Home monitoring of peak expiratory flow rate (PEFR), at face value, provides a simple and relatively inexpensive method of objectively evaluating pulmonary function in all patients. However, peak-flow meter measurements must be interpreted carefully. The PEFR can be "normal" even when a patient has considerable symptoms.[1-3] Also, because the test is extremely effort-dependent,[4] the measured PEFR may be "abnormal" when the patient's disease is, in fact, controlled.

The insensitivity of the test requires that it be used in carefully selected situations. Home PEFR monitoring is particularly useful in the very stoic patient (e.g., a patient who consistently denies symptoms of asthma but consistently has poor spirometric measurements at follow-up).[5] In such a case, the clinician must determine the optimal PEFR for the patient by obtaining the measurement when the patient is optimally controlled (e.g., after prednisone burst therapy) and then using that value as the target PEFR. Routine home PEFR monitoring is also indicated for patients with severe asthma.

Long-term patient monitoring must include an assessment of the extent to which the disease interferes with the patient's life. Monitoring of an acute exacerbation in children must include assessment of the acute symptoms (e.g., coughing, dyspnea), some signs that the parents can easily assess at home (e.g., respiratory rate, presence of retractions, the patient's comfort level), and the response of these signs and symptoms to treatment. The response to treatment is critically important in determining the need for prednisone burst therapy, which should be instituted as soon as the indication is established.

Monitoring of patients with asthma includes involvement of the patient and parents in diligently following a number of signs and symptoms. Home PEFR monitoring may be part of the plan for selected patients. Educating the patient and parents about the appropriate response to clinical problems is an important role for pharmacists.

1. Johnston I, Anderson HR, Patel S. Variability of peak flow in wheezy children. *Thorax*. 1984; 39:583-7.
2. Sly PD, Hibbert ME, Landau LI. Diurnal variation of peak expiratory flow rate in asthmatic children. *Pediatr Pulmonol*. 1986; 2:141-6.
3. Mihatsch W, Geelhoed GC, Landau LI et al. Time course of change in oxygen saturation and peak expiratory flow in children admitted to hospital with acute asthma. *Thorax*. 1990; 45:438-41.
4. National Asthma Education Program. Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health/National Heart, Lung and Blood Institute, 1991, publication no. 91-3042.
5. Weinberger M. Managing asthma. Baltimore: Williams & Wilkins; 1990.

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Use of succimer

We would like to comment on the article[1] and editorial[2] about succimer in the December issue of *Clinical Pharmacy*.

McNeil Laboratories (a subsidiary of Johnson & Johnson) sought FDA approval for succimer as an orphan drug. Purely coincidental, perhaps, is the fact that the Agency for Toxic Substances and Disease Registry (ATSDR)[3] and the Centers for Disease Control (CDC)[4] estimated that there were approximately 200,000 children in the United States with a blood lead concentration (BLC) greater than 25 µg/dL. Consideration for orphan-drug status requires that the number of potential patients in the United States not exceed 200,000. More recent CDC guidelines, however, have stated that acceptable BLCs are <10 µg/dL; with this lower concentration, 2.4 million children in the United States might be candidates for succimer therapy.

Our understanding is that McNeil applied for orphan-drug status intentionally and that this action was not required by the FDA. Orphan-drug status gives some very specific advantages to the drug company. The drug is not patented because it is not, strictly speaking, a "new drug," and the company has an exclusive right to market the product. Further, the cost of evaluating an orphan drug becomes a tax write-off for the company. Finally, it is well known that a drug that becomes accepted in the treatment of one disease rapidly becomes usable in the treatment of other diseases. Because there is no restriction on how a physician uses a particular drug, succimer, which is effective in treating other metal poisonings, may be prescribed for indications not included in the package labeling.

To its credit, McNeil has taken the position that it will not advertise succimer or attempt to educate physicians about using the drug for any indication other than the treatment of lead poisoning.

The FDA approved succimer even though very few patients had been treated with the drug in the United States. Certainly, the FDA cannot be faulted for its action. The drug's orphan-drug status suggested that, since relatively few patients were thought to be eligible for treatment, it was unnecessary to subject a large number of patients to safety and efficacy studies.

We have had clinical experience using this drug since 1989. We recently reported that succimer-associated adverse effects occurred in a relatively high proportion of 68 patients.[5] Rash developed in 7–10% of adults and 5% of children. Small reductions in hemoglobin concentration occurred in 12% of the patients; we cannot relate this change to any clinical problems. One of our patients twice developed a potentially life-threatening hyperthermic reaction; one of these episodes occurred in a controlled clinical research setting. We have heard anecdotal accounts from other practitioners whose experience with succimer-associated adverse effects has paralleled ours. There are now reports of succimer-associated neutropenia and, in some animals, thrombocytopenia. The frequency of adverse effects may be so great that many physicians may be reluctant to use succimer for lead poisoning.

As to the editorial by Banner,[2] we believe the author missed the point of the succimer controversy. The FDA did not really establish a "cookbook" mandate for treatment. Unless we miss our guess, this drug will be used in large numbers of patients with a BLC below that specified in the package labeling.

1. Mann KV, Travers JD. Succimer, an oral lead chelator. *Clin*

Pharm. 1991; 10:914-22.
2. Banner W Jr. Succimer: controversial issues involving the release of a new product. *Clin Pharm.* 1991; 10:942. Editorial.
3. Agency for Toxic Substances and Disease Registry. The nature and extent of lead poisoning in children in the United States: a report to Congress. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 1988.
4. Centers for Disease Control. Preventing lead poisoning in young children: a statement by the Centers for Disease Control, 1991. Atlanta, GA: Centers for Disease Control; 1991.
5. Marcus S, Okose P, Jennis T et al. Untoward effects of oral dimercaptosuccinic acid in the treatment of lead poisoning. Paper presented at the Annual Scientific Meeting of the American Academy of Clinical Toxicology, American Association of Poison Control Centers, American Board of Medical Toxicology, and Canadian Association of Poison Control Centers. Toronto, Ontario, Canada: 1991 Oct.

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Drs. Marcus and Ruck are in error regarding how the Orphan Drug Act was applied to the development and approval of succimer. The Orphan Drug Act, which amended the Federal Food, Drug and Cosmetic Act as of January 4, 1983, discussed rare diseases and conditions without specifying numerical prevalence thresholds. In March 1984 Johnson & Johnson Baby Products filed an orphan-drug designation request with the FDA's office of orphan products development, and in May 1984 the request was granted for the use of succimer in the treatment of lead poisoning in children. In October 1984 the Orphan Drug Act was amended to further define a rare disease or condition as one that (1) affects <200,000 persons in the United States or (2) affects >200,000 persons in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for the disease or condition will be recovered from United States sales of that drug. Among the relatively few incentives offered by the act are (1) tax credits for clinical research performed by the sponsor before approval and (2) a seven-year market exclusivity.

Neither the 1985 CDC guidelines[1] nor the 1988 ATSDR report to Congress[2] had been published when the orphan-designation request was made. The two documents most pertinent to the prevalence and management of lead poisoning in children were the 1978 CDC guidelines[3] and the report by Mahaffey et al.,[4] which described the data from the second National Health and Nutrition Examination Survey (NHANES II). The former defined lead poisoning in children (regardless of the presence of symptoms) as a BLC of ≥50 µg/dL with an erythrocyte protoporphyrin (EP) concentration of ≥250 µg/dL. The latter indicated that in 1978 approximately 30,000 children (six months to five years old) had a BLC of ≥50 µg/dL.

The 1985 CDC guidelines[1] redefined lead poisoning in children as a BLC of ≥25 µg/dL with an EP concentration of ≥35 µg/dL. Chelation therapy was recommended for children with either (1) a BLC of ≥55 µg/dL or (2) a BLC of ≥25 µg/dL in conjunction with an EP concentration of ≥35 µg/dL and a positive edetate (EDTA) provocative challenge. The 1988 ATSDR report[2] applied the data from NHANES II and projected them to the 1984 United States population; the estimate was that approximately 200,000 children had a BLC of >25 µg/dL. The 1985 CDC guidelines,[1] as mentioned above, indicated that only a fraction of these children were candidates for chelation therapy.

The 1991 CDC guidelines[5] still do not recommend chelation therapy for children with a BLC of <25 µg/dL. They do eliminate the recommendation that EP concentration be considered, but continue to recommend that, when possible, an EDTA provocative challenge be performed before a decision is made to start chelation therapy. Even with these revised guidelines, the ATSDR report would still estimate that <200,000 children in the United States would have been candidates for chelation therapy in 1984.

We mentioned in our paper that clinical experience with succimer has been limited. Mild to moderate neutropenia has been observed recently in some patients receiving the drug.[6] Although a causal relationship to succimer has not been definitely established, neutropenia has been reported with other drugs in the same chemical class. We have modified the product's package insert accordingly. Even so, oral succimer offers many advantages over previously available agents when it is used appropriately as part of a comprehensive therapeutic plan. Succimer can be used effectively to reduce the lead burden in children for whom the drug is indicated.

1. Centers for Disease Control. Preventing lead poisoning in young children: a statement by the Centers for Disease Control, 1985. Atlanta, GA: Centers for Disease Control, 1985; DHHS publication no. 99-2230.
2. Agency for Toxic Substances and Disease Registry. The nature and extent of lead poisoning in children in the United States: a report to Congress. Atlanta, GA: Agency for Toxic Substances and Disease Registry; 1988.
3. Centers for Disease Control. Preventing lead poisoning in young children: a statement by the Centers for Disease Control, April 1978. Atlanta, GA: Department of Health, Education, and Welfare; 1978.
4. Mahaffey KR, Annest JL, Roberts J et al. National estimates of blood lead levels: United States 1976–1980. Association with selected demographic and socioeconomic factors. *N Engl J Med.* 1982; 307:573-9.
5. Centers for Disease Control. Preventing lead poisoning in young children: a statement by the Centers for Disease Control, 1991. Atlanta, GA: Centers for Disease Control; 1991.
6. McNeil Consumer Products Company. Chemet package insert. Fort Washington, PA; 1991 November.

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The primary issue raised in my editorial is generic: Should the FDA establish indications for drug use that are based solely on a single biochemical measure? This has not been the usual approach to prescribing drugs, and so to limit a drug's use to instances when this single indicator is present seems ill advised. The decision to treat an individual patient should be based on numerous factors, including age, exposure circumstances, other biochemical measures, and physical findings. It is easy to imagine circumstances in which reliance on the BLC alone could result in overtreatment or undertreatment of a specific child. Drs. Marcus and Ruck believe that children will be treated with succimer even if they have a BLC below that in the package labeling. Either the arbitrary labeling is then incorrect or these gentlemen have a rather cynical view of the community of practitioners.

The most recent CDC guidelines do not support the inappropriate prescribing of succimer, as Drs. Marcus

and Ruck suggest, and would not alter the applicability of the Orphan Drug Act to this agent. If anything, the recent data in this country point to the diminishing size of the population with a BLC in the range suggested for treatment and reinforce the appropriateness of the Orphan Drug Act in helping to develop succimer.

The unimpressive and small series of adverse effects presented by Drs. Marcus and Ruck reinforces the need for adverse-effect monitoring but in no way diminishes the need for succimer. The frequency of adverse effects with the currently available chelators is well enough known that it does not bear repeating. All of the available data both here and abroad continue to support oral succimer as being safer than injectable chelation therapy.

It is surprising to read such a negative commentary on a drug that has been long awaited by the bulk of the toxicology community. Toxicologists should be taking an affirmative attitude by encouraging Phase IV data collection on succimer as it enters the market and by educating physicians on the drug's appropriate use.

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