

NORTHFIELD LABORATORIES INC /DE/
 Form 424B2
 January 19, 2005

THE INFORMATION IN THIS PRELIMINARY PROSPECTUS SUPPLEMENT IS NOT COMPLETE AND MAY BE CHANGED. THIS PRELIMINARY PROSPECTUS SUPPLEMENT AND THE ACCOMPANYING PROSPECTUS ARE NOT AN OFFER TO SELL THESE SECURITIES AND THEY ARE NOT SOLICITING AN OFFER TO BUY THESE SECURITIES IN ANY STATE WHERE THE OFFER OR SALE IS NOT PERMITTED.

FILED PURSUANT TO RULE 424(B)(3)
 REGISTRATION NO. 333-121622

PRELIMINARY PROSPECTUS SUPPLEMENT SUBJECT TO COMPLETION JANUARY 19, 2005

(TO PROSPECTUS DATED DECEMBER 23, 2004)

3,500,000 SHARES

(NORTHFIELD LABORATORIES INC. LOGO)

COMMON STOCK

We are offering all of the 3,500,000 shares of common stock offered by this prospectus supplement.

Our common stock is quoted on the Nasdaq National Market under the symbol "NFLD." On January 14, 2005, the last reported sales price of our common stock on the Nasdaq National Market was \$21.02 per share.

INVESTING IN OUR COMMON STOCK INVOLVES A HIGH DEGREE OF RISK. BEFORE BUYING ANY SHARES, YOU SHOULD CAREFULLY READ THE DISCUSSION OF MATERIAL RISKS OF INVESTING IN OUR COMMON STOCK IN "RISK FACTORS" BEGINNING ON PAGE S-8.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS SUPPLEMENT OR THE ACCOMPANYING PROSPECTUS IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

	PER SHARE	TOTAL
Public offering price	\$	\$
Underwriting discounts and commissions	\$	\$
Proceeds, before expenses, to us	\$	\$

The underwriters may also purchase up to an additional 525,000 shares of common stock at the public offering price, less the underwriting discounts and commissions, to cover over-allotments, if any, within 30 days of the date of this prospectus supplement. If the underwriters exercise this option in full, the total underwriting discounts and commissions will be \$, and our total proceeds, before expenses, will be \$.

The underwriters are offering the common stock as set forth under "Underwriting." Delivery of the shares will be made on or about ,

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

2005.

Sole Book-Running Manager

UBS INVESTMENT BANK

SG COWEN & CO.

HARRIS NESBITT

You should rely only on the information contained and incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not, and the underwriters have not, authorized anyone to provide information different from that contained or incorporated by reference in this prospectus supplement or the accompanying prospectus. You should not assume that the information in this prospectus supplement and accompanying prospectus is accurate as of any date after their respective dates. These documents do not constitute an offer to sell or a solicitation of an offer to buy these shares of common stock in any circumstances under which the offer or solicitation is unlawful.

TABLE OF CONTENTS

PROSPECTUS SUPPLEMENT -----	PAGE ----
Prospectus supplement summary.....	S-1
Risk factors.....	S-8
Special note regarding forward-looking statements.....	S-20
Use of proceeds.....	S-21
Capitalization.....	S-22
Market price of common stock.....	S-23
Dividend policy.....	S-23
Dilution.....	S-23
Underwriting.....	S-25
Incorporation of certain documents by reference.....	S-28
Legal matters.....	S-28

PROSPECTUS -----	PAGE ----
About this prospectus.....	1
Where you can find more information...	1
Forward-looking information.....	3
Our business.....	3
Risk factors.....	4
Use of proceeds.....	11
Ratio of earnings to fixed charges and preference dividends.....	11
Dilution.....	11
Description of the securities we may offer.....	12
Plan of distribution.....	15
Legal matters.....	17

Experts..... 17

PolyHeme(R) is a registered trademark of Northfield Laboratories Inc.

Prospectus supplement summary

This summary highlights selected information appearing elsewhere or incorporated by reference in this prospectus supplement and accompanying prospectus and may not contain all of the information that is important to you. This prospectus supplement and accompanying prospectus include information about the shares we are offering as well as information regarding our business and detailed financial data. You should read this prospectus supplement and accompanying prospectus in their entirety, including the information incorporated by reference in this prospectus supplement and accompanying prospectus.

Unless the context requires otherwise, the words "Northfield," "we," the "Company," "us" and "our" refer to Northfield Laboratories Inc.

BUSINESS OVERVIEW

Northfield Laboratories Inc. is a leader in the development of a safe and effective alternative to transfused blood for use in the treatment of acute blood loss. We are presently conducting a pivotal Phase III trial of our human hemoglobin-based blood substitute, PolyHeme(R). We believe PolyHeme has the potential to improve survival in critically injured patients and to thereby transform the treatment of trauma.

We are presently developing PolyHeme for a unique indication: the early treatment of urgent, life-threatening blood loss following trauma when donated blood may not be immediately available. We believe that this indication addresses a critical unmet medical need, since some trauma patients bleed to death before they have access to blood.

We are pursuing a unique regulatory strategy in order to seek Food and Drug Administration, or FDA, approval of PolyHeme. We are conducting the first-ever pivotal Phase III trial in the United States in which a human blood substitute is being used to treat severely injured and bleeding patients, beginning at the scene of injury and continuing during transport to the hospital and the early period of hospitalization. Because of the life-saving potential of PolyHeme, our trial is being conducted under a federal regulation, 21 CFR 50.24, that permits certain types of emergency research using an exception from the requirement for prospective informed consent by individual patients. Our current trial is based on our experience in prior clinical trials documenting the potential life-sustaining capability of PolyHeme when given in rapid, massive infusions to critically injured patients in the hospital.

We have also taken advantage of Special Protocol Assessment, or SPA, one of the features of the Food and Drug Modernization Act of 1997. Our SPA reflects an agreement with FDA on our trial design, the trial endpoints and the broad concepts for clinical indications those endpoints will support in an application for product approval by FDA. The assessment of efficacy in our trial will be based on the data on patient survival at 30 days. A key feature of our SPA is the agreement on dual primary endpoints of superiority and non-inferiority between the treatment and control groups. Either of these endpoints will provide evidence of efficacy.

As part of our trial protocol, an Independent Data Monitoring Committee, or IDMC, consisting of independent medical and biostatistical experts is responsible for periodically evaluating the safety data from the trial and making recommendations relating to continuation or modification of the trial protocol to minimize any identified risks to patients. The IDMC has completed its first two reviews of data on mortality and serious adverse events in the first 120 patients enrolled in the trial and has recommended that the trial continue without modification. This is the first time that a trial of a human blood substitute has passed this patient evaluation milestone in a high risk trauma population.

We believe that PolyHeme ultimately represents a substantial global market opportunity, based on the need for a universally compatible, immediately available oxygen carrying product and PolyHeme's potential for eventual approval for multiple indications.

S-1

OUR PRODUCT

Our product, PolyHeme, is a unique human hemoglobin-based oxygen carrier in development for the treatment of urgent, large volume blood loss in trauma and resultant surgical settings, with a particular focus on settings where blood is not immediately available.

PolyHeme is a solution of chemically modified human hemoglobin which simultaneously restores lost blood volume and hemoglobin levels. Hemoglobin is the oxygen-carrying component of the red blood cell. PolyHeme is designed for rapid, massive infusion, which is the way blood is transfused in trauma patients.

We purchase donated red blood cells from The American Red Cross and Blood Centers of America for use as the starting material for PolyHeme. We use a proprietary process of separation, filtration, chemical modification, purification and formulation to produce PolyHeme. Hemoglobin is first extracted from red blood cells and filtered to remove impurities. The hemoglobin is next chemically modified using a multi-step process to create a polymerized form of hemoglobin. The modified hemoglobin is then incorporated into a solution which can be administered as an alternative to transfused blood. PolyHeme is designed to avoid potential undesirable effects such as vasoconstriction, kidney dysfunction, liver dysfunction and gastrointestinal distress. One unit of PolyHeme contains 50 grams of modified hemoglobin, approximately the same functional amount of hemoglobin delivered by one unit of transfused blood.

We believe PolyHeme will have the following important benefits:

UNIVERSAL COMPATIBILITY. Our clinical studies to date indicate that PolyHeme is universally compatible and accordingly does not require blood typing prior to use. The potential benefits of universal compatibility include the ability to use PolyHeme immediately, the elimination of transfusion reactions and the reduction of the inventory burden associated with maintaining sufficient quantities of all blood types.

OXYGEN-CARRYING ABILITY. Our clinical studies indicate that PolyHeme carries as much oxygen and loads and unloads oxygen in a manner similar to transfused blood.

BLOOD VOLUME REPLACEMENT. Infusion of PolyHeme also restores blood volume. Therefore, PolyHeme should be useful as an oxygen-carrying resuscitative fluid in the treatment of hemorrhagic shock resulting from extensive blood loss.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

IMPACT ON DISEASE TRANSMISSION. We believe, and laboratory tests have thus far indicated, that the manufacturing process used to produce PolyHeme greatly reduces the concentration of infectious agents known to be responsible for the transmission of blood-borne diseases. There are no currently approved methods in this country to reduce the quantity of such infectious agents in red blood cells.

EXTENDED SHELF LIFE. We estimate that PolyHeme has a shelf life in excess of 12 months under refrigerated conditions, well in excess of the 28 to 42 day refrigerated shelf life currently permitted for blood.

OUR PIVOTAL PHASE III TRIAL

We are currently enrolling patients in a pivotal Phase III trial in which PolyHeme is being used for the first time in civilian, urban trauma settings to treat severely injured patients in hemorrhagic shock before they reach the hospital. Under this protocol, treatment with PolyHeme begins at the scene of the injury or in the ambulance and continues during transport and the initial 12 hour post-injury period in the hospital. Since blood is not presently carried in ambulances, the use of PolyHeme in this setting has the potential to improve survival and address a critical, unmet medical need.

S-2

As of the date of this prospectus supplement, 16 clinical sites in the United States were enrolling patients in our pivotal Phase III trial and two other sites had received final Institutional Review Board, or IRB, approval and were preparing to begin patient enrollment. Nine additional sites were engaged in the pre-trial public disclosure and community consultation process. Each of the sites participating in the trial is designated as a Level I trauma center, indicating its capacity to treat the most severely injured trauma patients. We anticipate that a total of 25 or more clinical sites across the United States will eventually participate in the trial. The trial has an expected enrollment of 720 patients.

As part of our trial protocol, the IDMC is responsible for periodically evaluating the safety data from the trial and making recommendations relating to the continuation or modification of the trial protocol to minimize any identified risks to patients. The protocol includes four planned evaluations by the IDMC that occur after 60, 120, 250 and 500 patients have been enrolled and monitored for a 30-day follow up period. The IDMC focuses its reviews on mortality and serious adverse events and evaluates all safety data as the trial continues. We receive a recommendation from the IDMC after each review, but we will not have access to the trial data reviewed by the IDMC until the trial is completed.

In July 2004, the IDMC recommended that our trial continue without modification based on the committee's initial review of blinded data on mortality and serious adverse events from the first 60 patients enrolled in the trial. In October 2004, the IDMC again recommended continuation of the trial without modification based on its review of data following enrollment of the first 120 patients in our trial. The length of time for completion of the IDMC review after each enrollment target is reached is expected to become longer as the number of enrolled patients increases. Enrollment in the trial continues during the period of 30-day follow-up, data preparation and analysis and meetings of the IDMC, so the disclosure of the IDMC recommendation does not correspond to the current status of patient enrollment. We anticipate that the IDMC will complete its third review of trial data on the first 250 patients enrolled in our trial and make a recommendation to us in the second calendar quarter of 2005.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

Our current goal is to complete the patient enrollment phase of our trial by the end of calendar 2005. Our ability to achieve this goal will depend, in part, on the number of clinical sites participating in our trial and the ability of these sites to enroll patients at the projected rates.

TRIAL DESIGN AND CLINICAL ENDPOINTS

We have reached agreement with FDA on Special Protocol Assessment, or SPA, for our pivotal Phase III trial. SPA is designed to facilitate the review and approval of drug and biological products by allowing for FDA evaluation of the trial sponsor's proposed design and size of clinical trials intended to form the primary basis for an efficacy claim in a Biologics License Application submitted to FDA. If agreement is reached between FDA and the trial sponsor, SPA will document the terms and conditions under which the clinical trial will be conducted. Our SPA reflects an agreement with FDA on our trial design, the trial endpoints and the broad concepts for clinical indications those endpoints will support in an application for product approval by FDA.

Our pivotal Phase III trial is being conducted under a federal regulation that permits research to be conducted in certain emergent, life-threatening situations using an exception from the requirement for prospective informed consent by individual patients. Participation by each clinical trial site is overseen by an IRB. Under the applicable federal regulation, an IRB may give approval for patient enrollment in trials in emergency situations without requiring individual informed consent provided specific criteria are met. Patients must be in a life-threatening situation for which available treatments are unproven or unsatisfactory and scientific evidence must be needed to assess the safety and effectiveness of alternative treatments. The experimental therapy being evaluated must also provide patients potential for direct clinical benefit. In addition, medical intervention must be required before informed consent can be obtained and it must be impracticable to conduct the trial using only consenting patients. Where informed consent is feasible, the sponsor's consent procedures and forms must be reviewed and approved by the IRB, and attempts to obtain informed consent must be documented by the sponsor.

S-3

Before enrollment can begin, the regulation requires public disclosure of information about the trial, including the potential risks and benefits, and the formation of an independent monitoring committee to oversee the trial. Consultation must also occur with representatives of the community where the study will be conducted and from which the study population will be drawn. Each of the clinical sites participating in our current trial has completed the required public disclosure and community consultation procedures and received IRB approval to enroll patients in accordance with the trial protocol.

Under our trial protocol, patients enrolled in the trial are randomly assigned to either a treatment group or a control group. The treatment group receives PolyHeme at the scene of the injury or in the ambulance during transport and continues to receive PolyHeme, if necessary, during the initial 12 hour post-injury period in the hospital. Patients in the treatment group may receive a maximum of six units of PolyHeme. The control group receives saline solution in the field and donated blood, if necessary, in the hospital.

Evaluation of the efficacy data generated in our pivotal Phase III trial will focus on patient survival at 30 days after the date of injury. The mortality rate observed for patients in the treatment group in our trial will be compared statistically with the mortality rate for patients in the control group. A key feature of our SPA is the agreement on dual primary end points of superiority and non-inferiority between the treatment and control groups. The trial design is unusual in that meeting either of the primary endpoints of superiority or

non-inferiority will provide evidence of efficacy.

Our trial is being conducted in urban settings because urban Level I trauma centers have the patient volume, resources and sophistication to conduct a clinical trial of this complexity. In urban areas, however, transit times in the ambulance may be brief, and the control group will reach the hospital, where patients will have access to blood, in relatively short periods of time. The observed outcome in our trial may therefore not demonstrate the expected magnitude of survival benefit that might occur if the trial were being conducted in the rural setting, where more extended transport times are typical and where the availability of blood may be limited. It is therefore possible that the observed survival rate in the treatment group may trend towards the survival rate observed in patients in the control group who have rapid access to blood. This outcome would represent non-inferiority, which would satisfy one of the dual primary endpoints for efficacy in our trial protocol.

THE MARKET OPPORTUNITY

Transfused blood represents a multi-billion dollar market in the United States. We estimate that approximately 14 million units of blood are transfused in the United States each year. The transfusion market in the United States consists of two principal segments. The acute blood loss segment, which we estimate comprises approximately 60% of the transfusion market, includes transfusions required in connection with trauma, surgery and unexpected blood loss. The chronic blood loss segment, which we believe represents approximately 40% of the transfusion market, includes transfusions in connection with general medical applications and chronic anemias.

We believe that PolyHeme will be most useful in the treatment of acute blood loss. The principal clinical settings in which patients experience acute blood loss are unplanned blood loss in trauma, emergency surgery and other causes of urgent hemorrhage, and planned blood loss in elective surgery. For trauma and emergency surgical procedures, the immediate availability and universal compatibility of PolyHeme may provide significant advantages over transfused blood by avoiding the delay and opportunities for error associated with blood typing. In elective surgery, PolyHeme has the potential to increase transfusion safety for patients and health care professionals.

In addition to the foregoing applications for which blood is currently used, there exist potential sources of demand for which blood is not currently used and for which PolyHeme may be suitable. These include applications in which the required blood type is not immediately available or in which transfusions are desirable but not given for fear of a transfusion reaction due to difficulty in identifying

S-4

compatible blood. For example, we believe PolyHeme may be used by Emergency Medical Technicians at the scene of injury and during transport to the hospital by ground or air ambulance. Emergicenters and surgicenters also both experience events where PolyHeme may be useful. In addition, the United States military has expressed interest in the use of blood substitutes for the treatment of battlefield casualties. There may also be potential market opportunities for PolyHeme in novel areas such as ischemia and oncology.

We believe that the initial indication we are seeking for PolyHeme--unavailability of red blood cells--represents the greatest clinical and commercial opportunity for the product since it addresses a critical unmet medical need and has the potential to provide a survival benefit. At present, no adequate alternative to blood exists for the treatment of patients with life-threatening hemorrhage who need replacement of lost oxygen-carrying

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

capacity. PolyHeme is the first human blood substitute to pursue this indication, and our goal is for PolyHeme to be first to the market for this indication.

We recently engaged a national consulting firm to conduct an independent assessment of the potential market opportunity for PolyHeme. Using a variety of primary and secondary sources along with original research, their analysis indicates a potential market opportunity in the United States for PolyHeme's initial indication of unavailability in excess of 350,000 units per year, representing an estimated market value of \$400 to \$500 million. In addition, the global opportunity for our initial indication, as well as multiple other potential indications, is estimated to substantially exceed this initial domestic market opportunity.

OUR STRATEGY

Our strategy is to achieve sustainable profitability and growth by developing, marketing and selling an effective alternative to transfused blood for use in the treatment of acute blood loss. To reach these goals we are focusing on the following objectives:

- complete our pivotal Phase III trial;
- prepare and submit a Biologics License Application to FDA for the approval of PolyHeme;
- expand our current manufacturing capabilities to support the commercial launch of PolyHeme; and
- build sales, marketing and distribution capabilities in support of the commercialization of PolyHeme.

OUR CORPORATE INFORMATION

We were incorporated in Delaware in 1985. Our principal executive offices are located at 1560 Sherman Avenue, Suite 1000, Evanston, Illinois 60201-4800, and our telephone number is (847) 864-3500. We maintain an Internet website at www.northfieldlabs.com. We have not incorporated by reference into this prospectus supplement or the accompanying prospectus the information in, or that can be accessed through, our website, and you should not consider it to be a part of this prospectus supplement or the accompanying prospectus.

S-5

The offering

Common stock we are offering.....	3,500,000 shares
Common stock to be outstanding after this offering.....	25,051,364 shares
Use of proceeds.....	We intend to use the net proceeds from this offering to fund our post-enrollment activities in our clinical trial, to prepare and submit a Biologics License Application to FDA, to construct a 75,000 unit per year manufacturing facility to produce PolyHeme for commercial sale, to build sales, marketing and distribution capabilities, and for other general

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

corporate purposes. See "Use of proceeds."

Nasdaq National Market symbol..... NFLD

The number of shares of common stock outstanding after this offering is based on the actual number of shares outstanding as of November 30, 2004 and excludes:

1,418,892 shares of common stock issuable upon exercise of options and warrants outstanding as of November 30, 2004 at a weighted average exercise price of \$8.92 per share; and

554,240 shares of common stock available as of November 30, 2004 for issuance under our 2003 Equity Compensation Plan and Stock Option Plan for New Employees.

Unless we specifically state otherwise, all information in this prospectus supplement assumes that the underwriters do not exercise their option to purchase up to 525,000 shares of common stock to cover over-allotments, if any.

S-6

Summary financial data

The tables below present summary statement of operations and balance sheet data. The summary financial data for the years ended May 31, 2002, May 31, 2003 and May 31, 2004 are derived from our audited financial statements for those periods. We derived the summary financial data as of November 30, 2004 and for the six months ended November 30, 2003 and 2004 from our unaudited financial statements. The unaudited financial statement data include, in our opinion, all adjustments (consisting only of normal recurring adjustments) that are necessary for a fair presentation of our financial position and results of operations for these periods. Operating results for the six months ended November 30, 2004 are not necessarily indicative of the results that may be expected for our fiscal year ending May 31, 2005.

This information is only a summary and should be read together with our historical financial statements and related notes and "Management's discussion and analysis of financial condition and results of operations" contained in our periodic reports filed with the SEC and incorporated by reference into this prospectus supplement. For more details on how you can obtain our SEC reports incorporated by reference into this prospectus supplement, see "Where you can find more information" in the accompanying prospectus.

	YEAR ENDED MAY 31,			SIX MONTHS ENDED NOVEMBER 30,	
STATEMENT OF OPERATIONS DATA:	2004	2003	2002	2004	2003
(IN THOUSANDS, EXCEPT PER SHARE DATA)					
Revenues:	\$ --	\$ --	\$ --	\$ --	\$ --
Costs and expenses:					
Research and development.....	10,777	8,819	8,843	8,216	4,757
General and administrative.....	3,854	3,643	2,700	1,859	1,704
Interest income (net).....	131	212	826	276	48
Net loss.....	(14,574)	(12,250)	(10,717)	(9,799)	(6,488)
Net loss per share--basic and diluted...	(0.86)	(0.86)	(0.75)	(0.46)	(0.42)
Shares used in calculation of per share					

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

data..... 16,932 14,266 14,266 21,422 15,561

BALANCE SHEET DATA:	NOVEMBER 30, 2004	
	ACTUAL	AS ADJUSTED (1)
	(UNAUDITED, IN THOUSANDS)	
Cash and marketable securities.....	33,854	102,860
Total assets.....	35,520	104,526
Total liabilities.....	2,085	2,085
Deficit accumulated during development stage.....	(134,838)	(134,838)
Total shareholders' equity(2).....	33,434	102,440

-
- (1) As adjusted to give effect to the sale by us of the 3,500,000 shares of our common stock in this offering, after deducting estimated underwriting discounts and commissions and estimated offering expenses to be paid by us.
 - (2) Excludes 1,206,500 shares of common stock reserved for issuance upon the exercise of stock options and 212,392 shares of common stock reserved for issuance upon the exercise of warrants outstanding as of November 30, 2004. An additional 554,240 shares of common stock were available for issuance as of November 30, 2004 under our 2003 Equity Compensation Plan and Stock Option Plan for New Employees.

S-7

Risk factors

Investing 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 before purchasing our common stock. If any of the following risks actually occur, our business, financial condition and results of operations could materially suffer. As a result, the trading price of our common stock could decline, and you might lose all or part of your investment.

RISK RELATED TO OUR BUSINESS

WE ARE A DEVELOPMENT STAGE COMPANY WITHOUT REVENUES OR PROFITS.

Northfield was founded in 1985 and is a development stage company. Since 1985, we have been engaged primarily in the development and clinical testing of PolyHeme. No revenues have been generated to date from commercial sales of PolyHeme. Our revenues to date have consisted solely of license fees. We cannot ensure that our clinical testing will be successful, that regulatory approval of PolyHeme will be obtained, that we will be able to manufacture PolyHeme at an acceptable cost and in appropriate quantities or that we will be able to successfully market and sell PolyHeme. We also cannot ensure that we will not encounter unexpected difficulties which will have a material adverse effect on us, our operations or our properties.

WE HAVE A HISTORY OF LOSSES AND OUR FUTURE PROFITABILITY IS UNCERTAIN.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

From our inception through November 30, 2004, we have incurred net operating losses totaling \$134,838,000. We will require substantial additional expenditures to complete clinical trials, to pursue regulatory approval for PolyHeme, to establish commercial scale manufacturing processes and facilities, and to establish marketing, sales and administrative capabilities. These expenditures are expected to result in substantial losses for at least the next few years and are expected to substantially exceed our currently available capital resources. The expense and the time required to realize any product revenues or profitability are highly uncertain. We cannot ensure that we will be able to achieve product revenues or profitability on a sustained basis or at all.

WE ARE DEVELOPING A SINGLE PRODUCT THAT IS SUBJECT TO A HIGH LEVEL OF TECHNOLOGICAL RISK.

To succeed as a company, we must develop PolyHeme commercially and sell adequate quantities of PolyHeme at a high enough price to generate a profit. We may not accomplish either of these objectives. Our operations have to date consisted primarily of the development and clinical testing of PolyHeme. We do not expect to realize product revenues unless we successfully develop and achieve commercial introduction of PolyHeme. We expect that such revenues, if any, will be derived solely from sales of PolyHeme directly or through licensees. We also expect the use of PolyHeme initially to be limited to the acute blood loss segment of the transfusion market. The biomedical field has undergone rapid and significant technological changes. Technological developments may result in PolyHeme becoming obsolete or non-competitive before we are able to recover any portion of the research and development and other expenses we have incurred to develop and clinically test PolyHeme. Any such occurrence would have a material adverse effect on us and our operations.

S-8

RISK FACTORS

WE ARE REQUIRED TO COMPLETE OUR CURRENT CLINICAL TRIAL BEFORE WE MAY SELL POLYHEME COMMERCIALY AND WE MAY BE REQUIRED TO CONDUCT ADDITIONAL CLINICAL TRIALS IN THE FUTURE.

The results of our clinical trials conducted to date are not sufficient to demonstrate adequately the safety and effectiveness of PolyHeme in order to obtain approval from FDA for the commercial sale of PolyHeme. We are currently conducting a pivotal Phase III trial in which PolyHeme is being used for the first time in civilian trauma applications to treat severely injured patients before they reach the hospital. Under this protocol, treatment with PolyHeme begins at the scene of the injury or in the ambulance and continues during transport and the initial 12 hour post-injury period in the hospital. This trial will be expensive and time-consuming and the timing of the FDA review process is uncertain. Our trial may be delayed due to failure to conduct the trial in accordance with regulatory requirements, a lower than anticipated enrollment rate of patients or insufficient supply of product or other materials necessary for the conduct of the trial. We or FDA may in the future suspend our clinical trial at any time if it is believed that the subjects participating in the trial are being exposed to unacceptable health risks.

We cannot ensure that we will be able to complete our current clinical trial successfully or that FDA will not require us to conduct additional clinical trials of PolyHeme in the future. If FDA approval for the commercial sale of PolyHeme is obtained, it may include significant limitations on the indicated uses for which PolyHeme may be marketed. FDA requires a separate approval for each proposed indication for the use of PolyHeme in the United States. If we

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

want to expand PolyHeme's indications, we will have to design additional clinical trials, submit the trial designs to FDA for review and complete those trials successfully.

Our business, financial condition and results of operations are critically dependent on receiving FDA approval of PolyHeme. A significant delay in our clinical trial or a failure to achieve FDA approval for commercial sales of PolyHeme would have a material adverse effect on us and could result in the cessation of our business.

COMPLETION OF OUR PIVOTAL PHASE III CLINICAL TRIAL IS DEPENDENT ON THE NUMBER OF CLINICAL TRIAL SITES PARTICIPATING IN THE TRIAL AND THE RATE AT WHICH WE ARE ABLE TO ENROLL PATIENTS IN THE TRIAL.

Two clinical sites did not receive IRB approval for their participation in our pivotal Phase III trial. It is possible the other prospective clinical sites may decide not to participate in our trial or may fail to obtain IRB approval for their participation in the trial. One or more of the clinical sites currently enrolling patients may also discontinue their participation in our trial in the future. Our projections relating to completion of the enrollment phase of our trial are based, in part, on assumptions regarding the number of clinical sites enrolling patients in our trial. If we are unable to include additional clinical sites in our trial or our current clinical sites discontinue their participation in our trial, the trial may be significantly delayed and we may be unable to complete the trial.

Our pivotal Phase III trial is being conducted under a federal regulation that allows research to be conducted in certain emergent, life-threatening situations using an exception from the requirement for prospective informed patient consent. Under our trial protocol, members of the public can take steps to avoid being enrolled in our trial and patients enrolled in our trial are permitted to terminate their participation at any time. Our trial may be delayed, and we may be unable to complete the trial, if a significant number of individuals decline to participate in the trial or if patients enrolled in the trial terminate their participation before the end of the 30-day post-treatment evaluation period required under our trial protocol.

S-9

RISK FACTORS

SAFETY DATA FROM OUR PIVOTAL PHASE III CLINICAL TRIAL WILL BE REVIEWED BY AN INDEPENDENT COMMITTEE, WHICH COULD RECOMMEND THAT THE TRIAL BE HALTED OR MODIFIED.

As part of our trial protocol, an Independent Data Monitoring Committee, or IDMC, consisting of independent medical and biostatistical experts is responsible for periodically evaluating the safety data from the trial and making recommendations relating to the continuation or modification of the trial protocol to minimize any identified risks to patients. The IDMC focuses its reviews on mortality and serious adverse events and evaluates all safety data as the trial continues. We anticipate that the IDMC will complete its third review of trial data on the first 250 patients enrolled in our trial and make a recommendation to us in the second calendar quarter of 2005. If the IDMC believes the data from our trial give rise to safety concerns, the IDMC could recommend that our trial be halted or substantially modified. A recommendation of this type could significantly delay the completion of our trial and could prevent us from completing the trial.

THERE MAY BE LIMITATIONS IN THE SUPPLY OF THE STARTING MATERIAL FOR POLYHEME.

We currently purchase donated red blood cells from The American Red Cross and Blood Centers of America for use as the starting material for PolyHeme. We have also entered into an agreement with hemerica, Inc., a subsidiary of Blood Centers of America, under which hemerica would supply us with up to 160,000 units per year of packed red cells, the source material for PolyHeme. We have not purchased any blood supplies under this agreement to date. We have plans to enter into long-term supply arrangements with other blood collectors. We cannot ensure that we will be able to enter into satisfactory long-term arrangements with blood bank operators, that the price we may be required to pay for starting material will permit us to price PolyHeme competitively or that we will be able to obtain an adequate supply of starting material. Additional demand for blood may arise from competing blood substitute products, some of which are derived from human blood, thereby limiting our available supply of starting material.

THE MARKET MAY NOT ACCEPT OUR PRODUCT.

Even if PolyHeme is approved for commercial sale by FDA, the degree of market acceptance of PolyHeme by physicians, healthcare professionals and third party payors, and our profitability and growth will depend on a number of factors, including:

- relative convenience and ease of administration;
- the prevalence and severity of any adverse side effects;
- effectiveness of our sales and marketing strategy; and
- the price of PolyHeme compared with other blood substitute products.

In addition, even if PolyHeme does achieve market acceptance, we may not be able to maintain that market acceptance over time if new products are introduced that are more favorably received than PolyHeme or render PolyHeme obsolete.

WE RELY ON THIRD PARTIES TO COORDINATE OUR CLINICAL TRIALS AND PERFORM DATA COLLECTION AND ANALYSIS, WHICH MAY RESULT IN COSTS AND DELAYS THAT PREVENT US FROM SUCCESSFULLY COMMERCIALIZING OUR PRODUCT.

We do not have the ability to conduct our clinical trials independently. We rely and will continue to rely on clinical investigators, third-party clinical research organizations and consultants to perform some or all of the functions associated with clinical trials. In particular, as part of our trial protocol, an Independent Data Monitoring Committee consisting of independent medical and biostatistical

S-10

RISK FACTORS

experts is responsible for periodically evaluating the safety data from the trial and making recommendations relating to the continuation or modification of the trial protocol to minimize any identified risks to patients.

Our clinical trial may be delayed, suspended or terminated if:

- these third parties do not successfully carry out their contractual duties or regulatory obligations or meet expected deadlines;
- these third parties need to be replaced; or

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

the quality or accuracy of the data obtained by third parties is compromised due to their failure to adhere to our clinical protocol or regulatory requirements or for other reasons.

Failure to perform by these third parties may increase our development costs, delay our ability to obtain regulatory approval and prevent the commercialization of our product.

OUR ACTIVITIES ARE AND WILL CONTINUE TO BE SUBJECT TO EXTENSIVE GOVERNMENT REGULATION.

Our research, development, testing, manufacturing, marketing and distribution of PolyHeme are, and will continue to be, subject to extensive regulation, monitoring and approval by FDA. The regulatory approval process to establish the safety and effectiveness of PolyHeme and the safety and reliability of our manufacturing process has already consumed considerable time and expenditures. The data obtained from clinical trials are susceptible to varying interpretations, which could delay, limit or prevent FDA regulatory approval. Even if we demonstrate evidence of efficacy, our data may not demonstrate safety. We cannot ensure that, even after extensive clinical trials, regulatory approval will ever be obtained for PolyHeme. If PolyHeme is approved, it would be the first human blood substitute ever to receive FDA approval.

We will be required to submit a Biologics License Application, or BLA, with FDA in order to obtain regulatory approval for the commercial sale of PolyHeme in the United States. Under FDA guidelines, FDA may comment upon the acceptability of a BLA following its submission. After a BLA is submitted there is an initial review by FDA to be sure that all of the required elements are included in the submission. There can be no assurance that the submission will be accepted for filing or that FDA may not issue a refusal to file, or RTF. If an RTF is issued, there is opportunity for dialogue between the sponsor and FDA in an effort to resolve all concerns. There can be no assurance that such a dialogue will be successful in leading to the filing of the BLA. We received an RTF from FDA in November 2001 in connection with our submission of a BLA seeking approval to market PolyHeme for use in the treatment of urgent, life-threatening blood loss based on data from patients in the hospital setting only. The subsequent dialogue with FDA resulted in the mutual decision to proceed with our current pivotal Phase III trial, which starts in the prehospital setting. If a new BLA submission is filed, the timing of the FDA review process is uncertain and there can be no assurance that the full review will result in product approval. Moreover, if regulatory approval of PolyHeme is granted, the approval may include limitations on the indicated uses for which PolyHeme may be marketed. Further clinical trials will likely be required to gain approval to promote the use of PolyHeme for any additional indications.

Further, discovery of previously unknown problems with PolyHeme or unanticipated problems with our manufacturing facilities, even after FDA approval of PolyHeme for commercial sale, may result in the imposition of significant restrictions, including withdrawal of PolyHeme from the market or restrictions on approved indications. Additional laws and regulations may also be enacted which could prevent or delay regulatory approval of PolyHeme, including laws or regulations relating to the price or cost-effectiveness of medical products. Other laws and regulations may be enacted that could require us to comply with post-marketing requirements for PolyHeme that may be time-consuming and expensive. Any delay or failure to achieve regulatory approval of commercial sales of PolyHeme or to

S-11

RISK FACTORS

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

maintain compliance with current or future laws and regulations is likely to have a material adverse effect on our financial condition.

FDA continues to monitor products even after they receive approval. If and when FDA approves PolyHeme, its manufacture and marketing will be subject to ongoing regulation, including compliance with current good manufacturing practices, adverse event reporting requirements and FDA's general prohibitions against promoting products for unapproved or "off-label" uses. We are also subject to inspection and market surveillance by FDA for compliance with these and other requirements. Any enforcement action resulting from failure, even by inadvertence, to comply with these requirements could affect the manufacture and marketing of PolyHeme. In addition, FDA could withdraw a previously approved product from the market upon receipt of newly discovered information. FDA could also require us to conduct additional, and potentially expensive, studies in areas outside our approved indicated uses.

The lack of established criteria for evaluating the safety and effectiveness of blood substitute products could also delay or prevent FDA approval. In October 2004, FDA published for comment a draft guidance document indicating suggested criteria for testing the safety and efficacy of oxygen therapeutics as substitutes for human red blood cells and providing guidance on the design of clinical trials to assess the risks and benefits associated with the use of such products. The draft guidance document was based in part on a conference on blood substitute products convened at National Institutes of Health in 1999. The draft guidance will not be finalized and implemented until completion of a public comment process. We cannot be certain when the definitive guidance will be issued by FDA or what effect, if any, the definitive guidance may have on our clinical trial. It is possible that, as a result of the definitive guidance, we may be required to undertake additional pre-clinical or clinical trials or modify the way data from our trial are analyzed or presented. FDA's definitive guidance relating to the evaluation of the effectiveness of blood substitute products could delay or prevent FDA regulatory approval of PolyHeme. In addition, delay or rejection could be caused by other future changes in FDA policies and regulations.

WE MAY NEED TO RAISE ADDITIONAL CAPITAL TO CONTINUE OUR BUSINESS.

We currently believe we have sufficient capital resources to complete the enrollment phase of our clinical trials. As more fully described under "Use of Proceeds," we intend to use the proceeds of this offering to fund our post-enrollment activities in our clinical trial, to prepare and submit a BLA application to FDA, to construct a 75,000 unit per year manufacturing facility to produce PolyHeme for commercial sale, to build sales, marketing and distribution capabilities and for other general corporate purposes. We may be required to raise capital, in addition to the proceeds of this offering, to continue our business. Our future capital requirements will depend on many factors, including the scope and results of our clinical trials, the timing and outcome of regulatory reviews, administrative and legal expenses, the status of competitive products, the establishment of manufacturing capacity and the establishment of collaborative relationships. We cannot ensure that additional funding will be available or, if it is available, that it can be obtained on terms and conditions we will deem acceptable. Any additional funding derived from the sale of equity securities may result in significant dilution to our existing stockholders, including purchasers in this offering.

WE CURRENTLY MANUFACTURE POLYHEME AT A SINGLE LOCATION AND, IF WE WERE UNABLE TO UTILIZE THIS FACILITY, OUR ABILITY TO MANUFACTURE POLYHEME WILL BE SIGNIFICANTLY AFFECTED, AND WE WILL BE DELAYED OR PREVENTED FROM COMPLETING OUR CLINICAL TRIALS AND COMMERCIALIZING POLYHEME.

We currently manufacture PolyHeme at a single location and we have no alternative manufacturing capacity in place at this time. Damage to this

manufacturing facility due to fire, contamination, natural

S-12

RISK FACTORS

disaster, power loss, unauthorized entry or other events could force us to cease the manufacturing of PolyHeme. Any lack of supply could, in turn, delay our clinical trials and any potential commercial sales. In addition, if the facility or the equipment in the facility is significantly damaged or destroyed for any reason, we may not be able to replace our manufacturing capacity for an extended period of time, and our business, financial condition and results of operations will be materially and adversely affected.

FAILURE TO INCREASE MANUFACTURING CAPACITY MAY IMPAIR POLYHEME'S MARKET ACCEPTANCE AND PREVENT US FROM ACHIEVING PROFITABILITY.

Currently, we have a manufacturing capacity of approximately 10,000 units of PolyHeme per year. Commercial-scale manufacturing of PolyHeme will require the construction of a manufacturing facility significantly larger than that currently being used to produce PolyHeme for our clinical trials. A commercial-scale manufacturing facility will be subject to FDA inspections and extensive regulation, including compliance with current good manufacturing practices and FDA approval of scale-up changes. Failure to comply may result in enforcement action, which may significantly delay or suspend manufacturing operations. We have no experience in large-scale manufacturing, and there can be no assurance that we can achieve large-scale manufacturing capacity. It is also possible that we may incur substantial cost overruns and delays compared to existing estimates in building and equipping a large-scale manufacturing facility. Moreover, in order to seek FDA approval of the sale of PolyHeme produced at a larger-scale manufacturing facility, we may be required to conduct additional studies with product manufactured at that facility. A significant delay in achieving scale-up of commercial manufacturing capabilities would have a material adverse effect on sales of PolyHeme.

THERE ARE SIGNIFICANT COMPETITORS DEVELOPING SIMILAR PRODUCTS.

We may be unable to compete successfully in developing and marketing our product. If approved for commercial sale, PolyHeme will compete directly with established therapies for acute blood loss and may compete with other technologies currently under development. We cannot ensure that PolyHeme will have advantages which will be significant enough to cause medical professionals to adopt it rather than continue to use established therapies or to adopt other new technologies or products. We also cannot ensure that the cost of PolyHeme will be competitive with the cost of established therapies or other new technologies or products. The development of blood substitute products is a continuously evolving field. Competition is intense and may increase. Several companies have developed or are in the process of developing technologies which are, or in the future may be, the basis for products which will compete with PolyHeme. Certain of these companies are pursuing different approaches or means of accomplishing the therapeutic effects sought to be achieved through the use of PolyHeme. Some of these companies may have substantially greater financial resources, larger research and development staffs, more extensive facilities and more experience in testing, manufacturing, marketing and distributing medical products. We cannot ensure that one or more other companies will not succeed in developing technologies or products which will become available for commercial use prior to PolyHeme, which will be more effective or less costly than PolyHeme or which would otherwise render PolyHeme obsolete or non-competitive.

WE DO NOT HAVE EXPERIENCE IN THE SALE AND MARKETING OF MEDICAL PRODUCTS.

If approved for commercial sale, we currently intend to market PolyHeme in the United States using our own sales force. We have no experience in the sale or marketing of medical products. Our ability to implement our sales and marketing strategy for the United States will depend on our ability to recruit, train and retain a marketing staff and sales force with sufficient technical expertise. We cannot ensure that we will be able to establish an effective marketing staff and sales force, that the cost of

S-13

RISK FACTORS

establishing such a marketing staff and sales force will not exceed revenues from the sale of PolyHeme or that our marketing and sales efforts will be successful.

OUR PROFITABILITY WILL BE AFFECTED IF WE INCUR PRODUCT LIABILITY CLAIMS IN EXCESS OF OUR INSURANCE COVERAGE.

The testing and marketing of medical products, even after FDA approval, have an inherent risk of product liability. Claims by users of PolyHeme, or by others selling PolyHeme, could expose us to substantial product liability. We maintain limited product liability insurance coverage for our clinical trials in the total amount of \$10 million. However, our profitability would be adversely affected by a successful product liability claim in excess of our insurance coverage. We cannot ensure that product liability insurance will be available in the future or be available on reasonable terms.

Our pivotal Phase III trial is being conducted under a federal regulation that allows research to be conducted in certain emergent, life-threatening situations using an exception from the requirement for informed patient consent. Under the applicable federal regulation, an IRB may give approval for patient enrollment in trials in emergency situations without requiring individual informed consent provided specific criteria are met. Individual informed consent is often a defense raised against product liability claims asserted by patients participating in clinical trials of medical products. We cannot ensure that IRB approval of patient enrollment in our trial, even if given in full compliance with the applicable federal regulations, will provide us with a defense against product liability claims by patients participating in our trial. It is also possible that we may be subject to legal claims by patients objecting to being enrolled in our trial without their individual informed consent, even if the patients do not suffer any injuries in connection with our trial.

WE DEPEND ON THE SERVICES OF A LIMITED NUMBER OF KEY PERSONNEL.

Our success is highly dependent on the continued services of a limited number of skilled managers and scientists. The loss of any of these individuals could have a material adverse effect on us. In addition, our success will depend, among other factors, on the recruitment and retention of additional highly skilled and experienced management and technical personnel. We cannot ensure that we will be able to retain existing employees or to attract and retain additional skilled personnel on acceptable terms given the competition for such personnel among numerous large and well-funded pharmaceutical and health care companies, universities and non-profit research institutions.

OUR ABILITY TO GENERATE REVENUE FROM OUR PRODUCT WILL DEPEND ON REIMBURSEMENT AND DRUG PRICING POLICIES AND REGULATIONS.

Our ability to achieve acceptable levels of reimbursement for PolyHeme by

governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize PolyHeme. We cannot be sure that reimbursement in the United States, Europe or elsewhere will be available for PolyHeme or, if reimbursement should become available, that it will not be decreased or eliminated in the future. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize PolyHeme, and may not be able to obtain a satisfactory financial return on PolyHeme.

Third-party payers increasingly are challenging prices charged for medical products and services. Also, the trend toward managed health care in the United States and the changes in health insurance programs, as well as legislative proposals to reform health care or reduce government insurance programs, may result in lower prices for pharmaceutical products, including PolyHeme. Cost-cutting measures that health care providers are instituting, and the effect of any health care reform, could harm our ability to sell PolyHeme. Moreover, we are unable to predict what additional legislation or

S-14

RISK FACTORS

regulation, if any, relating to the health care industry or third-party coverage and reimbursement may be enacted in the future or what effect this legislation or regulation would have on our business. In the event that governmental authorities enact legislation or adopt regulations which affect third-party coverage and reimbursement, demand for PolyHeme may be reduced, thereby harming our sales and profitability.

FAILURE TO OBTAIN REGULATORY APPROVAL IN FOREIGN JURISDICTIONS WOULD PREVENT OUR PRODUCT FROM BEING MARKETED ABROAD.

We have entered into license agreements with Pfizer Inc., formerly known as Pharmacia Corporation, and Hemocare Ltd., an Israeli corporation, to develop, manufacture and distribute PolyHeme in certain European, Middle Eastern and African countries. The license agreements permit Pfizer and Hemocare to sell PolyHeme in return for the payment of royalties based upon sales of PolyHeme in the licensed territories. In order for Pfizer, Hemocare or anyone else, including us, to market our products in the European Union and many other foreign jurisdictions, we or licensees must obtain separate regulatory approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ from that required to obtain FDA approval. The foreign regulatory approval process entails all of the risks associated with obtaining FDA approval. We and our licensees may fail to obtain foreign regulatory approvals on a timely basis, if at all. Approval by FDA does not ensure approval by regulatory authorities in other countries, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by FDA. We and our licensees may not be able to file for, and may not receive, necessary regulatory approvals to commercialize our product in any market. If we or our licensees fail to obtain these approvals, our business, financial condition and results of operations could be materially and adversely affected.

OUR FINANCIAL RESULTS COULD BE AFFECTED BY CHANGES IN THE ACCOUNTING RULES GOVERNING THE RECOGNITION OF STOCK-BASED COMPENSATION EXPENSE.

The Financial Accounting Standards Board recently issued its Statement of Financial Accounting Standards No. 123 (revised 2004), Share-Based Payment (Statement 123R), which addresses the accounting for employee stock options.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

Statement 123R requires that the cost of all employee stock options, as well as other equity-based compensation arrangements, be reflected in financial statements based on the estimated fair value of the awards. We expect to adopt SFAS 123R for the period ending November 30, 2005. We will assess the impact of the transition to this new accounting standard during the upcoming months. Upon our implementation of Statement 123R, we could be required to recognize significant additional compensation expense.

FAILURE TO MAINTAIN EFFECTIVE INTERNAL CONTROLS OVER FINANCIAL REPORTING COULD HAVE A MATERIAL ADVERSE EFFECT ON OUR BUSINESS, OPERATING RESULTS AND STOCK PRICE.

Beginning with our annual report for our fiscal year ending May 31, 2005, Section 404 of the Sarbanes-Oxley Act of 2002 will require us to include a report by our management on our internal controls over financial reporting. This report must contain an assessment by management of the effectiveness of our internal controls over financial reporting as of the end of our fiscal year and a statement as to whether or not our internal controls are effective. The report must also contain a statement that our independent auditors have issued an attestation report on management's assessment of such internal controls.

In order to achieve timely compliance with Section 404, we have begun a process to document and evaluate our internal controls over financial reporting. Our efforts to comply with Section 404 have resulted in, and are likely to continue to result in, significant costs, the commitment of time and

S-15

RISK FACTORS

operational resources and the diversion of management's attention. If our management identifies one or more material weaknesses in our internal controls over financial reporting, we will be unable to assert our internal controls are effective. If we are unable to assert that our internal controls over financial reporting are effective, or if our independent auditors are unable to attest that our management's report is fairly stated or they are unable to express an opinion on our management's evaluation or on the effectiveness of our internal controls, our business may be harmed. Market perception of our financial condition and the trading price of our stock may be adversely affected and customer perception of our business may suffer.

WE ARE SUBJECT TO A VARIETY OF FEDERAL, STATE AND LOCAL LAWS, RULES AND REGULATIONS RELATED TO THE DISCHARGE OR DISPOSAL OF TOXIC, VOLATILE OR OTHER HAZARDOUS CHEMICALS.

Although we believe that we are in material compliance with these laws, rules and regulations, the failure to comply with present or future regulations could result in fines being imposed on us, suspension of production or cessation of operations. Third parties may also have the right to sue to enforce compliance. Moreover, it is possible that increasingly strict requirements imposed by environmental laws and enforcement policies thereunder could require us to make significant capital expenditures. The operation of a manufacturing plant entails the inherent risk of environmental damage or personal injury due to the handling of potentially harmful substances, and there can be no assurance that we will not incur material costs and liabilities in the future because of an accident or other event resulting in personal injury or unauthorized release of such substances to the environment. In addition, we generate hazardous materials and other wastes that are disposed of at various offsite facilities. We may be liable, irrespective of fault, for material cleanup costs or other liabilities incurred at these disposal facilities in the event of a release of hazardous

substances by such facilities into the environment.

RISKS RELATED TO OUR INTELLECTUAL PROPERTY

OUR SUCCESS DEPENDS UPON OUR ABILITY TO PROTECT OUR INTELLECTUAL PROPERTY AND OUR PROPRIETARY TECHNOLOGY.

Our success depends in part on our ability to obtain and maintain intellectual property protection for PolyHeme as well as our technology and know-how. Our policy is to seek to protect PolyHeme and our technologies by, among other methods, filing United States and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of PolyHeme. The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. Our ability to maintain and solidify our proprietary position for our technology will depend on our success in obtaining effective patent claims and enforcing those claims once granted. We do not know whether any of our patent applications will result in the issuance of any patents. Our issued patents and those that may issue in the future may be challenged, invalidated, rendered unenforceable or circumvented, which could limit our ability to stop competitors from marketing related products or the length of term of patent protection that we may have for PolyHeme. Our United States patents have expiration dates that extend to 2017. The broadest of our issued patents expires in May 2006. Although we expect to be granted an extension of this patent to 2011, we cannot ensure that an extension will not be for less than five years or that it will be granted at all. In addition, the rights granted under any issued patents may not provide us with competitive advantages against competitors with similar compounds or technologies. Furthermore, our competitors may independently develop similar technologies or duplicate any technology developed by us in a manner that does not infringe our patents or other intellectual property. Because of the extensive time required for development, testing and regulatory review of PolyHeme, it is possible that, before

S-16

RISK FACTORS

PolyHeme can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantages of the patent.

WE RELY ON TRADE SECRETS AND OTHER CONFIDENTIAL INFORMATION TO MAINTAIN OUR PROPRIETARY POSITION.

In addition to patent protection, we also rely on protection of trade secrets, know-how and confidential and proprietary information. To maintain the confidentiality of trade secrets and proprietary information, we have entered into confidentiality agreements with our employees, consultants and collaborators upon the commencement of their relationships with us. These agreements require that all confidential information developed by the individual or made known to the individual by us during the course of the individual's relationship with us be kept confidential and not disclosed to third parties. Our agreements with employees also provide that inventions conceived by the individual in the course of rendering services to us will be our exclusive property. Individuals with whom we have these agreements may not comply with their terms. In the event of the unauthorized use or disclosure of our trade secrets or proprietary information, these agreements, even if obtained, may not provide meaningful protection for our trade secrets or other confidential information. To the extent that our employees, consultants or contractors use technology or know-how owned by others in their work for us, disputes may arise

as to the rights in related inventions. Adequate remedies may not exist in the event of unauthorized use or disclosure of our confidential information. The disclosure of our trade secrets would impair our competitive position and could have a material adverse effect on our operating results, financial condition and future growth prospects.

WE MAY BE INVOLVED IN LAWSUITS TO PROTECT OR ENFORCE OUR PATENTS, WHICH COULD BE EXPENSIVE AND TIME CONSUMING.

Competitors may infringe our patents. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover its technology. An adverse determination of any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings brought by the United States Patent and Trademark Office may be necessary to determine the priority of inventions with respect to our patent applications or those of our collaborators or licensors. Litigation or interference proceedings may fail and, even if successful, may result in substantial costs and be a distraction to our management. We may not be able to prevent misappropriation of our proprietary rights, particularly in countries where the laws may not protect such rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

We may not prevail in any litigation or interference proceeding in which we are involved. Even if we do prevail, these proceedings can be very expensive and distract our management.

S-17

RISK FACTORS

THIRD PARTIES MAY OWN OR CONTROL PATENTS OR PATENT APPLICATIONS THAT ARE INFRINGED BY OUR PRODUCT OR TECHNOLOGIES.

Our success depends in part on avoiding the infringement of other parties' patents and proprietary rights. In the United States, patent applications filed in recent years are confidential for 18 months, while older applications are not published until the patent issues. As a result, there may be patents of which we are unaware, and avoiding patent infringement may be difficult. We may inadvertently infringe third-party patents or patent applications. These third parties could bring claims against us that, even if resolved in our favor, could cause us to incur substantial expenses and, if resolved against us, could additionally cause us to pay substantial damages. Further, if a patent infringement suit were brought against us, we could be forced to stop or delay research, development, manufacturing or sales of PolyHeme in the country or countries covered by the patent we infringe, unless we can obtain a license from the patent holder. Such a license may not be available on acceptable terms, or

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

at all, particularly if the third party is developing or marketing a product competitive with PolyHeme. Even if we were able to obtain a license, the rights may be nonexclusive, which would give our competitors access to the same intellectual property.

We also may be required to pay substantial damages to the patent holder in the event of an infringement. Under some circumstances in the United States, these damages could be triple the actual damages the patent holder incurs. If we have supplied infringing products to third parties for marketing or licensed third parties to manufacture, use or market infringing products, we may be obligated to indemnify these third parties for any damages they may be required to pay to the patent holder and for any losses the third parties may sustain themselves as the result of lost sales or damages paid to the patent holder.

Any successful infringement action brought against us may also adversely affect marketing of PolyHeme in other markets not covered by the infringement action. Furthermore, we may suffer adverse consequences from a successful infringement action against us even if the action is subsequently reversed on appeal, nullified through another action or resolved by settlement with the patent holder. The damages or other remedies awarded, if any, may be significant. As a result, any infringement action against us would likely delay the regulatory approval process, harm our competitive position, be very costly and require significant time and attention of our key management and technical personnel.

RISKS RELATED TO THE OFFERING

OUR STOCK PRICE COULD BE VOLATILE AND YOUR INVESTMENT COULD SUFFER A DECLINE IN VALUE.

The market price of our common stock has fluctuated significantly in response to a number of factors, many are which are beyond our control, including:

regulatory developments relating to our PolyHeme blood substitute product;

announcements by us relating to the results of our clinical trials of PolyHeme;

developments relating to our efforts to obtain additional financing to fund our operations;

announcements by us regarding transactions with potential strategic partners;

announcements relating to blood substitute products being developed by our competitors;

changes in industry trends or conditions;

our issuance of additional debt or equity securities; and

sales of significant amounts of our common stock or other securities in the market.

S-18

RISK FACTORS

In addition, the stock market in general, and the Nasdaq National Market and the biotechnology industry market in particular, have experienced significant price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of listed companies. These broad market and industry

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

factors may seriously harm the market price of our common stock, regardless of our operating performance. In the past, securities class action litigation has often been instituted following periods of volatility in the market price of a company's securities. A securities class action suit against us could result in substantial costs, potential liabilities and the diversion of our management's attention and resources.

ANTI-TAKEOVER PROVISIONS CONTAINED IN OUR CHARTER AND BYLAWS COULD DISCOURAGE POTENTIAL TAKEOVER ATTEMPTS.

Our certificate of incorporation contains a "fair price" provision which requires approval of the holders of at least 80% of our voting stock, excluding shares held by certain interested stockholders and their affiliates, as a condition to mergers or certain other business combinations with, or proposed by, any holder of 15% or more of our voting stock, except in cases where approval of our disinterested directors is obtained or certain minimum price criteria and other procedural requirements are satisfied. In addition, our board of directors has the authority, without further action by our stockholders, to fix the rights and preferences and issue shares of preferred stock. These provisions, and other provisions of our certificate of incorporation and bylaws and Delaware law, may have the effect of deterring hostile takeovers or delaying or preventing changes in our control or management, including transactions in which stockholders might otherwise receive a premium for their shares over the then prevailing market prices.

THERE IS A LARGE NUMBER OF SHARES THAT MAY BE SOLD IN THE MARKET FOLLOWING THIS OFFERING, WHICH MAY DEPRESS THE MARKET PRICE OF OUR COMMON STOCK.

Sales of a substantial number of shares of our common stock or securities convertible into or exercisable for our common stock in the public market following this offering could cause the market price of our common stock to decline. If there are more shares of common stock offered for sale than buyers are willing to purchase, then the market price of our common stock may decline to a market price at which buyers are willing to purchase the offered shares of common stock and sellers remain willing to sell the shares. All of the shares sold in the offering will be freely tradeable without restriction or further registration under the Securities Act, except for any shares purchased by our "affiliates" as defined in Rule 144 of the Securities Act.

OUR MANAGEMENT HAS BROAD DISCRETION TO DETERMINE HOW TO USE THE PROCEEDS RECEIVED FROM THIS OFFERING.

Our management will have broad discretion as to the application of the net proceeds of this offering and could use them for purposes other than those contemplated at the time of this offering. Our stockholders may not agree with the manner in which our management chooses to allocate and spend the net proceeds. Moreover, our management may use the net proceeds for corporate purposes that may not increase the market price of our common stock.

YOU WILL EXPERIENCE IMMEDIATE AND SUBSTANTIAL DILUTION.

The public offering price of the securities offered hereby is likely to be substantially higher than the book value per share of our common stock. Investors purchasing common stock in this offering will, therefore, incur immediate dilution in net tangible book value per share of common stock. Investors will also incur additional dilution upon the exercise of outstanding stock options and warrants. See "Dilution" for a more detailed discussion of the dilution you will incur in this offering.

Special note regarding forward-looking statements

This prospectus supplement and the accompanying prospectus, including the documents we incorporate by reference, contain forward-looking statements concerning, among other things, our prospects, clinical and regulatory developments affecting our potential product and our business strategies. These forward-looking statements are identified by the use of such terms as "intends," "expects," "plans," "estimates," "anticipates," "forecasts," "should" and "believes" and are in certain cases followed by a cross reference to "Risk Factors."

These forward-looking statements involve risks and uncertainties. Actual results may differ materially from those predicted by the forward-looking statements because of various factors and possible events, including those discussed under "Risk Factors." Because these forward-looking statements involve risks and uncertainties, actual results may differ significantly from those predicted in these forward-looking statements. You should not place undue weight on these statements. These statements speak only as of the date of this prospectus supplement or, in the case of any document incorporated by reference, the date of that document.

All subsequent written and oral forward-looking statements attributable to Northfield or any person acting on our behalf are qualified by the cautionary statements in this section. We will have no obligation to revise these forward-looking statements.

S-20

Use of proceeds

We estimate that the net proceeds from the sale of the 3,500,000 shares of common stock we are offering will be approximately \$69.0 million (or approximately \$79.4 million if the underwriters' over-allotment option is exercised in full) after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We expect to use the net proceeds from this offering:

- to fund our post-enrollment activities in our clinical trial;
- to prepare and submit a Biologics License Application to FDA;
- to construct a 75,000 unit per year manufacturing facility to produce PolyHeme for commercial sale;
- to build sales, marketing and distribution capabilities in support of the commercialization of PolyHeme; and
- for general corporate purposes.

We have retained an engineering firm to provide us with preliminary engineering studies and cost estimates with respect to the construction of an expanded manufacturing facility adjacent to our current manufacturing plant in Mt. Prospect, Illinois. Based on these studies and estimates, we believe that a manufacturing facility with the capacity to produce 75,000 units of PolyHeme per

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

year could be built at this location in a period of approximately 16 to 20 months at a cost of \$35 to \$40 million.

The amounts and timing of these expenditures, including the timing of the commencement of construction of our planned manufacturing facility, will depend on numerous factors, such as the progress of our clinical trials, regulatory developments affecting our product and the competitive environment for our product. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering. Accordingly, we will retain broad discretion over the use of these proceeds.

Pending any ultimate use of any portion of the proceeds, we intend to invest the proceeds in a variety of capital preservation investments, including short-term and long-term, interest-bearing, investment-grade securities and money-market funds.

S-21

Capitalization

The following table sets forth our unaudited cash and marketable securities and capitalization as of November 30, 2004:

on an actual basis; and

on an as adjusted basis to give effect to the sale of 3,500,000 shares of our common stock, after deducting estimated underwriting discounts and commissions and estimated offering expenses to be paid by us.

This table should be read with "Management's discussion and analysis of financial condition and results of operations" and our financial statements and the related notes incorporated by reference in this prospectus supplement and the accompanying prospectus.

	AS OF NOVEMBER 30, 2004	
	ACTUAL	AS ADJUSTED
	(UNAUDITED)	
	(IN THOUSANDS, EXCEPT SHARE AND PER SHARE DATA)	
Cash and marketable securities.....	\$ 33,854	\$ 102,860
	=====	=====
Shareholders' equity:		
Preferred stock, \$0.01 par value; 5,000,000 shares authorized; no shares issued or outstanding, actual and as adjusted.....	--	--
Common stock, \$0.01 par value; 30,000,000 shares authorized; 21,551,364 shares issued and outstanding, actual; 25,051,364 shares issued and outstanding, as adjusted.....	216	251
Additional paid-in capital.....	168,227	237,198
Deficit accumulated during development stage.....	(134,838)	(134,838)
Deferred compensation.....	(170)	(170)

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

Total shareholders' equity.....	\$ 33,434	\$ 102,440
	=====	=====

The number of shares of common stock outstanding is based on the actual number of shares outstanding as of November 30, 2004 and excludes:

1,418,892 shares of common stock underlying options and warrants outstanding as of November 30, 2004 at a weighted average exercise price of \$8.92 per share; and

554,240 shares of common stock available as of November 30, 2004 for issuance under our 2003 Equity Compensation Plan and Stock Option Plan for New Employees.

S-22

Market price of common stock

Our common stock is traded publicly through the Nasdaq National Market under the symbol "NFLD." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sales price reported by the Nasdaq National Market. These prices do not include retail markups, markdowns or commissions.

	HIGH	LOW

YEAR ENDED MAY 31, 2003		
First quarter.....	\$ 5.66	\$ 3.00
Second quarter.....	5.86	3.75
Third quarter.....	6.63	3.30
Fourth quarter.....	8.85	4.95
YEAR ENDED MAY 31, 2004		
First quarter.....	\$ 9.84	\$ 5.95
Second quarter.....	7.81	5.50
Third quarter.....	12.14	4.96
Fourth quarter.....	19.74	11.34
YEAR ENDING MAY 31, 2005		
First quarter.....	\$15.28	\$ 9.42
Second quarter.....	18.83	12.36
Third quarter (through January 14, 2005).....	23.88	17.60

As of November 30, 2004, there were approximately 500 holders of record of our common stock. On January 14, 2005, the last sale price reported on the Nasdaq National Market for our common stock was \$21.02 per share.

Dividend policy

We have never declared or paid our stockholders dividends, and we do not anticipate paying any cash dividends in the foreseeable future as we intend to retain any earnings for use in our business. The payment of any future cash dividends on our common stock will also depend upon our earnings and financial needs and will be subject to applicable legal and contractual restrictions.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

Dilution

If you invest in our common stock, you will experience dilution to the extent of the difference between the public offering price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. Our net tangible book value at November 30, 2004 was \$33,434,000, or \$1.55 per share of common stock. Net tangible book value per share is equal to our total tangible assets minus total liabilities, all divided by the number of outstanding shares of our common stock on November 30, 2004. Assuming that we issue 3,500,000 shares common stock in this offering at a public offering price of \$21.02 per share (the last reported sale price of our common stock on the Nasdaq National Market on January 14, 2005), with estimated net proceeds to us (after assumed commissions and expenses) of \$69,006,000, our pro forma net tangible book value at November 30, 2004 would have been \$102,440,000, or \$4.09 per share. This represents an immediate increase in the tangible book value of \$2.54 per share to our existing stockholders and an immediate

S-23

DILUTION

dilution of \$16.93 per share to new investors purchasing common stock in this offering, as illustrated in the following table:

Assumed public offering price per share.....	\$21.02
Net tangible book value per share as of November 30, 2004.....	\$1.55
Increase per share attributable to the offering.....	2.54

As adjusted net tangible book value per share after this offering.....	4.09

Dilution per share to new investors.....	\$16.93
	=====

If the underwriters exercise their over-allotment option in full, the as adjusted net tangible book value as of November 30, 2004 would have been \$4.41 per share, representing an increase to existing stockholders of \$2.86 per share, and there will be an immediate dilution of \$16.61 per share to new investors.

The foregoing table does not take into effect further dilution to new investors that could occur upon the exercise of outstanding options and warrants having a per share exercise price less than the offering price per share in this offering. As of November 30, 2004, there were:

1,418,892 shares of common stock underlying outstanding options and warrants at a weighted average exercise price of \$8.92 per share; and

554,240 shares of common stock available for issuance under our 2003 Equity Compensation Plan and Stock Option Plan for New Employees.

S-24

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

Underwriting

We are offering the shares of our common stock described in this prospectus supplement through the underwriters named below. UBS Securities LLC, SG Cowen & Co., LLC and Harris Nesbitt Corp. are the representatives of the underwriters. UBS Securities LLC is the sole book-runner of this offering. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, each of the underwriters has severally agreed to purchase the number of shares of common stock listed next to its name in the following table:

UNDERWRITERS	NUMBER OF SHARES

UBS Securities LLC	
SG Cowen & Co., LLC	
Harris Nesbitt Corp.	

Total.....	3,500,000
	=====

The underwriting agreement provides that the underwriters must buy all of the shares if they buy any of them. However, the underwriters are not required to take or pay for the shares covered by the underwriters' over-allotment option described below.

Our common stock is offered subject to a number of conditions, including:

- receipt and acceptance of our common stock by the underwriters; and
- the underwriters' right to reject orders in whole or in part.

In connection with this offering, certain of the underwriters or securities dealers may distribute prospectuses electronically.

OVER-ALLOTMENT OPTION

We have granted the underwriters an option to buy up to 525,000 additional shares of our common stock. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with this offering. The underwriters have 30 days from the date of this prospectus supplement to exercise this option. If the underwriters exercise this option, they will each purchase additional shares approximately in proportion to the amounts specified in the table above.

COMMISSIONS AND DISCOUNTS

Shares sold by the underwriters to the public will initially be offered at the offering price set forth on the cover of this prospectus supplement. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to \$ per share from the public offering price. Any of these securities dealers may resell any shares purchased from the underwriters to other brokers or dealers at a discount of up to \$ per share from the public offering price. If all the shares are not sold at the public offering price, the representatives may change the offering price and the other selling terms. Sales of shares made outside of the United States may be made by affiliates of the underwriters.

 UNDERWRITING

The following table shows the per share and total underwriting discounts and commissions we will pay to the underwriters, assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional 525,000 shares.

	NO EXERCISE	FULL EXERCISE
Per share.....	\$	\$
Total.....	\$	\$

We estimate that the total expenses of this offering payable by us, not including the underwriting discounts and commissions, will be approximately \$150,000.

In compliance with NASD guidelines, the maximum commission or discount to be received by any NASD member or independent broker-dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus supplement.

NO SALES OF SIMILAR SECURITIES

We, our executive officers and directors have entered into lock-up agreements with the underwriters. Under these agreements, we and each of these persons may not, without the prior written approval of UBS Securities LLC, subject to limited exceptions, offer, sell, contact to sell or otherwise dispose of or hedge our common stock or securities convertible into or exercisable or exchangeable for our common stock. These restrictions will be in effect for a period of 90 days after the date of this prospectus supplement. The 90-day lock-up period may be extended under certain circumstances where we announce or pre-announce earnings or material news or a material event within approximately 18 days prior to, or approximately 16 days after, the termination of the 90-day period. At any time and without public notice, UBS Securities LLC may in its sole discretion release all or some of the securities from these lock-up agreements.

INDEMNIFICATION AND CONTRIBUTION

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act. If we are unable to provide this indemnification, we will contribute to payments the underwriters and their controlling persons may be required to make in respect of those liabilities.

NASDAQ NATIONAL MARKET QUOTATION

Our common stock is quoted on the Nasdaq National Market under the symbol "NFLD."

PRICE STABILIZATION, SHORT POSITIONS, PASSIVE MARKET MAKING

In connection with this offering, the underwriters may engage in activities that stabilize, maintain or otherwise affect the price of our common stock, including:

stabilizing transactions;
short sales;
purchases to cover positions created by short sales;
imposition of penalty bids;
syndicate covering transactions; and
passive market making.

Stabilizing transactions consist of bids or purchases made for the purpose of preventing or retarding a decline in the market price of our common stock while this offering is in progress. These transactions

S-26

UNDERWRITING

may also include making short sales of our common stock, which involve the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering. Short sales may be "covered short sales," which are short positions in an amount not greater than the underwriters' over-allotment option referred to above, or may be "naked short sales," which are short positions in excess of that amount.

The underwriters may close out any covered short position by either exercising their over-allotment option, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchased in this offering.

The underwriters also may impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of that underwriter in stabilizing or short covering transactions.

As a result of these activities, the price of our common stock may be higher than the price that otherwise might exist in the open market. If these activities are commenced, they may be discontinued by the underwriters at any time. The underwriters may carry out these transactions on the Nasdaq National Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in our common stock on the Nasdaq National Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on the Nasdaq National Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

AFFILIATIONS

The underwriters and their affiliates have provided and may provide certain commercial banking, investment banking and financial advisory services for us for which they receive fees. The underwriters and their affiliates may from time to time in the future engage in transactions with us and perform services for us in the ordinary course of their business.

S-27

Incorporation of certain documents by reference

The SEC allows us to "incorporate by reference" into this prospectus supplement the information we have filed with the SEC. The information we incorporate by reference into this prospectus supplement is an important part of this prospectus supplement, and later information that we file with the SEC will automatically update and supersede some of this information. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934 until we sell all of the securities covered by this prospectus supplement. The documents we incorporate by reference are:

our Annual Report on Form 10-K for the year ended May 31, 2004 filed with the SEC on August 16, 2004 (file no. 000-24050);

our Quarterly Reports on Form 10-Q for the quarters ended August 31, 2004 and November 30, 2004 filed with the SEC on October 12, 2004 and January 10, 2005, respectively (file no. 000-24050); and

the description of our common stock contained in our Registration Statement on Form 8-A, Registration No. 33-76856, filed with the SEC on March 25, 1994, including any amendments or reports filed for the purpose of updating this description.

Information in Current Reports on Form 8-K furnished to the SEC, including under Item 2.02 or 7.01 of Form 8-K prior, on or subsequent to the date of this prospectus supplement is not being and will not be incorporated herein by reference.

You may request a copy of these filings (other than an exhibit to the filings unless we have specifically incorporated that exhibit by reference into the filing), at no cost, by writing or telephoning us at the following address:

Northfield Laboratories Inc.
1560 Sherman Avenue
Suite 1000
Evanston, Illinois 60201-4800
(847) 864-3500

Legal matters

Baker & McKenzie LLP, Chicago, Illinois, will pass upon the validity of the issuance of the common stock offered by this prospectus supplement. Willkie Farr & Gallagher LLP, New York, New York, is counsel for the underwriters in

connection with this offering.

S-28

PROSPECTUS

\$100,000,000

(NORTHFIELD LABORATORIES INC. LOGO)

COMMON STOCK
PREFERRED STOCK
DEPOSITARY SHARES
STOCK PURCHASE CONTRACTS
WARRANTS
DEBT SECURITIES

THE SECURITIES OFFERED BY THE PROSPECTUS INVOLVED A HIGH DEGREE OF RISK. SEE "RISK FACTORS" BEGINNING ON PAGE 4.

We will provide you with the specific terms of the particular securities being offered in supplements to this prospectus. You should read this prospectus and each related supplement carefully before you invest. This prospectus may not be used to sell securities unless accompanied by a prospectus supplement.

Our common stock is quoted on the Nasdaq Stock Market's National Market System under the symbol "NFLD." The last reported sale price of our common stock on December 17, 2004 was \$20.18 per share.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR PASSED UPON THE ADEQUACY OR ACCURACY OF THIS PROSPECTUS. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this prospectus is December 23, 2004.

TABLE OF CONTENTS

About this prospectus.....	1
Where you can find more information...	1
Forward-looking information.....	3
Our business.....	3
Risk factors.....	4
Use of proceeds.....	11
Ratio of earnings to fixed charges and preference dividends.....	11
Dilution.....	11
Description of the securities we may offer.....	12
Plan of distribution.....	15
Legal matters.....	17
Experts.....	17

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a "shelf" registration process. Using this process, we may offer the securities described in this prospectus in one or more offerings with a total initial offering price of up to \$100,000,000 or an equivalent amount in one or more foreign currencies. We may sell these securities separately or in units. This prospectus provides you with a general description of the securities we may offer. Each time we offer securities, we will provide you a prospectus supplement that will contain information about the specific terms of that particular offering. The prospectus supplement may also add, update or change information contained in this prospectus. To obtain additional information that may be important to you, you should read the exhibits filed by us with the registration statement of which this prospectus is a part or our other filings with the SEC. You also should read this prospectus and any prospectus supplement together with the additional information described below under "Where You Can Find More Information."

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the SEC. You can read and copy any materials we file with the SEC at its Public Reference Room at 450 Fifth Street, N.W., Washington, D.C. 20549. You can obtain information about the operations of the SEC Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains a web site that contains information we file electronically with the SEC, which you can access over the Internet at www.sec.gov. You may also access the information we file electronically with the SEC through our website at www.northfieldlabs.com.

The SEC 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. The information we incorporate by reference is an important part of this prospectus, and later information that we file with the SEC will automatically update and supersede some of this information. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934 until we sell all of the securities covered by this prospectus. The documents we incorporate by reference are:

our Annual Report on Form 10-K for the year ended May 31, 2004;

our Quarterly Report on Form 10-Q for the quarter ended August 31, 2004; and

1

the description of our common stock contained in our Registration Statement on Form 8-A, Registration No. 33-76856, filed with the SEC on March 25, 1994, including any amendments or reports filed for the purpose of updating this description.

Information in Current Reports on Form 8-K furnished to the SEC, including under Item 2.02 or 7.01 of Form 8-K prior, on or subsequent to the date hereof is not being and will not be incorporated herein by reference.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

You may request a copy of these filings (other than an exhibit to the filings unless we have specifically incorporated that exhibit by reference into the filing), at no cost, by writing or telephoning us at the following address:

Northfield Laboratories Inc.
1560 Sherman Avenue
Suite 1000
Evanston, Illinois 60201-4800
(847) 864-3500

You should rely only on the information incorporated by reference or provided in this prospectus or any prospectus supplement. We have not authorized anyone else to provide you with different information. We may only use this prospectus to sell securities if it is accompanied by a prospectus supplement. We are only offering the securities in states where the offer is permitted. You should not assume that the information in this prospectus or any prospectus supplement is accurate as of any date other than the date on the front of those documents.

2

Forward-looking information

This prospectus and the documents we incorporate by reference contain forward-looking statements concerning, among other things, our prospects, clinical and regulatory developments affecting our potential product and our business strategies. These forward-looking statements are identified by the use of such terms as "intends," "expects," "plans," "estimates," "anticipates," "forecasts," "should" and "believes" and are in certain cases followed by a cross reference to "Risk Factors."

These forward-looking statements involve risks and uncertainties. Actual results may differ materially from those predicted by the forward-looking statements because of various factors and possible events, including those discussed under "Risk Factors." Because these forward-looking statements involve risks and uncertainties, actual results may differ significantly from those predicted in these forward-looking statements. You should not place undue weight on these statements. These statements speak only as of the date of this prospectus or, in the case of any document incorporated by reference, the date of that document.

All subsequent written and oral forward-looking statements attributable to Northfield or any person acting on our behalf are qualified by the cautionary statements in this section. We will have no obligation to revise these forward-looking statements.

OUR BUSINESS

Northfield Laboratories Inc. is a leader in the development of a safe and effective alternative to transfused blood for use in the treatment of acute blood loss. Our PolyHeme(R) blood substitute product is a solution of chemically modified hemoglobin derived from human blood. PolyHeme simultaneously restores lost blood volume and hemoglobin levels and is designed for rapid, massive infusion. PolyHeme requires no cross-matching, and is therefore immediately available and compatible with all blood types. PolyHeme has an extended shelf life compared to blood. We believe PolyHeme is the only blood substitute in development that has been well tolerated when infused in patients in clinical trials in sufficient quantities for the treatment of urgent, large volume blood loss in trauma and surgical settings, with a particular focus on situations where donated blood is not immediately available.

We are currently enrolling patients in a pivotal Phase III trial in which PolyHeme is being used for the first time in civilian, urban trauma settings to treat severely injured patients in hemorrhagic shock before they reach the hospital. Under this protocol, treatment with PolyHeme begins at the scene of the injury or in the ambulance and continues during transport and the initial 12 hour post-injury period in the hospital. Since blood is not routinely carried in ambulances, the use of PolyHeme in this setting has the potential to improve survival and address a critical, unmet medical need.

Our principal executive offices are located at 1560 Sherman Avenue, Suite 1000, Evanston, Illinois 60201-4800, and our telephone number is (847) 864-3500. We maintain an Internet Web site at www.northfieldlabs.com. We make available free of charge on our Web site our Form 10-Ks, Form 10-Qs, Form 8-Ks and other documents that we file with or furnish to the Securities and Exchange Commission, or "SEC," as soon as reasonably practicable after filing with the SEC. The information contained on our Web site, or on other Web sites linked to our Web site, is not a part of this document.

3

Risk factors

The securities offered by this prospectus involve a high degree of risk. You should consider the following risk factors when reviewing the information contained in this prospectus. You also should consider the other information incorporated by reference in this prospectus. These risk factors may be supplemented and amended by any risk factors set forth in a prospectus supplement.

RISK RELATED TO OUR BUSINESS

WE ARE REQUIRED TO COMPLETE OUR CURRENT CLINICAL TRIAL BEFORE WE MAY SELL POLYHEME COMMERCIALY AND WE MAY BE REQUIRED TO CONDUCT ADDITIONAL CLINICAL TRIALS IN THE FUTURE.

The results of our clinical trials conducted to date are not sufficient to demonstrate adequately the safety and effectiveness of PolyHeme in order to obtain approval from FDA for the commercial sale of PolyHeme. We are currently conducting a pivotal Phase III trial in which PolyHeme is being used for the first time in civilian trauma applications to treat severely injured patients before they reach the hospital. Under this protocol, treatment with PolyHeme begins at the scene of the injury, continues during transport to the hospital by ambulance and further in the hospital. This trial will be expensive and time-consuming and the timing of the FDA review process is uncertain. We cannot ensure that we will be able to complete our current clinical trial successfully or that FDA will not require us to conduct additional clinical trials of PolyHeme in the future. If FDA approval for the commercial sale of PolyHeme is obtained, it may include significant limitations on the indicated uses for which PolyHeme may be marketed. Our business, financial condition and results of operations are critically dependent on receiving FDA approval of PolyHeme. A significant delay in our clinical trial or a failure to achieve FDA approval for commercial sales of PolyHeme would have a material adverse effect on us and could result in the cessation of our business. We or FDA may in the future suspend our clinical trial at any time if it is believed that the subjects participating in the trial are being exposed to unacceptable health risks.

OUR ACTIVITIES ARE AND WILL CONTINUE TO BE SUBJECT TO EXTENSIVE GOVERNMENT

REGULATION.

Our research, development, testing, manufacturing, marketing and distribution of PolyHeme are, and will continue to be, subject to extensive regulation, monitoring and approval by FDA. The regulatory approval process to establish the safety and effectiveness of PolyHeme and the safety and reliability of our manufacturing process has already consumed considerable time and expenditures. The data obtained from clinical trials are susceptible to varying interpretations, which could delay, limit or prevent FDA regulatory approval. The lack of established criteria for evaluating the effectiveness of blood substitute products could also delay or prevent FDA regulatory approval. In addition, delay or rejection could be caused by changes in FDA policies and regulations. We cannot ensure that, even after extensive clinical trials, regulatory approval will ever be obtained for PolyHeme.

We will be required to submit a Biologics License Application, or BLA, with FDA in order to obtain regulatory approval for the commercial sale of PolyHeme in the United States. Under FDA guidelines, FDA may comment upon the acceptability of a BLA following its submission. After a BLA is submitted there is an initial review by FDA to be sure that all of the required elements are included in the submission. There can be no assurance that the submission will be accepted for filing or that FDA may not issue a refusal to file, or RTF. If an RTF is issued, there is opportunity for dialogue between the sponsor and FDA in an effort to resolve all concerns. There can be no assurance that such a dialogue will be successful in leading to the filing of the BLA. We received an RTF from FDA in November 2001 in connection with our submission of a BLA seeking approval to market PolyHeme for use in the treatment of urgent, life-threatening blood loss based on data from patients in the hospital setting only.

4

RISK FACTORS

The subsequent dialogue with FDA resulted in the mutual decision to proceed with the current pivotal Phase III trial that starts in the prehospital setting. If a new BLA submission is filed, there can be no assurance that the full review will result in product approval. Moreover, if regulatory approval of PolyHeme is granted, the approval may include limitations on the indicated uses for which PolyHeme may be marketed.

Further, even if such regulatory approval is obtained, we do not presently have manufacturing facilities to produce sufficient quantities of PolyHeme to achieve profitability. In order to seek FDA approval of the sale of PolyHeme produced at a larger-scale manufacturing facility, we may be required to conduct a portion of our clinical trials with product manufactured at that facility. Discovery of previously unknown problems with PolyHeme or unanticipated problems with our manufacturing facilities, even after FDA approval of PolyHeme for commercial sale, may result in the imposition of significant restrictions, including withdrawal of PolyHeme from the market. Additional laws and regulations may also be enacted which could prevent or delay regulatory approval of PolyHeme, including laws or regulations relating to the price or cost-effectiveness of medical products. Any delay or failure to achieve regulatory approval of commercial sales of PolyHeme is likely to have a material adverse effect on our financial condition.

FDA continues to monitor products even after they receive agency approval. If and when FDA approves PolyHeme, its manufacture and marketing will be subject to ongoing regulation, including compliance with current good manufacturing practices, adverse event reporting requirements and FDA's general prohibitions against promoting products for unapproved or "off-label" uses. We are also

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

subject to inspection and market surveillance by FDA for compliance with these and other requirements. Any enforcement action resulting from failure, even by inadvertence, to comply with these requirements could affect the manufacture and marketing of PolyHeme. In addition, FDA could withdraw a previously approved product from the market upon receipt of newly discovered information. FDA could also require us to conduct additional, and potentially expensive, studies in areas outside our approved indicated uses.

WE ARE A DEVELOPMENT STAGE COMPANY WITHOUT REVENUES OR PROFITS.

Northfield was founded in 1985 and is a development stage company. Since 1985, we have been engaged primarily in the development and clinical testing of PolyHeme. No revenues have been generated to date from commercial sales of PolyHeme. Our revenues to date have consisted solely of license fees. We cannot ensure that our clinical testing will be successful, that regulatory approval of PolyHeme will be obtained, that we will be able to manufacture PolyHeme at an acceptable cost and in appropriate quantities or that we will be able to successfully market and sell PolyHeme. We also cannot ensure that we will not encounter unexpected difficulties which will have a material adverse effect on us, our operations or our properties.

WE HAVE A HISTORY OF LOSSES AND OUR FUTURE PROFITABILITY IS UNCERTAIN.

From Northfield's inception through August 31, 2004, we have incurred net operating losses totaling \$129,906,524. We will require substantial additional expenditures to complete clinical trials, to pursue regulatory approval for PolyHeme, to establish commercial scale manufacturing processes and facilities, and to establish marketing, sales and administrative capabilities. These expenditures are expected to result in substantial losses for at least the next few years and are expected to substantially exceed our currently available capital resources. The expense and the time required to realize any product revenues or profitability are highly uncertain. We cannot ensure that we will be able to achieve product revenues or profitability on a sustained basis or at all.

5

RISK FACTORS

WE MAY NEED TO RAISE ADDITIONAL CAPITAL TO CONTINUE OUR BUSINESS.

We currently believe we have sufficient capital resources to complete the enrollment phase of our clinical trials. We intend to use the proceeds of this offering to fund our post-enrollment activities in our clinical trial and to prepare and submit a BLA application to FDA, to prepare for the commercial launch of PolyHeme, to fund ongoing business operations and for other general corporate purposes. Our specific use of the proceeds of this offering will be described in the prospectus supplement that will accompany this prospectus. We may be required to raise capital, in addition to the proceeds of this offering, to continue our business. Our future capital requirements will depend on many factors, including the scope and results of our clinical trials, the timing and outcome of regulatory reviews, administrative and legal expenses, the status of competitive products, the establishment of manufacturing capacity and the establishment of collaborative relationships. We cannot ensure that additional funding will be available or, if it is available, that it can be obtained on terms and conditions we will deem acceptable. Any additional funding derived from the sale of equity securities may result in significant dilution to our existing stockholders.

WE ARE DEVELOPING A SINGLE PRODUCT THAT IS SUBJECT TO A HIGH LEVEL OF

TECHNOLOGICAL RISK.

Our operations have to date consisted primarily of the development and clinical testing of PolyHeme. We do not expect to realize product revenues unless we successfully develop and achieve commercial introduction of PolyHeme. We expect that such revenues, if any, will be derived solely from sales of PolyHeme. We also expect the use of PolyHeme initially to be limited to the acute blood loss segment of the transfusion market. The biomedical field has undergone rapid and significant technological changes. Technological developments may result in PolyHeme becoming obsolete or non-competitive before we are able to recover any portion of the research and development and other expenses we have incurred to develop and clinically test PolyHeme. Any such occurrence would have a material adverse effect on us and our operations.

WE ARE NOT CERTAIN THAT WE WILL BE ABLE TO MANUFACTURE POLYHEME COMMERCIALY.

Commercial-scale manufacturing of PolyHeme will require the construction of a manufacturing facility significantly larger than that currently being used to produce PolyHeme for our clinical trials. We have no experience in large-scale manufacturing, and there can be no assurance that we can achieve large-scale manufacturing capacity. It is also possible that we may incur substantial cost overruns and delays compared to existing estimates in building and equipping a large-scale manufacturing facility. Moreover, in order to seek FDA approval of the sale of PolyHeme produced at a larger-scale manufacturing facility, we may be required to conduct a portion of our clinical trials with product manufactured at that facility. A significant delay in achieving scale-up of commercial manufacturing capabilities would have a material adverse effect on sales of PolyHeme. Additionally, the manufacture of PolyHeme will be subject to extensive government regulation. Among the conditions for marketing approval is that our quality control and manufacturing procedures conform to FDA's good manufacturing practice regulations. We cannot ensure that we will be able to obtain the necessary regulatory clearances or approvals to manufacture PolyHeme on a timely basis or at all.

THERE MAY BE LIMITATIONS IN THE SUPPLY OF THE STARTING MATERIAL FOR POLYHEME.

We currently purchase donated blood from The American Red Cross and Blood Centers of America for use as the starting material for PolyHeme. We have also entered into an agreement with hemerica, Inc., a subsidiary of Blood Centers of America, under which hemerica would supply us with up to 160,000 units per year of packed red cells, the source material for PolyHeme. We have not purchased any blood supplies under this agreement to date. We have plans to enter into long-term supply

6

RISK FACTORS

arrangements with other blood collectors. We cannot ensure that we will be able to enter into satisfactory long-term arrangements with blood bank operators, that the price we may be required to pay for starting material will permit us to price PolyHeme competitively or that we will be able to obtain an adequate supply of starting material. Additional demand for blood may arise from competing blood substitute products, some of which are derived from human blood, thereby limiting our available supply of starting material.

THERE ARE SIGNIFICANT COMPETITORS DEVELOPING SIMILAR PRODUCTS.

If approved for commercial sale, PolyHeme will compete directly with established therapies for acute blood loss and may compete with other technologies currently

under development. We cannot ensure that PolyHeme will have advantages which will be significant enough to cause medical professionals to adopt it rather than continue to use established therapies or to adopt other new technologies or products. We also cannot ensure that the cost of PolyHeme will be competitive with the cost of established therapies or other new technologies or products. The development of blood substitute products is a continuously evolving field. Competition is intense and may increase. Several companies have developed or are in the process of developing technologies which are, or in the future may be, the basis for products which will compete with PolyHeme. Certain of these companies are pursuing different approaches or means of accomplishing the therapeutic effects sought to be achieved through the use of PolyHeme. Some of these companies may have substantially greater financial resources, larger research and development staffs, more extensive facilities and more experience than Northfield in testing, manufacturing, marketing and distributing medical products. We cannot ensure that one or more other companies will not succeed in developing technologies or products which will become available for commercial use prior to PolyHeme, which will be more effective or less costly than PolyHeme or which would otherwise render PolyHeme obsolete or non-competitive.

WE DO NOT HAVE EXPERIENCE IN THE SALE AND MARKETING OF MEDICAL PRODUCTS.

If approved for commercial sale, we intend to market PolyHeme in the United States using our own sales force. We have no experience in the sale or marketing of medical products. Our ability to implement our sales and marketing strategy for the United States will depend on our ability to recruit, train and retain a marketing staff and sales force with sufficient technical expertise. We cannot ensure that we will be able to establish an effective marketing staff and sales force, that the cost of establishing such a marketing staff and sales force will not exceed revenues from the sale of PolyHeme or that our marketing and sales efforts will be successful.

THE MARKET MAY NOT ACCEPT OUR PRODUCT.

We anticipate that the market price for PolyHeme, if FDA approval is received, will exceed the cost of transfused blood. Competitors may also develop new technologies or products which are more effective or less costly than PolyHeme. We cannot ensure that the price of PolyHeme, considered in relation to PolyHeme's expected benefits, will be perceived by health care providers and third party payors as cost-effective, or that the price of PolyHeme will be competitive with transfused blood or with other new technologies or products. Our results of operations may be adversely affected if the price of PolyHeme is not considered cost-effective or if PolyHeme does not otherwise receive market acceptance.

OUR PATENTS AND OTHER PROPRIETARY RIGHTS MAY NOT PROTECT OUR TECHNOLOGY.

Our ability to compete effectively with other companies will depend, in part, on our ability to protect and maintain the proprietary nature of our technology. We cannot be certain as to the degree of protection offered by our patents or as to the likelihood that additional patents in the United States

7

RISK FACTORS

and certain other countries will be issued based upon pending patent applications. We cannot be certain that we were the first creator of the inventions covered by our patents or pending patent applications or that we were the first to file patent applications for our inventions. The high costs of enforcing patent and other proprietary rights may also limit the degree of

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

protection afforded to us. We also rely on unpatented proprietary technology, and we cannot ensure that others may not independently develop the same or similar technology or otherwise obtain access to our proprietary technology. We cannot ensure that our patents or other proprietary rights will be determined to be valid or enforceable if challenged in court or administrative proceedings or that we will not become involved in disputes with respect to the patents or proprietary rights of third parties. An adverse outcome from these proceedings could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to stop using this technology, any of which would result in a material adverse effect on our results of operations.

OUR PROFITABILITY WILL BE AFFECTED IF WE INCUR PRODUCT LIABILITY CLAIMS IN EXCESS OF OUR INSURANCE COVERAGE.

The testing and marketing of medical products, even after FDA approval, have an inherent risk of product liability. We maintain limited product liability insurance coverage for our clinical trials in the total amount of \$10 million. However, our profitability will be adversely affected by a successful product liability claim in excess of our insurance coverage. We cannot guarantee that product liability insurance will be available in the future or be available on reasonable terms.

WE DEPEND ON THE SERVICES OF A LIMITED NUMBER OF KEY PERSONNEL.

Our success is highly dependent on the continued services of a limited number of skilled managers and scientists. The loss of any of these individuals could have a material adverse effect on us. In addition, our success will depend, among other factors, on the recruitment and retention of additional highly skilled and experienced management and technical personnel. We cannot ensure that we will be able to retain existing employees or to attract and retain additional skilled personnel on acceptable terms given the competition for such personnel among numerous large and well-funded pharmaceutical and health care companies, universities and non-profit research institutions.

HEALTH CARE REFORM AND CONTROLS ON HEALTH CARE SPENDING MAY LIMIT THE PRICE WE CAN CHARGE FOR POLYHEME AND THE AMOUNT WE CAN SELL.

The federal government and private insurers have considered ways to change, and have changed, the manner in which health care services are provided in the United States. Potential approaches and changes in recent years include controls on health care spending and the creation of large purchasing groups. In the future, it is possible that the government may institute price controls and limits on Medicare and Medicaid spending. These controls and limits might affect the payments we collect from sales of our product. Assuming we succeed in bringing PolyHeme to market, uncertainties regarding future health care reform and private market practices could affect our ability to sell PolyHeme in large quantities at profitable pricing.

UNCERTAINTY OF THIRD-PARTY REIMBURSEMENT COULD AFFECT OUR PROFITABILITY.

Sales of medical products largely depend on the reimbursement of patients' medical expenses by governmental health care programs and private health insurers. There is no guarantee that governmental health care programs or private health insurers will reimburse our sales of PolyHeme, or permit us to sell our product at high enough prices to generate a profit.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

RISKS RELATED TO THE OFFERING

OUR STOCK PRICE COULD BE VOLATILE AND YOUR INVESTMENT COULD SUFFER A DECLINE IN VALUE.

The market price of our common stock has fluctuated significantly in response to a number of factors, many are which are beyond our control, including:

- regulatory developments relating to our PolyHeme blood substitute product;
- announcements by us relating to the results of our clinical trials of PolyHeme;
- developments relating to our efforts to obtain additional financing to fund our operations;
- announcements by us regarding transactions with potential strategic partners;
- announcements relating to blood substitute products being developed by our competitors;
- changes in industry trends or conditions;
- our issuance of additional debt or equity securities; and
- sales of significant amounts of our common stock or other securities in the market.

In addition, the stock market in general, and the Nasdaq National Market and the biotechnology industry market in particular, have experienced significant price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of listed companies. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our operating performance. In the past, securities class action litigation has often been instituted following periods of volatility in the market price of a company's securities. A securities class action suit against us could result in substantial costs, potential liabilities and the diversion of our management's attention and resources.

ANTI-TAKEOVER PROVISIONS CONTAINED IN OUR CHARTER AND BYLAWS COULD DISCOURAGE POTENTIAL TAKEOVER ATTEMPTS.

Our certificate of incorporation contains a "fair price" provision which requires approval of the holders of at least 80% of our voting stock, excluding shares held by certain interested stockholders and their affiliates, as a condition to mergers or certain other business combinations with, or proposed by, any holder of 15% or more of our voting stock, except in cases where approval of our disinterested directors is obtained or certain minimum price criteria and other procedural requirements are satisfied. In addition, our board of directors has the authority, without further action by our stockholders, to fix the rights and preferences and issue shares of preferred stock. These provisions, and other provisions of our certificate of incorporation and bylaws and Delaware law, may have the effect of deterring hostile takeovers or delaying or preventing changes in our control or management, including transactions in which stockholders might otherwise receive a premium for their shares over the then prevailing market prices.

THERE IS A LARGE NUMBER OF SHARES THAT MAY BE SOLD IN THE MARKET FOLLOWING THIS OFFERING, WHICH MAY DEPRESS THE MARKET PRICE OF OUR COMMON STOCK.

Sales of a substantial number of shares of our common stock or securities

convertible into or exercisable for our common stock in the public market following this offering could cause the market price of our common stock to decline. If there are more shares of common stock offered for sale than buyers are willing to purchase, then the market price of our common stock may decline to a market price at which buyers are willing to purchase the offered shares of common stock and sellers remain willing to sell the shares. All of the shares sold in the offering will be freely tradeable without

9

RISK FACTORS

restriction or further registration under the Securities Act, except for any shares purchased by our "affiliates" as defined in Rule 144 of the Securities Act.

YOU WILL EXPERIENCE IMMEDIATE AND SUBSTANTIAL DILUTION.

The public offering price of the securities offered hereby is likely to be substantially higher than the book value per share of our common stock. Investors purchasing common stock in this offering may, therefore, incur immediate dilution in net tangible book value per share of common stock. Investors will also incur additional dilution upon the exercise of outstanding stock options and warrants. See "Dilution" for a more detailed discussion of the dilution you will incur in this offering.

10

Use of proceeds

Unless we inform you otherwise in the prospectus supplement, we intend to use the proceeds of this offering to fund our post-enrollment activities in our clinical trial and to prepare and submit a BLA application to FDA, to prepare for the commercial launch of PolyHeme, to fund ongoing business operations and for other general corporate purposes. Our specific use of the proceeds of this offering will be described in the prospectus supplement that will accompany this prospectus. Pending any specific application, we may initially invest funds in short-term marketable securities.

Ratio of earnings to fixed charges and preference dividends

We reported no revenues or earnings during our last five fiscal years. During this period, we did not have any debt or related interest expense and were not a party to any capital lease arrangements. No preference securities were outstanding during this period.

Dilution

Our net tangible book value at August 31, 2004 was \$36,748,000, or \$1.72 per share of common stock. Net tangible book value per share represents total tangible assets less total liabilities divided by the number of outstanding shares of our common stock on August 31, 2004. Assuming that we issue an aggregate of \$100 million of common stock at an assumed public offering price of \$20.18 per share (the last reported sale price of our common stock on the Nasdaq National Market on December 17, 2004), with estimated net proceeds to us (after assumed commissions and expenses) of \$93,850,000, our pro forma net tangible

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

book value at August 31, 2004 would have been \$130,598,000 or \$4.96 per share. This represents an immediate increase in the tangible book value of \$3.24 per share to our existing stockholders and an immediate dilution of \$15.22 per share to new investors purchasing common stock in this offering, as illustrated in the following table:

Assumed public offering price per share(1).....	\$20.18
Net tangible book value per share as of August 31, 2004...	\$1.72
Increase per share attributable to new investors.....	\$3.24
Pro forma net tangible book value per share after offering.....	\$ 4.96

Dilution per share to new investors.....	\$15.22
	=====

(1) We assumed an offering price of \$20.18 per share based on the last reported sale price of the common stock on the Nasdaq National Market on December 17, 2004. The assumed offering price of the common stock at the time any common stock is offered hereby may differ significantly from the offering price assumed for purposes of this prospectus.

The computations in the table above assume no exercise of any outstanding stock options or warrants after August 31, 2004. At August 31, 2004, there were options outstanding to purchase a total of 1,238,000 shares of our common stock at a weighted average exercise price of \$8.81 per share and warrants outstanding to purchase a total of 212,392 shares of our common stock at a weighted average exercise price of \$9.00 per share. If any of these options or warrants are exercised, there will be further dilution to new investors.

If the securities offered hereby are common stock, the prospectus supplement will include a revised dilution table setting forth any increase in net tangible book value to existing stockholders and any dilution to new investors based on the proposed number of shares of common stock to be offered and the public offering price at the time of such offering.

 11

Description of the securities we may offer

We may offer up to \$100,000,000 of common stock, preferred stock, depository shares, stock purchase contracts, warrants and debt securities, in one or more offerings and in any combination. A prospectus supplement, which we will provide each time we offer securities, will describe the specific amounts, prices and terms of these securities.

We may sell the securities to or through underwriters, dealers or agents or directly to purchasers. We, as well as any persons acting on our behalf, reserve the sole right to accept and to reject in whole or in part any proposed purchase of securities. Each prospectus supplement will set forth the names of any underwriters, dealers or agents involved in the sale of securities described in that prospectus supplement and any applicable fee, commission or discount arrangements with them.

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

COMMON STOCK

We may issue shares of our common stock either alone or underlying other registered securities convertible into or exercisable or exchangeable for shares of our common stock. Holders of our common stock are entitled to receive dividends declared by our board of directors out of funds legally available for the payment of dividends, subject to rights, if any, of preferred stock holders. Currently, we do not pay a dividend. The holders of our common stock are entitled to one vote per share and are not entitled to cumulative voting rights for the election of our directors. The holders of our common stock have no preemptive rights.

PREFERRED STOCK AND DEPOSITARY SHARES

We may issue preferred stock, in one or more series, alone or underlying other registered securities convertible into or exercisable or exchangeable for shares of our preferred stock. Our board of directors or a committee designated by the board will determine the dividend, voting and conversion rights and other provisions of the preferred stock at the time of sale. Each series of preferred stock will be more fully described in the particular prospectus supplement that will accompany this prospectus, including redemption provisions, rights in the event of liquidation, dissolution or the winding up of Northfield, voting rights and conversion rights. We may also issue fractional shares of preferred stock that will be represented by depositary shares and depositary receipts. Each particular series of depositary shares will be more fully described in the prospectus supplement that will accompany this prospectus.

WARRANTS

We may issue warrants for the purchase of common stock, preferred stock, depositary shares or debt securities. We may issue warrants independently or together with other securities. The specific terms of any warrants will be described in the prospectus supplement that will accompany this prospectus.

STOCK PURCHASE CONTRACTS

We may issue stock purchase contracts, including contracts obligating holders to purchase from us, and us to sell to the holders, a specified number of securities, at a future date or dates, or similar contracts issued on a "prepaid" basis, which in each case are referred to herein as "stock purchase contracts." The price per share of securities and the number of shares of securities may be fixed at the time the stock purchase contracts are issued or may be determined by reference to a specific formula set forth in the stock purchase contracts. The stock purchase contracts will require either the stock purchase price be paid at the time the stock purchase contracts are issued or that payment be made at a specified future date. The stock purchase contracts also may require us to make periodic payments to

12

DESCRIPTION OF THE SECURITIES WE MAY OFFER

the holders of the stock purchase contracts or vice versa, and such payments may be unsecured or refunded on some basis. The specific terms of any stock purchase contracts will be described in the prospectus supplement that will accompany this prospectus.

DEBT SECURITIES

GENERAL

Edgar Filing: NORTHFIELD LABORATORIES INC /DE/ - Form 424B2

We may issue secured or unsecured obligations in the form of either senior or subordinated debt. The senior debt securities and the subordinated debt securities are together referred to in this prospectus as "debt securities." The senior unsecured debt securities will have the same rank as all of our other unsecured unsubordinated debt. The subordinated debt securities generally will be entitled to payment only after payment of our senior debt. Senior debt generally includes all debt for money borrowed by us, except debt that is stated in the instrument governing the terms of that debt to be not senior to, or to have the same rank in right of payment as, or to be expressly junior to, the senior debt securities. We may issue debt securities that are convertible into or exchangeable for shares of common stock or other securities or property.

The senior and subordinated debt securities will be issued under separate indentures between a trustee and us. We have summarized the general features of the debt securities to be governed by the indentures. These indentures have been filed as exhibits or will be incorporated by reference into the registration statement that we have filed with the SEC of which this prospectus is a part. We encourage you to read these indentures. Instructions on how you can get copies of these documents are provided above in "Where You Can Find More Information."

GENERAL INDENTURE PROVISIONS THAT APPLY TO SENIOR AND SUBORDINATED DEBT
The following general indenture provisions will apply to any senior and subordinated debt securities:

each indenture allows debt to be issued in series with terms particular to each series;

neither indenture limits the amount of debt that we may issue or generally provides holders any protection should we engage in a highly leveraged transaction;

the indentures allow us to merge or to consolidate with another U.S. entity or convey, transfer or lease our properties and assets substantially as an entirety to another U.S. entity, as long as certain conditions are met. If these events occur, the other company will be required to assume our responsibilities on the debt securities, and we will be released from all liabilities and obligations, except in the case of a lease;

the indentures provide that the trustee and we may generally amend the indenture with the consent of holders of a majority of the total principal amount of the debt outstanding in any series to change certain of our obligations or your rights concerning the debt. However, to change the payment of principal, interest or adversely affect the right to convert or certain matters, every holder in that series must consent; and

we may discharge the indentures and defease restrictive covenants by depositing sufficient funds with the trustee to pay the obligations when due, as long as certain conditions are met. The trustee would pay all amounts due to you on the debt from the deposited funds.

EVENTS OF DEFAULT

Each of the following is an event of default under the indentures:

principal not paid when due;

any sinking fund payment not made when due;

13

DESCRIPTION OF THE SECURITIES WE MAY OFFER

failure to pay interest for 30 days;

covenants not performed for 90 days after notice; and

certain events of bankruptcy, insolvency or reorganization of Northfield.

A prospectus supplement may describe deletions of, or changes or additions to, the events of default.

REMEDIES

Upon an event of default, other than a bankruptcy, insolvency or reorganization, the trustee or holders of 25 percent of the principal amount outstanding in a series may declare the outstanding principal, plus accrued interest, if any, immediately payable. However, the holders of a majority in principal amount may, under certain circumstances, rescind this action.

INDENTURE PROVISIONS THAT APPLY ONLY TO THE SUBORDINATED DEBT SECURITIES

The subordinated indenture provides that the subordinated debt securities will be subordinated to all senior debt as defined in the subordinated indenture.

14

Plan of distribution

We may sell the offered securities in and outside the United States through underwriters, dealers or agents or directly to purchasers. The prospectus supplement will set forth the following information:

the terms of the offering;

the names of any underwriters, dealers or agents;

the purchase price;

the net proceeds to us;

any delayed delivery arrangements;

any underwriting discounts and other items constituting underwriters' compensation;

the initial public offering price;

any discounts or concessions allowed, reallocated or paid to dealers; and

any commissions paid to agents.

If we use underwriters in the sale of the offered securities, the underwriters will acquire the securities for their own account. The underwriters may resell the securities from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. Underwriters may offer the securities to the public either through underwriting syndicates represented by one or more managing underwriters or directly by one or more firms acting as underwriters. Unless we inform you otherwise in the prospectus supplement, the obligations of the underwriters to purchase the securities will be subject to conditions, and

the underwriters will be obligated to purchase all the securities if they purchase any of them. The underwriters may change from time to time any initial public offering price and any discounts or concessions allowed or reallocated or paid to dealers.

During and after an offering through underwriters, the underwriters may purchase and sell the securities in the open market. These transactions may include over allotment and stabilizing transactions and purchases to cover syndicate short positions created in connection with the offering. The underwriters may also impose a penalty bid, in which selling concessions allowed to syndicate members or other broker-dealers for the offered securities sold for their account may be reclaimed by the syndicate if the offered securities are repurchased by the syndicate in stabilizing or covering transactions. These activities may stabilize, maintain or otherwise affect the market price of the offered securities, which may be higher than the price that might otherwise prevail in the open market. If commenced, these activities may be discontinued at any time. If we use dealers in the sale of securities, we will sell the securities to them as principals. They may then resell those securities to the public at varying prices determined by the dealers at the time of resale. The dealers participating in any sale of our securities may be deemed to be underwriters within the meaning of the Securities Act with respect to any sale of those securities. We will include in the prospectus supplement the names of the dealers and the terms of the transaction.

We may sell the securities directly. In that event, no underwriters, dealers or agents would be involved. We may also sell the securities through agents we designate from time to time. In the prospectus supplement, we will name any agent involved in the offer or sale of the offered securities, and we will describe any commissions payable by us to the agent. Unless we inform you otherwise in the prospectus supplement, any agent will agree to use its reasonable best efforts to solicit purchases for the period of its appointment. We may sell the securities directly to institutional investors or others

15

PLAN OF DISTRIBUTION

who may be deemed to be underwriters within the meaning of the Securities Act with respect to any sale of those securities. We will describe the terms of any of these sales in the prospectus supplement.

We may have agreements with the underwriter, dealers and agents to indemnify them against civil liabilities, including liabilities under the Securities Act, or to contribute with respect to payments that the underwriter, dealers or agents may be required to make.

Underwriters, dealers and agents may engage in transactions with us or may perform services for us in the ordinary course of their businesses.

Underwriters, dealers and agents participating in a sale of securities may be deemed to be underwriters as defined in 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 under the Securities Act.

16

Legal matters

The validity of the securities offered herein will be passed upon for us by Baker & McKenzie LLP, Chicago, Illinois. If the securities are distributed in an underwritten offering, the underwriters will be advised by their own legal counsel with respect to any offering.

Experts

The financial statements of Northfield Laboratories Inc. as of May 31, 2004, and for each of the years in the three-year period ended May 31, 2004 and for the cumulative period from June 19, 1985 (inception) have been incorporated by reference herein and in the registration statement in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of such firm as experts in accounting and auditing.

With respect to the unaudited interim financial information of the period ended August 31, 2004, incorporated by reference herein, the independent registered public accounting firm has reported that they applied limited procedures in accordance with professional standards for a review of such information. However, their separate report included in Northfield Laboratories Inc.'s quarterly report on Form 10-Q for the quarter ended August 31, 2004, incorporated by reference herein, states that they did not audit and they do not express an opinion on that interim financial information. Accordingly, the degree of reliance on their report on such information should be restricted in light of the limited nature of the review procedures applied. The independent registered public accounting firm is not subject to the liability provisions of Section 11 of the Securities Act of 1933 for their report on the unaudited interim financial information because that report is not a "report" or a "part" of the registration statement prepared or certified by the independent registered public accounting firm within the meaning of Sections 7 and 11 of the Act.

The audit report covering the May 31, 2004 financial statements refers to a change in accounting due to the adoption of the provisions of Statement of Financial Accounting Standards No. 143, "Accounting for Asset Retirement Obligations."