



Overcoming Barriers to Drug Development in Lupus

Final Report

Prepared for: The Lupus Foundation of America, Inc.

Submitted by: The Lewin Group, Inc.

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EXECUTIVE SUMMARY

Lupus (also known as systemic lupus erythematosus or SLE) is a chronic, severe autoimmune disease for which there is presently no cure. In autoimmune disease, a person's own immune system turns its attack against the body's organs, tissues, and cells. In some diseases, the target of the attack is limited to a particular part of the body, but in lupus, the attack can affect multiple organs and organ systems, including the skin, joints, heart, lungs, kidneys, and brain.¹ No two cases of lupus are alike. Although it is a chronic disease, lupus typically waxes and wanes, meaning that people with lupus experience periods of illness, called "flares," and periods of relative wellness, or remission.² In severe lupus, such flares in the organs and organ systems can lead to kidney failure, heart attack, atherosclerosis, or even death.

Today, approximately 1.5 million Americans suffer from the disease and the worldwide prevalence is estimated to exceed 5 million.³ Although lupus primarily affects women in their early working and childbearing years, men, children, and teenagers can develop the disease as well. Lupus can interfere with a woman's ability to work, have or raise a family, or in some cases, even care for herself. Though people of all races and ethnic groups can develop lupus, women of color are two-to-three times more likely to develop lupus. Of particular concern are the disease's effects on African-American women, who are more likely to be affected at an earlier age, experience greater disease severity, have the highest overall death rate among people with lupus, and are three times more likely to die from the disease than Caucasian women.⁴

It has been 50 years since the U.S. Food and Drug Administration (FDA) last approved a new drug specifically to treat lupus. In the absence of any new drug approvals since then, people with lupus and their providers have had to choose among a range of currently available treatment options, the vast majority of which have not been approved by the FDA for lupus. As a result, the current standard of care for people with lupus involves extensive off-label use of medicines. This practice has profound implications for people with lupus and their providers, making it difficult to access particular medications used to treat lupus. Moreover, given greater payer scrutiny and demand for justification for off-label prescribing, physicians and their staff must devote greater time engaging with insurance companies to secure reimbursement for these medicines for patients with few or no viable therapeutic options. These challenges are exacerbated for people with lupus who are underinsured or lack health insurance altogether.

Side-effect profiles of the currently available treatment options for people with lupus are varied and often severe. They include fatigue, hair loss, joint pain, bone loss and osteoporosis, type 2 diabetes, and other adverse health effects. Immunosuppressants, one class of lupus treatments, can be particularly harmful for people with lupus, including the large proportion who are women of child-bearing age. Their long-term use can cause sterility, increase the risk of

¹ National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The Future Directions of Lupus Research, 2007.

² NIAMS. Systemic Lupus Erythematosus, 2003.

³ Department of Health and Human Services, Office of Minority Health. Accessed on August 18, 2009 at: <http://www.omhrc.gov/templates/browse.aspx?lvl=3&lvlid=282>.

⁴ Centers for Disease Control and Prevention, Trends in Deaths from Systemic Lupus Erythematosus - United States, 1979-1998. MMWR 2002;51:371-4.

infection, damage the liver, and may contribute to the higher incidence of certain cancers experienced by lupus patients (e.g., a three- to four-fold increase in non-Hodgkin lymphoma).⁵

Lupus continues to exercise a heavy toll on its victims, their loved ones, and the communities in which they work and live. Beyond even a single FDA-approved treatment, it is likely that an arsenal of FDA-approved treatments is needed to help manage this debilitating and life-threatening disease that manifests itself so differently across affected patients. Developing new treatments for lupus that are safe, effective, and tolerable has been particularly challenging given certain steep barriers to drug development and approval in lupus. Among these, some of the most prominent are the poorly understood biology of the disease, difficulties in clinical trial participant selection, challenges to selection of appropriate clinical trial endpoints, adapting instruments and tools for measuring disease activity in clinical trials, and the confounding role of background medications. These barriers are described on pages 10-13 of this report.

The Lupus Foundation of America, Inc. (LFA), commissioned The Lewin Group (Lewin) to prepare a report focusing on the multi-dimensional challenges related to the development and approval of new therapies to treat lupus and to develop recommendations for a path forward to address the unmet needs of individuals with lupus. The process for developing this report comprised two parts. The first was conducting a series of interviews with lupus experts across the country to identify the main current barriers to lupus drug development and approval. The second was to convene and facilitate an expert panel to elicit a broad range of informed opinions on obstacles to lupus drug development and approval and possible approaches for overcoming them.

Recommendations

Recommendation 1: A new coordinated national effort should be organized to overcome the barriers to drug development and approval in lupus. This effort must engage the agents that manage or have the potential to influence the barriers identified in this report. These include such federal agencies as the FDA; National Institutes of Health (NIH), including the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Allergy and Infectious Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, and National Heart, Lung, and Blood Institute; Agency for Healthcare Research and Quality; Centers for Disease Control and Prevention (CDC); DHHS Office of Minority Health; Department of Defense; Veterans Health Administration; industry; the lupus scientific community; national advocacy and health professional organizations; academic institutions; legislators; and the LFA. The precedent for productive collaboration involving some of these stakeholders has already resulted in the following:

- **Collective Data Analyses Initiative:** This initiative arose from the June 2009 expert panel meeting facilitated by The Lewin Group. Its aim is to stimulate data-sharing and more extensive analyses across companies and other organizations.
- **CDC National Lupus Patient Registry:** As encouraged by the LFA, Congress funded the establishment of this registry at CDC to develop the first comprehensive and reliable set of epidemiological data on the incidence and prevalence of all forms of lupus among various ethnic and racial groups.
- **Defining a lupus “flare”:** The LFA has coordinated an international effort to finalize a consensus definition of a lupus flare.

⁵ Gayed M, Bernatsky S, Ramsey-Goldman R, et al. Lupus and cancer. *Lupus* 2009;18(6):479-85.

Recommendation 2: The federal biomedical research effort should be greatly expanded to develop a better understanding of the biological mechanisms of lupus, including more basic and translational research on the pathophysiology and pathogenesis of the disease. This effort should focus on integration of bench research with clinical investigation.

Recommendation 3: The scientific community and NIH should collaborate on a research agenda to provide a clear pathway to drug development in lupus. The agenda should be shared with all relevant public and private entities having an interest in the disease.

The scientific community, the LFA, and its partners should coordinate a series of workshops and related expert meetings to address the design of clinical trials. Topics should include, but not be limited to: clinical trial participant selection, clinical trial endpoints, clinical measures/instruments and tools, and the role of background medications and the placebo effect, which are understood to have played critical roles in the failure of recent clinical trials. These efforts should generate a series of white papers addressing these issues. Consensus opinions, where they emerge, should be shared with regulators and legislators, as appropriate.

Recommendation 4: The NIH should establish and fund a consortium to expedite the identification and validation of biomarkers for lupus. This may include periodic meetings to assess the current state of knowledge, share data, and coordinate public and private sector research activities on biomarkers. Since 2004, a “biomarkers consortium” comprising ten academic medical centers has existed; however, funding for this effort has been limited.

Recommendation 5: The scientific community and industry should establish a technical expert panel to assess the two predominant instruments currently used in lupus clinical trials, the British Isles Lupus Activity Group (BILAG) Index and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), as well as other potential lupus assessment instruments, including industry-generated responder indices derived from the BILAG Index and SLEDAI. This panel may require a series of meetings and related staff support over a one-to-two year period.

Consideration should be given to such issues as:

- Improving inter-rater reliability
- Rigor of investigator training and education programs for using the instruments
- Developing an effective adjudication process
- Employing centralized readers
- Implementing data cleaning processes

Recommendation 6: The LFA and its partners should conduct a systematic review of cyclophosphamide to assess its treatment effect. Cyclophosphamide is a chemotherapy used to treat moderate-to-severe flares, and is considered the standard of care, but has not been approved by the FDA for the treatment of lupus. If the treatment effect of cyclophosphamide could be established, it would offer an alternative validated path to FDA approval by allowing for a non-inferiority study of a drug candidate for lupus nephritis.

- This effort could start with a formal systematic review, including meta-analysis as appropriate, of existing data generated from previous clinical trial experiences involving cyclophosphamide.
- The findings of the systematic review could be used to inform decisions regarding whether, and if so, how, to approach the FDA, and to pursue further clinical trials or other studies.
- As appropriate, findings of this effort could be incorporated into an update of the FDA Guidance for Industry, Systemic Lupus Erythematosus – Developing Drugs for Treatment, Draft Guidance, 2005.

Recommendation 7: The current interpretation of regulations pertaining to clinical trial design and related standards of evidence used to evaluate investigational drugs for lupus should be reexamined by the FDA, in cooperation with experts from industry, research, and the health professions.

- The hurdle of having to demonstrate to the FDA the clinical superiority of an experimental medicine against a non-approved standard of care may be impractical. In cooperation with independent experts, regulators should reassess the utility of non-inferiority and other clinical trial designs for lupus drug candidates. Consideration should be given to the totality of evidence on efficacy, adverse events, and pertinent patient reported outcomes, including such secondary endpoints as quality of life measures, when evaluating the results of lupus clinical trials.
- Toward integration of regulatory processes and expertise for drug development for the complex disease of lupus, FDA should reexamine the need for better coordination between its two review divisions responsible for evaluating lupus drug candidates: the Division of Anesthesia, Analgesia, and Rheumatology Products and the Division of Cardiovascular and Renal Drug Products. The former is responsible for reviewing drug candidates for general lupus; the latter is responsible for reviewing drug candidates for lupus nephritis.
- As appropriate, findings of this effort could be incorporated into an update of the FDA Guidance for Industry, Systemic Lupus Erythematosus – Developing Drugs for Treatment, Draft Guidance, 2005.

INTRODUCTION

This report examines the current state of lupus drug development and approval and presents a set of recommendations for a path forward to address the unmet needs of individuals with lupus. It begins with an overview of the unique challenges posed by the personal and population burden of lupus, including the nature of the disease, the difficulty of arriving at a clear diagnosis, and the limited number of treatment options available to people with lupus and their side effects. The report then considers the current barriers to drug development and approval, detailing how each has contributed to the longstanding inadequate medical response to lupus. The report concludes with a series of recommendations for overcoming these barriers.

I. A DIFFERENT DISEASE PARADIGM: THE UNIQUE CHALLENGES OF LUPUS

“Part of the reason why lupus remains challenging and mysterious to people is because it doesn’t fit the classic disease paradigm. There isn’t one clinical feature or symptom.” — S. Sam Lim, Emory University⁶

A. A Perilous Disease

Lupus is a chronic, severe autoimmune disease for which there is presently no cure. In autoimmune disease, a person’s own immune system turns its attack against the body’s organs, tissues, and cells. In some diseases, the target of the attack is limited to a particular part of the body, but in lupus, the attack can affect multiple organs and organ systems, including the skin, joints, heart, lungs, kidneys, and brain.⁷ No two cases of lupus are alike. In its more severe form, lupus can lead to kidney failure, heart attack, atherosclerosis, or even death.

Today, approximately 1.5 million Americans suffer from the disease and the worldwide prevalence is estimated to exceed 5 million. Although lupus primarily affects women in early adulthood, men, children, and teenagers can develop the disease as well. Though people of all races and ethnicities can develop lupus, women of color are two-to-three times more likely to develop the disease. Of particular concern are the disease’s effects on African-American women with lupus, who are more likely to be affected at an earlier age, experience greater disease severity, have the highest overall death rate among people with lupus, and are three times more likely to die from the disease than Caucasian women.⁸

Though lupus is considered a prototypical autoimmune disease, it stands apart from other chronic immunologic diseases in that the majority of therapies currently used have not been approved by the FDA for lupus and can have side effects more severe than the disease itself, making them untenable for long-term use. People with lupus display a variety of symptoms that wax and wane.⁹ Most people with lupus experience episodes called “flares”—worsening

⁶ S. Sam Lim, as quoted in Von Tesoriero, H. Drugs in testing show promise for lupus. Wall Street Journal, January 23, 2007.

⁷ NIAMS. 2007.

⁸ CDC. 2002.

⁹ Food and Drug Administration. Guidance for Industry. Systemic Lupus Erythematosus – Developing Drugs for Treatment, Draft Guidance, 2005.

signs and symptoms that eventually improve or may disappear completely for a time.¹⁰ Among these, some of the more common include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.¹¹ When lupus is systemic, a flare may contribute to damage to one or more organ systems. For some people with lupus, signs and symptoms may emerge suddenly. For others, they develop slowly. Symptoms may be mild or severe, temporary or permanent.¹² As a result, lupus can interfere with a woman's ability to work, have or raise a family, and, in some cases, even care for herself.¹³

B. Elusive and Complex Diagnosis

Although early diagnosis can enable intervening on the disease's cascading effects and mitigate its potential for harm, lupus has proved extraordinarily difficult to diagnose.¹⁴ It can sometimes take years before an accurate diagnosis is made. Because its many symptoms differ in type and severity, physicians frequently fail to recognize the disease. In part, this failure reflects insufficient education regarding lupus among primary care physicians who often serve as gatekeepers to such medical specialists as rheumatologists and nephrologists with more experience with the disease. It also reflects the absence of any confirmatory diagnostic test for lupus analogous to, for example, a fasting plasma glucose test used to diagnose diabetes. The lack of reliable and specific biomarkers¹⁵ for lupus limits physicians' ability to detect the disease, manage patients, and prescribe new therapies. Although preliminary research has identified a small set of promising candidate biomarkers for lupus, these are far from validated in rigorous studies for clinical use.¹⁶ Taken together, these factors lead not only to under-diagnosis but to misdiagnosis, which often lead to clinical interventions that exacerbate the disease and may even trigger flares.

C. No FDA-Approved Drug in 50 Years

It has been 50 years since the FDA last approved a new drug specifically to treat lupus (Figure 1). Whereas in the past a diagnosis of lupus often meant a decreased life span due to internal organ system involvement or to toxic effects of therapy, recent improvements in care have extended the survival of people with lupus who experience some of the most severe and life-threatening

¹⁰ For the purposes of identifying flares in the context of clinical trials, a 2005 FDA guidance states that a "flare should reflect an episode of increased disease activity and should correlate with a need for increase in or change in treatment on clinical grounds. Criteria for a major flare might include initiation of high-dose glucocorticoid therapy, a change in dose of immunosuppressive therapy, hospitalization or death." FDA, Guidance for Industry. Systemic Lupus Erythematosus – Developing Drugs for Treatment. Draft Guidance, 2005.

¹¹ NIAMS. 2003.

¹² NIAMS. 2007.

¹³ Ibid.

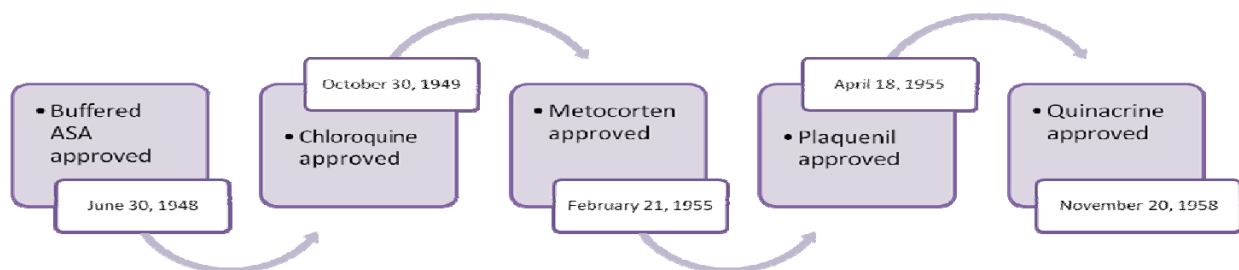
¹⁴ CDC, Eliminate Disparities in Lupus, Accessed on August 8, 2009 at: <http://www.cdc.gov/omhd/AMH/factsheets/lupus.htm>.

¹⁵ A biomarker is an objectively measured characteristic that is used as an indicator of normal biological processes, natural history of disease, or effect of a therapy. Examples are blood pressure for hypertension, bone density for osteoporosis, and glycated hemoglobin for diabetes.

¹⁶ Liu CC, Manzi S, Ahearn JM. Biomarkers for systemic lupus erythematosus: a review and perspective. *Curr Opin Rheumatol* 2005;17(5): 543-9.

manifestations of the disease.^{17,18} However, existing treatments for lupus remain far from adequate, largely because of their deleterious side effects. Moreover, many people with lupus continue to face significant challenges coping with the disease and its progression to end-stage organ involvement.¹⁹ The absence of FDA-approved treatments over these last five decades for this debilitating and life-threatening disease is the result of a cumulative failure of biomedical research and processes for new drug development and validation in this field.

Figure 1: No Lupus Drug Approvals Since 1958



Source: Lupus Foundation of America, Inc.

This failure has extended into the recent years of growing scientific, clinical, and commercial interest in the disease. Across the past decade, pharmaceutical companies have launched drug discovery and development programs specifically designed to target the disease. The goal of this research has been to develop treatment options for people with lupus that are safer, suitable for long-term use, and approved by the FDA specifically for lupus.

Despite a considerable investment of time, talent, and financial resources, the experience of the past decade has been disappointing.^{20,21} Several promising compounds have failed in clinical trials for lupus and for more specific lupus-related kidney disease, known as lupus nephritis (Table 1). While some of these drugs are still undergoing clinical trials for certain lupus-related indications, including lupus nephritis, each has previously failed to achieve its intended levels of improvement in patient outcomes (primary endpoints) in a general lupus trial.

¹⁷ Trager J, Ward MM. Mortality and causes of death in systemic lupus erythematosus. *Curr Opin Rheumatol* 2001;13(5):345-51.

¹⁸ Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. *Medicine (Baltimore)* 2006;85(3):147-56.

¹⁹ FDA. 2005.

²⁰ Von Tesoriero H. Drugs in testing show promise for lupus. *Wall Street Journal*, January 23, 2007.

²¹ Pollack A. Drug from Genentech and Biogen fails as lupus treatment. *New York Times*, April 30, 2008.

Table 1: Recent Lupus Clinical Trials Yielding Negative Results

Drug	Clinical Trial Sponsor(s)	Indication
Mycophenolate mofetil (CellCept®)	Vifor Pharma (formerly Aspreva Pharmaceuticals Corporation)	Lupus nephritis
TV-4710 (Edratide)	Teva Pharmaceutical Industries	Lupus
Abatacept (Orencia®)*	Bristol-Myers Squibb Company	Lupus
Prasterone (Prestara™)	Genelabs Technologies, Inc.	Lupus
Abetimus sodium (Riquent™)	La Jolla Pharmaceutical Company	Lupus and lupus nephritis
Rituximab (Rituxan®)	Genentech, Inc.	Lupus and lupus nephritis

*Currently undergoing a clinical trial for lupus nephritis

The persistent lack of a success along a regulatory pathway has consequences for the willingness of drug manufacturers to pursue FDA approval. Presently, some in industry perceive no clear pathway or system in place for the development of lupus therapies. Given the factors that can confound demonstrating a treatment effect of a new lupus therapy—including the difficulty of demonstrating clinical superiority against a non-approved standard of care, confounding effects of background medications, and challenges of selecting clinical endpoints—embarking on clinical trials for drugs that are already being used widely on an off-label basis can be risky.²² The recent string of trial failures poses disincentives for manufacturers, irrespective of patent status, of pursuing clinical trials that are designed to meet a standard of superiority versus a comparator.

These challenges notwithstanding, there are some promising compounds in the R&D pipeline. One of these, belimumab (Benlysta™, formerly LymphoStat-B®), recently met the primary endpoint in BLISS-52, the first of two pivotal phase 3 trials in participants with serologically active lupus. Results from a recent placebo-controlled trial showed that belimumab plus standard of care achieved a clinically and statistically significant improvement in patient response rate at week 52, compared with standard of care alone. Study results also showed that belimumab was generally well tolerated, with comparable adverse event rates to placebo groups.²³

Though the results from the recent belimumab trial are promising, considerable hurdles remain to secure FDA approval, including positive results for a second phase 3 trial (scheduled to be reported in November 2009). Lupus continues to exercise a heavy toll, and beyond the current promise of this one compound, this heterogeneous disease is likely to require an arsenal of innovative FDA-approved treatments.

²² In some severe cases, the chemotherapy agent cyclophosphamide is considered standard care, though it is not approved by the FDA for treatment of lupus.

²³ Human Genome Sciences and GlaxoSmithKline announce positive phase 3 study results for BENLYSTA™. Accessed July 20, 2009 at: <http://www.hgsi.com/latest/human-genome-sciences-and-glaxosmithkline-announce-positive-phase-3-study-results-for-benl.html>.

D. Current Treatment Options: Implications of Off-Label Drug Use

The majority of drugs used today to manage lupus lack FDA approval for a lupus indication. This applies not only to some of the drugs used to treat milder forms of the disease, but also to the immunosuppressant and experimental medicines used to treat its most severe manifestations. The practice of prescribing medicines for a purpose outside the scope of indications specified in a drug's FDA-approved labeling is known as "off-label" use. The gap between drugs that are approved for lupus and those that are used in practice reflects the inability to date of lupus drug trials to meet the regulatory standards required for FDA approval.

Given the lack of highly effective FDA-approved treatments for lupus, off-label prescribing is likely to remain a typical component of clinical care for people with the disease. This practice has profound implications for people with lupus and their providers. For people with lupus, off-label prescribing can make it difficult to access particular medications used to treat lupus, especially some of the more costly prescriptions that are infrequently covered by health insurance plans, thereby generating significant reimbursement challenges for vulnerable patients. Given greater payer scrutiny and demand for justification for off-label prescribing, physicians and their staff members must devote greater time to engaging with insurance companies to secure reimbursement for these medicines for patients with few or no viable therapeutic options. In some cases, physicians must admit their patients to hospitals to ensure their access to treatment. These challenges are exacerbated for people with lupus who are underinsured or lack health insurance altogether. As applies to certain other conditions, having to rely on off-label medications as standard care for lupus can impede access to those medications.

E. Severe Side-Effect Profiles of Current Treatment Options

While efforts to manage lupus have improved over the past half century—in part because of the growing off-label use of certain drugs—the quality of life for many people with lupus remains compromised. Some of the burden of this disease arises from the considerable side effects of certain treatments.

While aggressive treatments can mitigate some of the most severe manifestations of the disease, they carry substantial risks. Corticosteroids can have serious long-term side effects, including weight gain, easy bruising, osteoporosis, high blood pressure, diabetes, mood swings and increased risk of infection. These risks increase with higher doses and longer-term therapy. Side effects of antimalarials include insomnia, high blood pressure, diabetes, and osteoporosis leading to bone fractures and fragility. Immunosuppressants, one class of lupus treatments, can be particularly harmful for people with lupus, who are largely women in their child-bearing years. Long-term use of immunosuppressants can cause sterility, increase the risk of infection, damage the liver, and may contribute to the higher incidence of certain cancers experienced by lupus patients (e.g., a three- to four-fold increase in non-Hodgkin lymphoma).²⁴

²⁴ Gayed M, Bernatsky S, Ramsey-Goldman R, et al. Lupus and cancer. *Lupus* 2009;18(6):479-85.

II. METHODOLOGY

The Lupus Foundation of America, Inc., commissioned The Lewin Group to conduct a comprehensive study of the multidimensional challenges related to the development and approval of new therapies to treat lupus and to develop recommendations for a path forward to address the unmet needs of people with lupus. Lewin's approach for conducting this study comprised three parts: (1) conducting expert interviews to identify the current barriers to lupus drug development and approval, (2) convening and facilitating an expert panel meeting to elicit a broader range of opinions on the obstacles to lupus drug development and means for overcoming them, and (3) developing a report that summarizes the barriers identified and outlines recommendations for overcoming the barriers to drug development and approval in lupus.

A. Conduct Expert Interviews

Lewin began the study to identify the current barriers to drug development and approval in lupus by conducting a series of 19 telephone interviews with lupus experts representing academia, industry, and government. These interviews followed a semi-structured format, ultimately focused on the goal of identifying what each expert considered to be the "top barriers to lupus drug development and approval" today. The secondary aims of these interviews were to review the purpose and format of the forthcoming panel meeting and gain each expert's input regarding the main topic areas that should be discussed at the meeting. The information elicited from each of these expert interviews was subsequently used to develop the expert panel meeting agenda and provide background information and other input to this report.

B. Convene Expert Panel Meeting

Lewin convened and facilitated a two-day expert panel meeting held June 1-2, 2009, in Washington, DC. A multidisciplinary group of experts participated, including representatives from FDA, NIH, industry, and academic institutions and research centers across the country and globally. Rather than to achieve full consensus among the meeting participants across all of the discussion areas, the aim of this meeting was to elicit a broad range of informed opinions on the obstacles to lupus drug development and approval and means for overcoming them.

C. Develop Report

Using the information obtained from the expert interviews, related background information, and deliberations of the expert panel meeting, Lewin developed this report to: (1) summarize the key barriers to drug development and approval in lupus and (2) provide recommendations for overcoming the barriers to drug development and approval in lupus.

III. IDENTIFYING THE BARRIERS TO DRUG DEVELOPMENT IN LUPUS

The various barriers to lupus drug development and approval that were identified in the course of the interviews and during the expert panel meeting can be grouped into five main categories, summarized below: biology of the disease, clinical trial participant selection, selection of clinical endpoints, instruments and tools, and background medications.

A. Biology of the Disease

Lupus is a poorly understood, heterogeneous disease that presents itself differently from one patient to the next. The precise causes of lupus are unknown. While there is strong evidence for a genetic component and for infectious and non-infectious environmental contributors to lupus, any combination of these appears to differ across individuals. The limited understanding of the biological basis of the disease among different patients hinders identification of molecular targets and disease pathways for new drug development. Although some research has been conducted to learn more about some of its environmental triggers—certain medications or ultraviolet light, hormones, toxins, air pollution—much remains unknown about the etiology of lupus in order to help inform the development of targeted therapies.²⁵ The heterogeneity of its presentation across patients and a clinical course characterized by flares and remissions that are difficult to predict exacerbate the challenges of conducting clinical trials of investigational therapies.

B. Clinical Trial Participant Selection

Enrolling sufficient numbers of patients to conduct statistically valid clinical trials is especially challenging in lupus. First, in contrast to the uniformity in patient symptoms and risk factors that is typically sought in clinical trials to better enable determination of treatment effects, the heterogeneity of lupus makes it virtually impossible to assemble uniform patient groups. Further, because lupus symptoms wax and wane, individuals' disease activity can complicate clinical trial enrollment that may be based on presence or level of disease activity or assessment of outcomes at any particular duration of follow-up. These aspects of diversity in patients enrolled in a lupus trial can confound the assessment of drug efficacy and safety. Second, in contrast to such diseases as hypertension, coronary artery disease and diabetes, the pool of lupus patients available for enrollment in clinical trials is small, which can increase the difficulty of enrollment and delay and lengthen clinical trials. This disease heterogeneity among a smaller overall patient population raises the hurdles to new drug development and validation.

C. Selection of Clinical Endpoints

Success in clinical trials requires demonstrating a statistically-significant treatment effect of an active intervention against a placebo or current standard of care. Such an effect need not be broad-based. It can comprise just a single clinical endpoint that is known to be associated with a meaningful clinical outcome. In general, the more specific the endpoint (including patient outcomes), the easier it is to measure. Endpoints such as blood pressure and serum cholesterol can be quantified readily and reliably. But for lupus, where diverse symptoms wax and wane unpredictably, determining what, how, and when to measure can be far more complex. These problems are compounded by how these generally accepted methods for measuring improvements in people with lupus during clinical trials are used.

It may be possible eventually to rely on a set of yet-to-be discovered biomarkers to determine whether a drug candidate is capable of yielding a statistically and clinically significant treatment effect versus a placebo. Presently, however, lupus clinical trials typically rely on one of two

²⁵ NIAMS. 2007.

distinct approaches. The first is to target certain disease activity criteria or other measures that may indicate a change in the course of the disease. The second is to focus on a specific organ, typically the kidney, and target a “harder” clinical endpoint such as proteinuria, which, while silent to the patient, is an important marker for lupus nephritis that is readily measured using a laboratory test. Thus far, however, neither approach has contributed to an FDA approval.

While unique in many respects, lupus is not the only disease to pose such a challenge. Other medical conditions exist for which clearly discernible clinical endpoints have been difficult to define. There are some encouraging exceptions, however. Among these, perhaps the most significant that may be instructive for lupus drug development is rheumatoid arthritis (RA). Like lupus, RA is an autoimmune disease that frustrated R&D efforts for decades due to the absence of a generally accepted method for estimating improvement in disease activity during clinical trials. Many promising RA drug candidates ultimately failed to secure FDA approval due to their inability to demonstrate clinical efficacy in placebo-controlled trials. The development of a composite index for estimating improvement in individual RA patients during trials of slow-acting, disease-modifying antirheumatic drugs,²⁶ however, was a turning point in RA drug development, as the proposed criteria for individual improvement helped account for the placebo response. As such, the RA experience offers a model for lupus drug development that, if successfully deployed, would increase the chances of success.

Prior to embarking on costly, time-consuming phase 3 clinical trials, industry and academic researchers could conduct smaller, targeted phase 2 trials to establish proof of concept, identify potential target populations, establish a dosing regimen, and, potentially, develop more attainable endpoints for a larger, pivotal phase 3 study. At present, this approach appears to have been taken successfully by Human Genome Sciences, which used a retrospective analysis of its phase 2 data to develop a patient responder-index that proved instrumental in its recent successful phase 3 trial of Benlysta and is currently being used by BMS in clinical trials for abatacept.

D. Instruments and Tools

Assessing an investigational therapy in clinical trials requires one or more validated biomarkers, outcomes, or other parameters, often in the form of an index or instrument. In lupus, the two predominant indices for measuring disease activity are the BILAG Index and SLEDAI, both of which involve sets of multiple clinical parameters and provide overall individual scores.²⁷ Although both have proven validity with respect to assessing an individual’s disease activity, neither was designed for use in clinical trials. The translation of these disease activity indices from clinical practice to clinical trials has been described as a “painful growing process.”²⁸ Moreover, efforts to derive endpoints for drug efficacy from those respective instruments that are clinically meaningful as well as clinically achievable have proved extraordinarily challenging. As one lupus expert recently explained, “the real challenge

²⁶ Paulus HE, Egger MJ, Ward JR, Williams HJ. Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. *Arthritis Rheum* 1990;33(4):477-84.

²⁷ Petri M. Disease activity assessment in SLE: do we have the right instruments? *Ann Rheum Dis* 2007;66(Suppl 3):iii61-4.

²⁸ *Ibid.*

we face is how to construct appropriate clinical endpoints from the available instruments that currently exist.”²⁹

E. Role of Background Medications

The heterogeneity of lupus among patients and the range of medical regimens they follow augment the complexity of design and conduct of lupus clinical trials. The absence of a single, approved standard of care for lupus further compounds the challenge, as both the disease and the effort to treat it are moving targets. As one rheumatologist involved in lupus care and research explained, “Lupus trials involve a standard of care plus an experimental drug versus a standard of care plus placebo, *but the standard of care is not standardized.*”³⁰ In more typical clinical trials, study participants commonly refrain from taking additional medicines for their underlying condition in order to better isolate and quantify the effects of the investigational therapy. In contrast, participants in lupus trials take a wide range of medicines, including steroids, antimalarials, and powerful immunosuppressants.

The presence of these powerful, yet unapproved “background medicines” may have masked or confounded the impact of investigational therapies in many recent lupus clinical trials for two main reasons. The first is by contributing to a higher-than-expected positive response rate in the “placebo” or control arm of a trial, thereby raising the hurdle for demonstrating a net treatment effect for any experimental lupus candidates. The second is that study participants, regardless of the trial arm to which they are assigned, must continue to adhere to a non-approved standard of care for which the therapeutic effect remains unknown.

This issue poses a regulatory dilemma. Because the therapeutic effects of these background medicines have not been established in previous clinical trials, they are considered no more effective than a placebo from a regulatory perspective. If this were not the case, drug developers might gain FDA approval for a novel lupus drug or biologic by demonstrating that their candidate was “non-inferior” to the existing standard of care. As a lupus expert recently suggested, “Fifty percent of the barriers associated with developing new drugs for lupus would be removed if the FDA accepted non-inferiority trials for lupus candidates.”³¹ Indeed, such a path is frequently and successfully pursued by drug manufacturers in other disease areas. It remains blocked to lupus drug developers, however, despite agreement among many clinicians involved in managing lupus regarding the effectiveness of many of the drugs currently used to treat the disease.

IV. RECOMMENDATIONS

The lack of any new medications approved for lupus by the FDA since the 1950s—accompanied by only limited progress in key enabling elements of new drug development, including understanding of the biological mechanisms of the disease, biomarker development, validation of indices for use in clinical trials, and others—calls for a new coordinated national effort to overcome the barriers to drug development in lupus.

²⁹ Anonymous lupus expert, Lewin interview, June 2009.

³⁰ Anonymous lupus expert, Lewin interview, April 2009.

³¹ Anonymous lupus expert, Lewin interview, May 2009.

The following recommendations reflect deliberations of more than 40 participants from industry, government, and academia who served on the expert panel held in Washington, DC, on June 1-2, 2009, and the series of expert interviews conducted prior to that event.

Recommendations

Recommendation 1: A new coordinated national effort should be organized to overcome the barriers to drug development and approval in lupus. This effort must engage the agents that manage or have the potential to influence the barriers identified in this report. These include such federal agencies as the FDA; NIH, including the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Allergy and Infectious Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, and National Heart, Lung, and Blood Institute; Agency for Healthcare Research and Quality; CDC; DHHS Office of Minority Health; Department of Defense; Veterans Health Administration; industry; the lupus scientific community; national advocacy and health professional organizations; academic institutions; legislators; and the LFA. The precedent for productive collaboration involving some of these stakeholders has already resulted in the following:

- **Collective Data Analyses Initiative:** This initiative arose from the June 2009 expert panel meeting facilitated by The Lewin Group. Its aim is to stimulate data-sharing and more extensive analyses across companies and other organizations.
- **CDC National Lupus Patient Registry:** As encouraged by the LFA, Congress funded the establishment of this registry at CDC to develop the first comprehensive and reliable set of epidemiological data on the incidence and prevalence of all forms of lupus among various ethnic and racial groups.
- **Defining a lupus “flare”:** The LFA has coordinated an international effort to finalize a consensus definition of a lupus flare.

Recommendation 2: The federal biomedical research effort should be greatly expanded to develop a better understanding of the biological mechanisms of lupus, including more basic and translational research on the pathophysiology and pathogenesis of the disease. This effort should focus on integration of bench research with clinical investigation.

Recommendation 3: The scientific community and NIH should collaborate on a research agenda to provide a clear pathway to drug development in lupus. The agenda should be shared with all relevant public and private entities having an interest in the disease.

The scientific community, the LFA, and its partners should coordinate a series of workshops and related expert meetings to address the design of clinical trials. Topics should include, but not be limited to: clinical trial participant selection, clinical trial endpoints, clinical measures/instruments and tools, and the role of background medications and the placebo effect, which are understood to have played critical roles in the failure of recent clinical trials. These efforts should generate a series of white papers addressing these issues. Consensus opinions, where they emerge, should be shared with regulators and legislators, as appropriate.

Recommendation 4: The NIH should establish and fund a consortium to expedite the identification and validation of biomarkers for lupus. This may include periodic meetings to assess the current state of knowledge, share data, and coordinate public and private sector research activities on biomarkers. Since 2004, a “biomarkers consortium” comprising ten academic medical centers has existed; however, funding for this effort has been limited.

Recommendation 5: The scientific community and industry should establish a technical expert panel to assess the two predominant instruments currently used in lupus clinical trials, the BILAG Index and SLEDAI, as well as other potential lupus assessment instruments, including industry-generated responder indices derived from the BILAG Index and SLEDAI. This panel may require a series of meetings and related staff support over a one-to-two year period. Consideration should be given to such issues as:

- Improving inter-rater reliability
- Rigor of investigator training and education programs for using the instruments
- Developing an effective adjudication process
- Employing centralized readers
- Implementing data cleaning processes

Recommendation 6: The LFA and its partners should conduct a systematic review of cyclophosphamide to assess its treatment effect. Cyclophosphamide is a chemotherapy used to treat moderate-to-severe flares, and is considered the standard of care, but has not been approved by the FDA for treatment of lupus. If the treatment effect of cyclophosphamide could be established, it would offer an alternative validated path to FDA approval by allowing for a non-inferiority study of a drug candidate for lupus nephritis.

- This effort could start with a formal systematic review, including meta-analysis as appropriate, of existing data generated from previous clinical trial experiences involving cyclophosphamide.
- The findings of the systematic review could be used to inform decisions regarding whether, and if so, how, to approach the FDA, and to pursue further clinical trials or other studies.
- As appropriate, findings of this effort could be incorporated into an update of the FDA Guidance for Industry, Systemic Lupus Erythematosus – Developing Drugs for Treatment, Draft Guidance, 2005.

Recommendation 7: The current interpretation of regulations pertaining to clinical trial design and related standards of evidence used to evaluate investigational drugs for lupus should be reexamined by the FDA, in cooperation with experts from industry, research, and the health professions.

- The hurdle of having to demonstrate to the FDA the clinical superiority of an experimental medicine against a non-approved standard of care may be impractical. In cooperation with independent experts, regulators should reassess the utility of non-inferiority and other clinical trial designs for lupus drug candidates. Consideration should be given to the *totality of evidence* on efficacy, adverse events, and pertinent patient reported outcomes, including such secondary endpoints as quality of life measures, when evaluating the results of lupus clinical trials.
- Toward integration of regulatory processes and expertise for drug development for the complex disease of lupus, FDA should reexamine the need for better coordination between its two review divisions responsible for evaluating lupus drug candidates: the Division of Anesthesia, Analgesia, and Rheumatology Products and the Division of Cardiovascular and Renal Drug Products. The former is responsible for reviewing drug candidates for general lupus; the latter is responsible for reviewing drug candidates for lupus nephritis.
- As appropriate, findings of this effort could be incorporated into an update of the FDA Guidance for Industry, Systemic Lupus Erythematosus – Developing Drugs for Treatment, Draft Guidance, 2005.