Over the years, academic institutions, including dental schools, have become increasingly interested and involved in developing interactions with industry. The nature of such interactions has been evolving over many years, and there is a clear contrast between attitudes prevalent at the time I first entered dental school in the mid-1960s and the present. In the “early days,” dental academicians were, for the most part, disdainful of working with industry. One sensed that there was an implicit belief that dollars provided by industry were printed somewhere in the netherworld and, therefore, tainted, whereas dollars provided by other sources, including the government, followed a more pristine route from the heavens directly to academic institutions. Clearly, opinions have changed dramatically in the interim, and today it is rather common for academic institutions and industry to interact in a variety of ways. In this paper, I will first present an overview of the evolution of academic-industry partnerships in dentistry and their value to each of the partners; then discuss details to be considered by investigators seeking to work with industry; and, finally, review some of the issues and dilemmas that can arise from academic-industry interactions. I should note at the outset that much of this paper is based on my own experience and perceptions and that others in the field may have different viewpoints.

Academia as a Resource for Industry (and Vice Versa)

A significant early force driving the development of relationships between academia and industry was the need that industry had for sites at which to conduct clinical research and the ability of many dental schools to accommodate this need. From the standpoint of industry, the dental schools were potential good partners since they provided expertise in the conduct of clinical trials, as well as appropriate clinical facilities and the ability to recruit suitable subject populations. In addition, conducting clinical trials at schools with good academic reputations imparted enhanced credibility to the data produced, thereby enhancing, as well, the credibility of the products tested with the dental profession and with regulatory agencies.

Over the years, there has been a steady increase in the number of clinical studies conducted by industry, largely in response to two main driving forces: the development of study guidelines for the assessment of product effectiveness by organizations such as the U.S. Food and Drug Administration (FDA) and the American Dental Association (ADA), and the increasing rate of development of new technologies for the diagnosis, prevention, and treatment of a variety of oral diseases. From a dental school’s standpoint, the ability to attract clinical trials by industry provides an additional source of funds, especially in a period of diminishing funding from other sources, and also provides an opportunity for faculty members to participate in clinical research. Although not all clinical trials involve “cutting edge” technologies, the opportunity for faculty to participate in clinical trials that do is of particular interest because of the value this might have in advancing one’s academic career as a result of the publications and presentations that might ensue.
An additional dimension to academic-industry research relationships was introduced in 1980 with the passage of the Bayh-Dole Act, which modified existing U.S. patent law. This act allowed universities and investigators to patent discoveries made with federal support and to retain royalties and other fees resulting from the licensing and/or sale of such discoveries. It should be recognized that research in academic institutions can be a significant source of new technologies for dentistry, with the National Institute of Dental and Craniofacial Research (NIDCR) the major source of funding for this research. As a result, entrepreneurialism has been gaining an increasingly strong foothold in the halls of academia, and new types of relationships with industry have developed.

Clearly, the cost of developing and commercializing a new technology is well beyond the resources of individual investigators; thus patent holders have to either seek support from existing companies or establish startup companies with venture capital in order to translate their discoveries to clinical applications. Since the development of these new technologies and methods usually requires clinical trials to demonstrate safety and/or effectiveness, this acts as a positive feedback loop to stimulate the clinical research activities of dental schools.

The entrepreneurial mind-set has had other outcomes, as well. Academicians who gained prominence as either the discoverer or the clinical investigator of new technologies now began finding themselves in demand as consultants to industry, speakers for industry, or members of scientific advisory boards of new, startup companies. These relationships have often resulted in a blurring of the boundary between industry and academia, the consequences of which will be discussed in the third section of this paper.

The increasing variety of interactions between individual faculty members and industry has produced additional, salutary outcomes for dental schools in the form of support by industry of such things as student research, guest speakers, the establishment of clinical research facilities, and the provision of sample products and data from the latest clinical trials. The management of complex academic-industry relationships requires an awareness of potential upsides and downsides to ensure that these relationships will remain favorable to both partners and not jeopardize either the mission of the academic institution or its traditional values.

So You Want to Work with Industry—Now What?

Dental schools and dental faculty seeking to establish research relationships with industry do so most frequently in the realm of clinical investigations. This is not a trivial undertaking. If an institution is to be successful over the long term in conducting clinical trials for industry, it must establish the necessary infrastructure and have on its faculty individuals who have the experience, understanding, attention to detail, and discipline to properly conduct such trials.

In addition, there must be compliance with FDA regulations relating to good clinical practice as set forth in section 21 of the Code of Federal Regulations, with particular attention paid to the protection of human subjects and the structure and function of Institutional Review Boards constituted to review and approve study protocols. (A listing of these regulations can be found at www.fda.gov/oc/gcp/regulations/html.) Among other things, the required infrastructure includes a dedicated clinical research facility, adequate storage for clinical supplies, proper recordkeeping facilities, personnel to recruit subjects and maintain a subject registry, an adequate number of research assistants, a means of maintaining confidentiality of clinical records and study activities, and a duly constituted Institutional Review Board. Oftentimes, if an institution is seeking to initiate clinical research activities, it is necessary to provide training, or access to external training courses, to its clinical faculty in order to establish a cadre of competent clinical investigators. The fact that one might be an excellent clinician does not necessarily suggest that the same individual would be an excellent clinical investigator. Therefore, institutions should understand at the outset that a significant commitment is required to be successful in attracting clinical trials over the long term.

While a proper infrastructure is necessary for a company to consider conducting studies at a particular site, there are additional factors that will influence the final decision. Perhaps the most important of these is the ability and reputation of the principal investigator and study examiners. As one might anticipate, companies seek to conduct studies as well and as expeditiously as possible (after all,
time is money in business!). They, therefore, will tend to place studies with investigators and academic sites that have developed reputations for clinical trial competency in the area of interest and the ability to adhere to study schedules. Additional factors include the institution’s indirect cost rate—given two institutions with comparable capabilities, if one has an indirect cost rate substantially below the other’s, it will have an advantage in obtaining the study—and the ability to negotiate a contract acceptable to both parties in a timely fashion.

In the “old days,” the need for a formal contract between an academic institution and sponsoring company was the exception, rather than the rule. A company representative shook hands with an institutional representative, and the study would proceed with everyone hoping for the best. In most cases, but not all, the studies were completed according to plan. In today’s world, formal contracts between sponsor and academic institution are a necessity. These contracts cover the entire gamut of study issues, including such items as the study protocol and budget, payment terms, liability, number of completed subjects required, study completion date, procedures for protocol revision, confidentiality, publication and/or presentation of results, intellectual property considerations, and dispute resolution. Some academic institutions and companies are more efficient than others in developing and negotiating contracts, and clinical studies are usually conducted as a component of an overall product development plan and timetable. When contract negotiations become unduly prolonged from a company’s viewpoint, a sense of frustration with the academic institution can develop that could result in the study being placed elsewhere or a reluctance to interact with that institution in the future.

There are some important concepts that investigators should keep in mind when approaching or working with companies. First, they should be accurate in their representations and not try to fathom what the company would like to hear and fashion their communications accordingly. Second, they should understand that reputable companies do not conduct studies with the expectation of pre-established outcomes but, rather, are interested in conducting studies that test hypotheses about product effectiveness. Clearly, not all studies are going to show significant differences between a test product and control, either because the product is truly ineffective or because of the vagaries of statistical probability. It is important, therefore, that studies be conducted as rigorously as possible so that results, in turn, are as accurate as possible and not the outcome of poor execution.

Investigators should be especially careful to provide accurate information for contract clauses that commit them to specific timing or costs. In particular, there should be a realistic projection of the time needed to recruit and enter the required subject population, since this will affect other commitments, such as the projected study completion date. It has been my experience that even experienced investigators tend to drastically underestimate the time required for subject recruitment. This clearly has a number of “downstream” consequences, including delayed study completion and a concomitant diminishing of confidence in the study site.

Similarly, the budget should present the actual costs of conducting the study and a reasonable indirect cost rate. Companies generally have enough experience to anticipate approximate study costs. Therefore, the investigator should not present an artificially low budget in the belief that this will help him or her to “get” the study, nor should there be a greatly inflated budget in the belief that companies have deep pockets and will not notice the excessive cost. The former could create problems for the investigator and his or her institution, which will have to come up with the funds needed to complete the study, while the latter will cause the company to seek other sites at which to conduct the study. With respect to clinical research in particular, the vast majority of studies are product-related and designed to answer specific questions; thus, the funding levels typically tend to be less than those associated with National Institutes of Health (NIH) grants or research conducted by large pharmaceutical companies.

Investigators also need to adhere to requirements and conditions of the study protocol, and not arbitrarily and unilaterally change these in the course of conducting the study. Protocols usually contain provisions for making revisions; however, it is generally rare that this should be necessary once the study starts, especially for studies conducted for subsequent submission to the U.S. FDA or other national or international regulatory bodies. These organizations have strict requirements for the conduct of clinical trials, and there are formal procedures established to document changes in study design, etc. once the study has been initiated. Failure to adhere to these procedures could invalidate the study from a regulatory perspective. If an investigator has any issues with the study design, other aspects of the science, or study logistics, these should be discussed with the sponsor.
and resolved prior to study initiation and, preferably, prior to establishing the definitive study protocol.

Academic investigators should understand the role of clinical study monitors during the conduct of an industry-sponsored study. There are frequently misconceptions about why monitors periodically visit the study site. For example, the monitoring of a clinical trial has been thought of by some in academia as an attempt to influence the outcome of that trial. In fact, when properly performed, the objective of clinical monitoring is to check on the progress of the study and ensure conformance with the study protocol and recordkeeping requirements. The monitoring of certain clinical trials is required by the FDA (see, for example, 21 CFR 312.56). As such, the study monitor can be thought of as an extension of the “eyes and ears” of the FDA in providing assurance that the study has been performed as indicated. Therefore, investigators should understand this function and work with the study monitors to achieve the common goal of a well-conducted investigation.

The contract provision that often seems to generate the greatest amount of controversy between academicians and sponsors deals with the publication and/or presentation of study results. There is no question that conditions for publication should be agreed upon by both parties at the outset to preclude later disagreements. I have seen occasional instances in which a failure to agree on whether results of a given study should be published caused the sponsor to go to a different study site. It is important that sponsors be cognizant of the needs and values of academicians in determining publication policy. Certainly, the number and, more importantly, the quality of publications are important to the advancement of an academic career. Similarly, it is important that academic investigators be cognizant of the needs and values of industry. It is not unreasonable, for example, for a company to require delay in publication or presentation of study results if premature disclosure could jeopardize the patentability of a discovery. Companies in this position seek to submit the patent application as expeditiously as possible, so a brief delay in publication should not have a negative impact on a faculty member’s career. It is also reasonable for companies to request an appropriate period of time, typically forty-five to sixty days, to review proposed publications or presentations to prevent disclosure of information that could adversely affect future intellectual property rights and/or to provide editorial suggestions that might improve the publication.

Are there circumstances under which publication should be prohibited outright? Given the proposition that published studies should add something meaningful to our body of knowledge, there are situations in which it is reasonable to prohibit publication. However, when publication is to be prohibited, it is important that the decision not to publish be made prior to study initiation and that the prohibition be absolute and not be dependent upon study results.

There would, for example, be no reason to publish studies conducted to validate a study site—that is, studies conducted to determine the competence of an investigator/examiner and the ability of the study site to deal with the logistics needed to properly conduct the clinical trial. Why should publication of studies of this type be prohibited by the sponsor? To give one example, such studies might be short-term trials that compare a product or formulation that has been proven effective in numerous previous clinical trials to a negative control. If there is a clear difference between the two groups, this confirms the ability of the examiner and site to successfully conduct studies with the given class of products. On the other hand, if no difference is found between the groups (i.e., the study produces false negative results), this most likely indicates that the examiner and site need further training and expertise in conducting clinical trials and does not mean that the product or formulation is not effective. In either case, this type of study provides no new meaningful information and there is no scientific rationale for publication.

Pilot studies, conducted to get preliminary information to be used in further product development or in designing definitive trials, are another category of studies for which prohibition of publication could be appropriate. In this case, such factors as scientific merit and whether proprietary information would be disclosed could enter into the decision. Finally, there may be rare instances in which a company may not want other kinds of studies published. Here, again, the decision should be made initially and independent of study results.

Clearly, all funding organizations, be they corporate, governmental, or foundations, have certain rules and requirements. An academic investigator has the option of either accepting these or, if he or she feels they conflict with personal or institutional values, choosing not to accept funding from a given organization. There is a certain irony to the amount of concern among academicians about publication clauses in protocols and contracts. In my experience,
prohibition of publishing study results has not been the primary issue; rather, the challenge for companies most frequently has been getting their academic investigators to publish study results within a reasonable time frame if at all!

**Potential Conflicts and Concerns**

Up to this point, the benefits of academic-industry relationships have been emphasized, and it is clear that when properly constituted these can provide a win-win opportunity for both partners. There is a flip side to this, however, and much has been written about the potential that such relationships have for producing conflicts and less salutary outcomes.2-23; esp. 2,15,16,18,22 Perhaps the most extreme expression of these concerns is the title of a *New England Journal of Medicine* editorial, “Is academic medicine for sale?”12 which implicitly suggests that it could very well be. The basis for the concern relates to the potential for financial relationships to create conflicts of interest and thereby influence individual and/or institutional behavior and decision-making. This is an aspect of industry-academic relationships that should be recognized and dealt with proactively.

What is conflict of interest? A variety of definitions have been offered, from the standard dictionary definition to a more pragmatic working definition: “Conflict of interest is a set of conditions in which professional judgment concerning a primary interest (e.g., patient’s welfare or validity of research) tends to be unduly influenced by a secondary interest (e.g., financial gain).”16 It is important to note two things. First, the identification of a conflict of interest should not in and of itself be taken to suggest that unethical or otherwise undesirable behavior has occurred, but rather that conditions provide the potential for such behavior. Second, while some behaviors and decisions may be intentional and clearly influenced by financial relationships with industry, oftentimes these influences are subtle and can affect individuals and institutions in an almost subliminal manner. For example, an investigator or inventor of a new technology might unconsciously give greater emphasis to that technology than to effective competitive products in lectures and publications. This is an area of concern since the perception of questionable behaviors might be as powerful as reality and therefore deserving of attention by faculty members and their institutions.

Returning to the issue of industry-academic relationships, what are some circumstances leading to conflict of interest, and what are some of the undesirable (and unethical) outcomes that have been identified? Let me reemphasize that these are potential, not inevitable, outcomes of financial conflicts of interest.

When we consider the possible ways in which financial benefit can influence individual and institutional behaviors, it is often the worst-case scenarios that are imagined. With respect to individual academicians, financial conflicts of interest can result from their involvement in the development and commercialization of their discoveries: for example, the fact that they or their family members may hold significant equity positions in a company that is dependent for survival upon the product’s success. Other conflicts of interest may result from their serving as board members, consultants, speakers, and/or investigators for specific companies. Worst-case scenarios developing from such circumstances include: improper reporting of study data, ranging from outright falsification to selective reporting or emphasis of seemingly positive findings while ignoring less favorable results; lack of balance in presentations and publications in scientific forums and professional journals, with undue emphasis on a particular company’s product(s) (this is not an issue if the presentation or publication is clearly a promotional activity on behalf of a particular company); and the development of study protocols designed to produce results in favor of the sponsoring company’s product, rather than objectively test a hypothesis about effectiveness.

From an institution’s perspective, conflicts of interest can have an impact on its educational and research activities. If faculty become too heavily involved in and committed to extramural activities, such involvement may come at the expense of their academic responsibilities. Clearly, there is a delicate
balance here, as the fact that its faculty may be prominent in the research, consulting, and/or lecturing worlds outside of their own school reflects well on the school and may play a role in the recruitment of new faculty and students.

Additionally, there is concern that too strong an emphasis on commercial/entrepreneurial goals for a research program may, in the long run, have a detrimental effect on scientific advancement since significant discoveries are often made serendipitously in the course of conducting untargeted basic research. Again, a balance needs to be achieved in this case, as well, because royalties and licensing fees can become increasingly important to the financial well-being of dental schools as other sources of support dwindle.

And, finally, there is concern that an alignment between faculty members and/or institutions with specific companies may unduly influence the curriculum, resulting in less scientific objectivity than would otherwise be the case. The potential impact of financial relationships between industry and academia can be summed up in a statement from former Harvard President Derek Bok, who wrote “it will take very strong leadership to keep the profit motive from gradually eroding the values on which the welfare and reputation of universities ultimately depend.”\(^\text{19}\)

It is worth repeating at this point that conflicts of interest are no doubt ubiquitous and usually do not produce the sort of worst-case results outlined above. However, since they have the potential of doing so and since perception can at times be more powerful than reality, it is critical that academicians have an awareness of these issues and manage them appropriately. While the management of conflicts of interest is beyond the scope of this paper, a variety of programs involving oversight and disclosure have been suggested and implemented for this purpose.\(^\text{3,4,15,22}\)

### Conclusions

Relationships between industry and academia have become quite prevalent and, when constituted properly, present clear benefits for both partners. It can be expected that such relationships will be expanded and enhanced in the coming years, especially as other sources of support for our dental schools diminish and advances in biomedical research result in technologies that can be transferred to clinical applications. It will be critical that the conflicts of interest generated as a result of these relationships be managed properly so as to not adversely affect the values and missions of our dental schools.

### References