payment date(s) or the method(s) of calculation for dividends;

• whether dividends shall be cumulative or non-cumulative and, if cumulative, the date from which dividends on the preferred stock shall accumulate;

• the procedures for any auction and remarketing, if any, for the preferred stock;

• the provisions for a sinking fund, if any, for the preferred stock;

• the provisions for redemption, if applicable, of the preferred stock;

• any listing of the preferred stock on any securities exchange or market;

• the terms and conditions, if applicable, upon which the preferred stock will be convertible into common stock or another series of our preferred stock, including the conversion price (or its manner of calculation) and conversion period;

• the terms and conditions, if applicable, upon which preferred stock will be exchangeable into our debt securities, including the exchange price, or its manner of calculation, and exchange period;

• voting rights, if any, of the preferred stock;

• a discussion of any material and/or special U.S. federal income tax considerations applicable to the preferred stock;

• whether interests in the preferred stock will be represented by depositary shares;

• the relative ranking and preferences of the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of our affairs;

• any limitations on issuance of any series of preferred stock ranking senior to or on a parity with the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of our affairs; and

• any other specific terms, preferences, rights, limitations or restrictions on the preferred stock.

Rank

Unless otherwise specified in the prospectus supplement, with respect to dividend rights and rights upon liquidation, dissolution or winding up of Hemispherx, the preferred stock will rank:

• senior to all classes or series of our common stock, and to all equity securities issued by us the terms of which specifically provide that such equity securities rank junior to the preferred stock with respect to dividend rights or rights upon the liquidation, dissolution or winding up of us;

• on a parity with all equity securities issued by us that do not rank senior or junior to the preferred stock with respect to dividend rights or rights upon the liquidation, dissolution or winding up of us; and

• junior to all equity securities issued by us the terms of which do not specifically provide that such equity securities rank on a parity with or junior to the preferred stock with respect to dividend rights or rights upon the liquidation, dissolution or winding up of us (including any entity with which we may be merged or consolidated or to which all or substantially all of our assets may be transferred or which transfers all or substantially all of our assets).

As used for these purposes, the term “equity securities” does not include convertible debt securities.

Transfer Agent and Registrar

The transfer agent and registrar for any series or class of preferred stock will be set forth in the applicable prospectus supplement.

DESCRIPTION OF WARRANTS

We may issue debt warrants to purchase debt securities, as well as equity warrants to purchase common stock or preferred stock. The warrants may be issued independently or together with any securities and may be attached to or separate from the securities. The warrants may be issued directly by us or under warrant agreements to be entered into between us and a bank or trust company, as warrant agent, all as shall be set forth in the prospectus supplement relating to warrants being offered pursuant to such prospectus supplement. The following description of warrants will apply to the warrants offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of warrants may specify different or additional terms.

Debt Warrants

The applicable prospectus supplement will describe the terms of debt warrants offered, the warrant agreement relating to the debt warrants and the debt warrant certificates representing the debt warrants, including the following:

the title of the debt warrants;

the aggregate number of the debt warrants;

the price or prices at which the debt warrants will be issued;

• the designation, aggregate principal amount and terms of the debt securities purchasable upon exercise of the debt warrants, and the procedures and conditions relating to the exercise of the debt warrants;

• the designation and terms of any related debt securities with which the debt warrants are issued, and the number of debt warrants issued with each debt security;

• the date, if any, on and after which the debt warrants and the related debt securities will be separately transferable;

• the principal amount of debt securities purchasable upon exercise of each debt warrant;

• the date on which the right to exercise the debt warrants will commence, and the date on which this right will expire;

• the maximum or minimum number of debt warrants which may be exercised at any time;

• a discussion of any material Federal income tax considerations; and

• any other terms of the debt warrants and terms, procedures and limitations relating to the exercise of debt warrants.

Debt warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in the prospectus supplement. Prior to the exercise of their debt warrants, holders of debt warrants will not have any of the rights of holders of the debt securities purchasable upon exercise and will not be entitled to payment of principal or any premium, if any, or interest on the debt securities purchasable upon exercise.

Equity Warrants

The applicable prospectus supplement will describe the following terms of equity warrants offered:

• the title of the equity warrants;

• the securities (i.e., common stock or preferred stock) for which the equity warrants are exercisable;

the price or prices at which the equity warrants will be issued;

if applicable, the designation and terms of the common stock or preferred stock with which the equity warrants are issued, and the number of equity warrants issued with each share of common stock or preferred stock;

if applicable, the date on and after which the equity warrants and the related common stock or preferred stock will be separately transferable;

if applicable, a discussion of any material Federal income tax considerations; and

any other terms of the equity warrants, including terms, procedures and limitations relating to the exchange and exercise of equity warrants.

Prior to exercise of the equity warrants, holders of equity warrants will not be entitled, by virtue of being such holders, to vote, consent, receive dividends, receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter, or to exercise any rights whatsoever as our stockholders.

The exercise price payable and the number of shares of common stock or preferred stock purchasable upon the exercise of each equity warrant will be subject to adjustment in certain events, including the issuance of a stock dividend to holders of common stock or preferred stock or a stock split, reverse stock split, combination, subdivision or reclassification of common stock or preferred stock. In lieu of adjusting the number of shares of common stock or preferred stock purchasable upon exercise of each equity warrant, we may elect to adjust the number of equity warrants. No adjustments in the number of shares purchasable upon exercise of the equity warrants will be required until cumulative adjustments require an adjustment of at least 1% thereof. We may, at our option, reduce the exercise price at any time. No fractional shares will be issued upon exercise of equity warrants, but we will pay the cash value of any fractional shares otherwise issuable. Notwithstanding the foregoing, in case of any consolidation, merger, or sale or conveyance of our property in its entirety or substantially in its entirety, the holder of each outstanding equity warrant shall have the right to the kind and amount of shares of stock and other securities and property, including cash, receivable by a holder of the number of shares of common stock or preferred stock into which the equity warrant was exercisable immediately prior to such transaction.

Exercise of Warrants

Each warrant will entitle the holder to purchase for cash such principal amount of securities or shares of stock at such exercise price as shall in each case be set forth in, or be determinable as set forth in, the prospectus supplement relating to the warrants offered thereby. Warrants may be exercised at any time up to the close of business on the expiration date set forth in the prospectus supplement relating to the warrants offered thereby. After the close of business on the expiration date, unexercised warrants will become void.

The warrants may be exercised as set forth in the prospectus supplement relating to the warrants offered. Upon receipt of payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the prospectus supplement, we will, as soon as practicable, forward the securities purchasable upon such exercise. If less than all of the warrants represented by such warrant certificate are exercised, a new warrant certificate will be issued for the remaining warrants.

DESCRIPTION OF UNITS

The following description, together with the additional information we include in any applicable prospectus supplement, summarizes the general features of the units that we may offer under this prospectus. We may issue units consisting of two or more other constituent securities. These units may be issuable as, and for a specified period of time may be transferable only as a single security, rather than as the separate constituent securities comprising such units. While the features we have summarized below will generally apply to any units we may offer under this prospectus, we will describe the particular terms of any units that we may offer in more detail in the applicable prospectus supplement. The specific terms of any units may differ from the description provided below as a result of negotiations with third parties in connection with the issuance of those units, as well as for other reasons. Because the terms of any units we offer under a prospectus supplement may differ from the terms we describe below, you should rely solely on information in the applicable prospectus supplement if that summary is different from the summary in this prospectus.

We urge you to read the applicable prospectus supplement related to the specific units being offered, as well as the complete instruments that contain the terms of the securities that comprise those units. Certain of those instruments, or forms of those instruments, have been or will be filed as exhibits to the registration statement of which this prospectus is a part, and supplements to those instruments or forms may be incorporated by reference into the registration statement of which this prospectus is a part from reports we file with the Commission.

If we offer any units, certain terms of that series of units will be described in the applicable prospectus supplement, including, without limitation, the following, as applicable:

• the title of the series of units;

• identification and description of the separate constituent securities comprising the units;

• the price or prices at which the units will be issued;

• the date, if any, on and after which the constituent securities comprising the units will be separately transferable;

• a discussion of certain United States federal income tax considerations applicable to the units; and

• any other terms of the units and their constituent securities.

GLOBAL SECURITIES

Book-Entry, Delivery and Form

Unless we indicate differently in a prospectus supplement, the securities initially will be issued in book-entry form and represented by one or more global notes or global securities, or, collectively, global securities. The global securities will be deposited with, or on behalf of, The Depository Trust Company, New York, New York, as depository, or DTC, and registered in the name of Cede & Co., the nominee of DTC. Unless and until it is exchanged for individual certificates evidencing securities under the limited circumstances described below, a global security may not be transferred except as a whole by the depository to its nominee or by the nominee to the depository, or by the depository or its nominee to a successor depository or to a nominee of the successor depository.

DTC has advised us that it is:

- a limited-purpose trust company organized under the New York Banking Law,
- a “banking organization” within the meaning of the New York Banking Law,
- a member of the Federal Reserve System,
- a “clearing corporation” within the meaning of the New York Uniform Commercial Code, and
- a “clearing agency” registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC holds and provides asset servicing for issues of U.S. and non-U.S. equity issues, corporate and municipal debt issues, and money market instruments from many countries that its participants (“Direct Participants”) deposit with it. DTC also facilitates the post-trade settlement among Direct Participants of sales and other securities transactions in deposited securities, through electronic computerized book-entry transfers and pledges between Direct Participants’ accounts. This eliminates the need for physical movement of securities certificates. Direct Participants include both U.S. and non-U.S. securities brokers and dealers, banks, trust companies, clearing corporations, and certain other organizations. DTC is a wholly-owned subsidiary of The Depository Trust & Clearing Corporation (“DTCC”). DTCC is the holding company for DTC, National Securities Clearing Corporation and Fixed Income Clearing Corporation, all of which are registered clearing agencies. DTCC is owned by the users of its regulated subsidiaries. Access to the DTC system is also available to others such as both U.S. and non-U.S. securities brokers and dealers, banks, trust companies, and clearing corporations that clear through or maintain a custodial relationship with a Direct Participant, either directly or indirectly (“Indirect Participants”). The DTC Rules applicable to its Participants are on file with the Securities and Exchange Commission.

Purchases of securities under the DTC system must be made by or through Direct Participants, which will receive a credit for the securities on DTC’s records. The ownership interest of each actual purchaser of each security (“Beneficial Owner”) is in turn to be recorded on the Direct and Indirect Participants’ records. Beneficial Owners will not receive written confirmation from DTC of their purchase. Beneficial Owners are, however, expected to receive written confirmations providing details of the transaction, as well as periodic statements of their holdings, from the Direct or Indirect Participant through which the Beneficial Owner entered into the transaction. Transfers of ownership interests in the securities are to be accomplished by entries made on the books of Direct and Indirect Participants acting on behalf of Beneficial Owners. Beneficial Owners will not receive certificates representing their ownership interests in securities, except in the event that use of the book-entry system for the securities is discontinued.

To facilitate subsequent transfers, all global securities deposited by Direct Participants with DTC will be registered in the name of DTC’s partnership nominee, Cede & Co., or such other name as may be requested by an authorized representative of DTC. The deposit of securities with DTC and their registration in the name of Cede & Co. or such other DTC nominee will not effect any change in beneficial ownership. DTC has no knowledge of the actual Beneficial Owners of the securities; DTC’s records reflect only the identity of the Direct Participants to whose accounts such securities are credited, which may or may not be the Beneficial Owners. The Direct and Indirect Participants will be responsible for keeping account of their holdings on behalf of their customers.

Conveyance of notices and other communications by DTC to Direct Participants, by Direct Participants to Indirect Participants, and by Direct Participants and Indirect Participants to Beneficial Owners will be governed by arrangements among them, subject to any statutory or regulatory requirements as may be in effect from time to time. Beneficial Owners of securities may wish to take certain steps to augment the transmission to them of notices of significant events with respect to the securities, such as redemptions, tenders, defaults, and proposed amendments to the security documents. For example, Beneficial Owners of securities may wish to ascertain that the nominee holding the securities for their benefit has agreed to obtain and transmit notices to Beneficial Owners. In the alternative, Beneficial Owners may wish to provide their names and addresses to the registrar and request that copies of notices be provided directly to them.

Redemption notices will be sent to DTC. If less than all of the Securities within an issue are being redeemed, DTC's practice is to determine by lot the amount of the interest of each Direct Participant in such issue to be redeemed.

Neither DTC nor Cede & Co. (nor any other DTC nominee) will consent or vote with respect to Securities unless authorized by a Direct Participant in accordance with DTC's MMI Procedures. Under its usual procedures, DTC mails an Omnibus Proxy to us as soon as possible after the record date. The Omnibus Proxy assigns Cede & Co.'s consenting or voting rights to those Direct Participants to whose accounts Securities are credited on the record date, as identified in a listing attached to the Omnibus Proxy.

So long as the securities are in book-entry form, you will receive payments and may transfer securities only through the facilities of the depository and its direct and indirect participants. We will maintain an office or agency in the location specified in the prospectus supplement for the applicable securities, where notices and demands in respect of the securities and the indenture may be delivered to us and where certificated securities may be surrendered for payment, registration of transfer or exchange.

Redemption proceeds, distributions, and dividend payments on the Securities will be made to Cede & Co., or such other nominee as may be requested by an authorized representative of DTC. DTC's practice is to credit Direct Participants' accounts upon DTC's receipt of funds and corresponding detail information from us, on payable date in accordance with their respective holdings shown on DTC's records. Payments by Participants to Beneficial Owners will be governed by standing instructions and customary practices, as is the case with securities held for the accounts of customers in bearer form or registered in "street name," and will be the responsibility of such Participant and not of DTC, or us, subject to any statutory or regulatory requirements as may be in effect from time to time. Payment of redemption proceeds, distributions, and dividend payments to Cede & Co. (or such other nominee as may be requested by an authorized representative of DTC) is our responsibility, disbursement of such payments to Direct Participants will be the responsibility of DTC, and disbursement of such payments to the Beneficial Owners will be the responsibility of Direct and Indirect Participants.

Except under the limited circumstances described below, purchasers of securities will not be entitled to have securities registered in their names and will not receive physical delivery of securities. Accordingly, each beneficial owner must rely on the procedures of DTC and its participants to exercise any rights under the securities and the indenture.

The laws of some jurisdictions may require that some purchasers of securities take physical delivery of securities in definitive form. Those laws may impair the ability to transfer or pledge beneficial interests in securities.

DTC may discontinue providing its services as depository with respect to the securities at any time by giving reasonable notice to us. Under such circumstances, in the event that a successor depository is not obtained, security certificates are required to be printed and delivered.

As noted above, beneficial owners of a particular series of securities generally will not receive certificates representing their ownership interests in those securities. However, if:

DTC notifies us that it is unwilling or unable to continue as a depository for the global security or securities representing such series of securities or if DTC ceases to be a clearing agency registered under the Exchange Act at a time when it is required to be registered and a successor depository is not appointed within 90 days of the notification

to us or of our becoming aware of DTC's ceasing to be so registered, as the case may be;
• we determine, in our sole discretion, not to have such securities represented by one or more global securities; or
• an Event of Default has occurred and is continuing with respect to such series of securities,

we will prepare and deliver certificates for such securities in exchange for beneficial interests in the global securities. Any beneficial interest in a global security that is exchangeable under the circumstances described in the preceding sentence will be exchangeable for securities in definitive certificated form registered in the names that the depositary directs. It is expected that these directions will be based upon directions received by the depositary from its participants with respect to ownership of beneficial interests in the global securities.

We have obtained the information in this section and elsewhere in this prospectus concerning DTC and DTC's book-entry system from sources that are believed to be reliable, but we take no responsibility for the accuracy of this information.

CERTAIN PROVISIONS OF DELAWARE LAW AND OF THE COMPANY'S CERTIFICATE OF INCORPORATION AND BYLAWS

Delaware Takeover Statute

We are subject to Section 203 of the DGCL. This statute regulating corporate takeovers prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for three years following the date that the stockholder became an interested stockholder, unless:

prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares outstanding (a) shares owned by persons who are directors and also officers and (b) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to the date of the transaction, the business combination is approved by the board and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;

Subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Certificate of Incorporation and Bylaw Provisions

Provisions of our certificate of incorporation and bylaws may have the effect of making it more difficult for a third party to acquire, or discourage a third party from attempting to acquire, control of our company by means of a tender offer, a proxy contest or otherwise. These provisions may also make the removal of incumbent officers and directors more difficult. These provisions are intended to discourage certain types of coercive takeover practices and inadequate takeover bids and to encourage persons seeking to acquire control of Hemispherx to first negotiate with us. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common

stock. These provisions may make it more difficult for stockholders to take specific corporate actions and could have the effect of delaying or preventing a change in our control.

In particular, our certificate of incorporation and bylaws, as currently amended, provide for the following:

Advance Notice Requirement

Stockholder proposals to be brought before an annual meeting of our stockholders must comply with advance notice procedures. These advance notice procedures require timely notice and apply in several situations, including stockholder proposals relating to the nominations of persons for election to the board of directors. Generally, to be timely, notice must be received at our principal executive offices not less than 60 days nor more than 90 days prior to the first anniversary date of the annual meeting for the preceding year, or where a Stockholder Proposal relates to nomination of candidates for director, not less than 90 days nor more than 120 days prior to the first anniversary date of the annual meeting for the preceding year.

Issuance of Undesignated Preferred Stock

Our board of directors is authorized to issue, without further action by the stockholders, up to 5,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by the board of directors. As of the date of this prospectus, we have no shares of preferred stock designated or outstanding. The existence of authorized but unissued shares of preferred stock enables our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise.

Limitation of Liability and Indemnification of Officers and Directors

As permitted by Section 102 of the DGCL, we have adopted provisions in our certificate of incorporation and bylaws that limit or eliminate the personal liability of our directors for a breach of their fiduciary duty of care as a director. The duty of care generally requires that, when acting on behalf of the corporation, directors exercise an informed business judgment based on all material information reasonably available to them. Consequently, a director will not be personally liable to us or our stockholders for monetary damages or breach of fiduciary duty as a director, except for liability for:

- any breach of the director's duty of loyalty to us or our stockholders;
- any act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- any act related to unlawful stock repurchases, redemptions or other distributions or payment of dividends; or
- any transaction from which the director derived an improper personal benefit.

These limitations of liability do not affect the availability of equitable remedies such as injunctive relief or rescission. Our certificate of incorporation also authorizes us to indemnify our officers, directors and other agents to the fullest extent permitted under Delaware law.

As permitted by Section 145 of the DGCL, our bylaws provide that:

- we may indemnify our directors, officers, employees and agents to the fullest extent permitted by the DGCL, subject to limited exceptions;
- we may advance expenses to our directors, officers, employees and agents in connection with a legal proceeding to the fullest extent permitted by the DGCL, subject to limited exceptions; and
- the rights provided in our bylaws are not exclusive.

We have purchased a policy of directors' and officers' liability insurance that insures our directors and officers against the cost of defense, settlement or payment of a judgment in some circumstances.

LEGAL MATTERS

Silverman Shin Byrne & Gilchrest PLLC will issue an opinion about certain legal matters with respect to the securities.

EXPERTS

The consolidated financial statements of Hemispherx Biopharma, Inc. included in the Company's Annual Report (Form 10-K) as of December 31, 2014 and 2013 and for the years then ended being incorporated by reference in this Prospectus and Registration Statement have been audited by McGladrey LLP, an independent registered public accounting firm, as stated in their report, included therein, and being incorporated herein by reference. Such financial statements are incorporated herein by reference in reliance upon such report and upon the authority of such firm as experts in accounting and auditing.

LIMITATION ON LIABILITY AND DISCLOSURE OF COMMISSION POSITION ON

INDEMNIFICATION FOR SECURITIES ACT LIABILITIES

Our certificate of incorporation and bylaws provide that we will indemnify our directors and officers, and may indemnify our employees and other agents, to the fullest extent permitted by the DGCL. Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons pursuant to the foregoing provisions, or otherwise, we have been advised that, in the opinion of the Commission, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the Commission a registration statement on Form S-3 under the Securities Act, of which this prospectus forms a part. The rules and regulations of the Commission allow us to omit from this prospectus certain information included in the registration statement. For further information about us and our securities, you should refer to the registration statement and the exhibits and schedules filed with the registration statement. With respect to the statements contained in this prospectus regarding the contents of any agreement or any other document, in each instance, the statement is qualified in all respects by the complete text of the agreement or document, a copy of which has been filed as an exhibit to the registration statement.

We file reports, proxy statements and other information with the Commission under the Exchange Act. You may read and copy this information from the Public Reference Room of the Commission, 100 F Street, N.E., Room 1580, Washington, D.C. 20549, at prescribed rates. You may obtain information on the operation of the Public Reference Room by calling the Commission at 1-800-SEC-0330. The Commission also maintains an Internet website that contains reports, proxy statements and other information about issuers, like us, that file electronically with the Commission. The address of that website is *www.sec.gov*.

We also maintain a website at *www.hemispherx.net* through which you can access our filings with the Commission. The information contained in, or accessible through, our website is not a part of this prospectus.

INFORMATION INCORPORATED BY REFERENCE

The Commission allows us to “incorporate by reference” the information we file with it which means that we can disclose important information to you by referring you to those documents instead of having to repeat the information in this prospectus. The information incorporated by reference is considered to be part of this prospectus, and later information that we file with the Commission will automatically update and supersede this information. We incorporate by reference the documents listed below and any future information filed (rather than furnished) with the Commission under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act between the date of this prospectus and the termination of the offering and also between the date of the initial registration statement and prior to effectiveness of the registration statement, provided, however, that we are not incorporating any information furnished under any of Item 2.02 or Item 7.01 of any current report on Form 8-K:

our annual report on Form 10-K for the year ended December 31, 2014;

• our quarterly report on Form 10-Q for the quarter ended March 31, 2015;

• our current report on Form 8-K filed with the Commission on June 24, 2015;

• our preliminary proxy statement on Schedule 14A filed on July 7, 2015; and

- A description of our common stock contained in our registration statement on Form S-1, SEC File No. 333-117178, and any amendment or report filed for the purpose of updating this description.

These documents may also be accessed on our website at *www.hemispherx.net*. Except as otherwise specifically incorporated by reference in this prospectus, information contained in, or accessible through, our website is not a part of this prospectus.

We will furnish without charge to you, upon written or oral request, a copy of any or all of the documents incorporated by reference, including exhibits to these documents by writing or telephoning us at the following address:

Hemispherx Biopharma, Inc.

1617 JFK Boulevard, Ste. 500

Philadelphia, Pennsylvania 19103

Attention: Corporate Secretary

(215) 988-0800

HEMISPHERX BIOPHARMA, INC.

\$77,849,014

Common Stock

Preferred Stock

Warrants

Debt Securities

PROSPECTUS

August 4, 2015