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THE FIRST WORD

THE CASE OF THE CASE STUDY

There are two kinds of creativity: one breaks the bounds of convention to create new forms; the other revels in restriction and extracts from established forms all they can yield and more. The engineer in us is drawn to the latter, and to the odd bits of information that show us how others have dealt with imposed limitations.

Take some of the odd bits of information we came across at Biotech USA. For example, therapeutics that may be administered in the home are (in general) ineligible for reimbursement under the rules of the U.S. Health Care Finance Administration (HCFA), overseer of federal health-insurance programs. This is a significant datum—obvious in some quarters, obscure and overlooked in others—for those developing high-cost drugs for the U.S. market. It should be considered very early in R&D.

Or consider the U.S. Food and Drug Administration process validation rules: Among other requirements, they insist that biologicals processes be isolated from any source of "extraneous infectious agents"—including other processes or laboratories containing such microbes as *Escherichia coli*. With some 80 percent of new applications expected to come from companies seeking approval for multi-product facilities, more and more process developers will confront this requirement, which can be hard to come to terms with. In the past, many facility designers have thrown in the towel and divided their plants with solid walls, judging that the expense of duplicate facilities was more endurable than the additional validation headaches. Others are isolating their products in time rather than space, running their products—those with longer shelf lives—in batches.

Agriculture—especially agricultural biotechnology—is subject to an astounding collection of restrictions economic, regulatory, and scientific. Thus, a few agricultural and agrochemical R&D programs have shown extraordinary practical creativity—using biotechnological tools to develop non-recombinant (or non-living) products and avoiding microscopic scrutiny to which even the most benign genetically engineered organism is now liable.

Male sterility in plants is of obvious agbiotech interest: it offers environmentalists assurance that recombinant plants will not propagate throughout the landscape, while giving seed companies a double promise of protecting their valuable cell lines and ensuring sales to farmers over successive growing seasons. Indeed, two recent publications[1] may provide means for introducing male sterility into species where no natural male-sterile mutation is known.

More prosaic, though nonetheless interesting, is DNA Plant Technology's strategy for efficiently producing non-recombinant, male-sterile hybrids. The approach is simple in retrospect: DNAP researchers recombinantly linked a marker gene to a *natural* male-fertile gene in melons. In general, the most successful genes were those that produced an easy-to-spot visual cue—luciferases, for example, or beta-glucoronidase, which blue-tinted the coats of hemi- and homozygous male-fertile seeds. These plants were crossed with conventionally bred male-sterile melons, and then back-crossed with the male-sterile parent to produce plants for seed production. The visual marker system allowed fast, efficient screening to select the non-recombinant male-sterile hybrid seeds for sale.

There's a lot to say for simple, practical information. That is one of the reasons we are initiating a new occasional section, "Case Studies in Process Development," in this issue. It is particularly difficult to get solid information on real-world process-development experiences: the process-developer's reluctance to speak seems, understandably, to increase in direct proportion to the value of what he or she has to say. These case studies, part research paper and part review, will, we hope, add to the fund of solid practical experience in producing biologicals for clinical applications.

—Douglas McCormick

1. C. Mariani et al. 1990. Induction of male sterility in plants by a chimaeric ribonuclease gene. *Nature* 347:737-741. B.A. McClure, et al. 1990. Self-incompatibility in *Nicotiana alata* involves degradation of pollen RNA. *Nature* 347:757-760.