DRAFT –NOT FOR ATTRIBUTION

Regulatory, Legal and Ethical Challenges in Drug and Vaccine Approvals

For the past 15 years, there have been no end of meetings marked by repeated expressions of angst about the sorry state of vaccine supply, the lack of interest by the commercial sector in vaccine research and development and the problems in fostering the creation of promising new products. The concerns and tensions associated with this sorry state of affairs have markedly heightened as we have begun to face the challenges of developing and producing new products on a short time schedule – specifically products to deal with bioterrorist agents and new or emerging infections, such as bird flu.

Numerous recommendations have been made to try to fix a system such that it could serve to provide new and better vaccine products that were safe and effective. Despite the efforts of many, I don't believe that we have made much progress in solving the problems (Albeit, thanks to Jess Goodman, for his very recent efforts to facilitate the process of evaluation and licensure of flu vaccine. It is a bright light in an otherwise dim room). On several occasions the problems have appeared so intractable that the ultimate solution of a government owned vaccine production facility has been serious explored. Happily, for a number of reasons, that route has not been further pursued .However, my perception is that more tinkering with the system as it is currently structured and perceived by those responsible, will not accomplish much. A more fundamental reexamination of the failed system and a commitment to action is critical, albeit the task would be a formidable one.

At the heart of all of this is the question of risk and benefit — how this is considered and who makes the decisions.

Most of the issues — regulatory, legal and ethical stem from this. Today — in this closed meeting I will be frank in my analysis — without specifics, difficult to make progress

Problem. Risks

In passing, let me call attention to a series of 10 papers produced under the auspices of the National Vaccine Advisory Committee and just published in CID. Edited by Jerome Klein, it is entitled "Strengthening the supply of routinely administered vaccines in the U.S." It characterizes well many of the current dilemmas.

Problems associated with the development and production of vaccines for routine use are plaguing the US and, so far, despite the urgency of the situation, we haven't done well in developing policies and methods for dealing with vaccines to counter bioterrorism. After 9/11, our first crises in HHS related to smallpox vaccine. With little smallpox vaccine in the US or in other countries, with no production capacity, and a serious threat, procurement of vaccine was at the highest level of priority. During the first 3 years after 9/11, we spent a prodigious amount of time endeavoring to obtain, as quickly as possible, sufficient vaccine to cope with smallpox should there be a terrorist attack. It turned out to be unbelievably difficult and, at one point in the process, I was asked whether, if smallpox were released, we could again mount a successful eradication program. I had to reply that I thought we could except possibly for the United States. The saga would require a book but let me describe two of the less complex issues. Our first problem was to have the freeze-dried smallpox vaccine, Dryvax, that HHS had in storage, relicensed for ease of use should an epidemic occur. Wyeth had permitted the license to expire. Dryvax had been in continuing use in the US for perhaps 50 years and from 1967 in Africa, Asia and Latin America as well. The 15 million doses we had in storage at -20C had been produced in 1978 but continued to be used every year to vaccinate workers in orthopoxvirus laboratories. The vaccine titer had not changed over time. Despite this background of experience, our licensing authority required that a

whole new battery of human application studies of the vaccine be undertaken. Meanwhile, it was decreed that under emergency circumstances, a special IND protocol would have to be followed, including a multiple page form (17 pages in length in a first draft) and elaborate efforts to educate and to screen. How this would play out in an epidemic was a question but an even more complex screening was barely avoided. It was only with difficulty and multiple meetings that we were able to persuade an "expert" advisory group that pre-vaccination screening of all women for pregnancy and all others for HIV was hopelessly impractical, especially under epidemic circumstances.

A second problem.. As general instructions for vaccination were about to be released, a new issue arose. How many multiple punctures with the bifurcated needle should be used – was it 15 for all vaccinations or was it to be only 3 for primary vaccinees and 15 for revaccinees? It turns out that the ~~product~~ package insert ~~sheet~~ prepared in 1966 called for only 3 punctures for primaries. There were no studies that supported this recommendation in government files and, in fact, it was confirmed with the manufacturer that none had actually been done. The recommendation that all vaccinations be performed with 15 punctures grew out of early experiences in the global program in which it was discovered that there had been many failures when only 3 punctures were stipulated. Thus, hundreds of millions of vaccinations had subsequently been performed with the 15 puncture technique, resulting in a number of published papers, some of current vintage, which licensing staff actually co-authored. Nevertheless, more information was demanded – specifically, information on the results of vaccinating several hundreds of persons with 15 punctures. How many should be documented was left to the investigators. By then, several thousand persons had been vaccinated by CDC

and the military and these data were duly assembled. Eventually, after the expenditure of several million dollars and a great deal of effort, a report was submitted but it was rejected on the grounds that the data were not in the proper form. The effort to educate was finally abandoned. Thus, the instructions now appearing in vaccination sheets do not represent the best medical or public health practice.

Other adventures are currently in progress but best no further comment be offered. What is clear is that the U.S. licensing process is complex, costly, ponderous and sometimes quixotic. How much this has to do with the willingness of manufacturers to engage in production is unknown. Most U.S. vaccines are produced by only a single producer and when that producer experiences difficulty, the flow of vaccine stops. The last few years have been marked by repeated shortages of even the most common vaccines

- Note: flu vaccine last year. Chiron faltered leaving Sanofi-Pasteur as the only source for inactivated vaccine. In 1967, there were 26 vaccine manufacturers; today only 6. Last year, the U.K. had at least 7 manufacturers of flu vaccine to which they could turn.
- Why so few manufacturers?
  - Originally, it was said to be fear of liability and that was understandable. However, that was largely corrected in 1986 by the Vaccine Injury Compensation program.
  - Steadily changing GMP requirements are identified as a problem. Over the past decade, much more stringent and extensive recording requirements were introduced and these have been

continually evolving, overseen by a special group called Team Biologics, referred to by some as the "Inspection Nazis". Wyeth dropped production of adenovirus vaccine (now not produced by any company) as well as pneumococcal and flu vaccines because of costs needed to upgrade plant

- Increasing demands for ever more extensive and documented clinical trials

What avenues of inquiry might prove productive in reshaping the system. It seems to me that fundamental procedures for weighing risks and benefits of products need to be examined to assure that "risk" is not the dominant or virtually exclusive focus. Scientific and ethical issues are critical but are sometimes lost as legal and political concerns are brought to the fore. How these are to be weighed objectively and rationally is not readily apparent nor who it is that ultimately should have the decision. What I have found unsettling is the lack of serious involvement of those with practical public health experience.

The Advisory Committee on Immunization Practice (ACIP) once could have been helpful in this regard but its character has changed. That Committee was founded specifically because, until its founding, advice on immunization practice had been entirely in the hands of the Academy of Pediatrics Redbook Committee. The Red Book Committee itself was and is an excellent and knowledgeable group but primarily comprised of pediatricians from the academic community. In the early 1960s, they had recommended a steadily increasing number of doses of polio vaccine to be given and 4 as opposed to 3 doses of DTP in order to provide better protection. The proposals were

reasonable but were based primarily on the principle that more was better whether or not there was supporting epidemiological evidence was weak to negligible. However, for public health authorities, most of whom had marginal budgets, the burden of suddenly increasing the number of doses of vaccine by one-third or more inevitably meant cutting other services. Ethical issues were clearly involved but to weigh these, required knowledge of the trade-offs that were involved. ACIP was originally comprised to permit the examination of immunization policies from the public health vantage point, balancing risk and benefit and taking into account cost. However, as time passed, it came to be dominated by the academic sector and by a CDC Secretariat with little practical public health experience. As one reviews ACIP documents, it is apparent that advice on immunization practices is written primarily for the full-time academic, not for the clinic nurse who, in most cases, administers the vaccines. The exigencies of emergency vaccination programs seem to be totally unknown to those concerned.

How to constitute a group that can examine risk and benefit as well as practicality, ethical issues and cost is worthy of exploration. It is possible that the National Vaccine Advisory Committee (NVAC) might be able to discharge this responsibility. NVAC was created in 1986 but floundered as internal government efforts sought to destroy it. The Committee revived briefly in 1990 but soon after, was once again relegated to the side line until a revival of more recent date. It has never been adequately staffed or funded and is not so today. Another group that might have been able to provide useful counsel was the Secretary's Council on Public Health Emergency Preparedness but that Council, after a spasm of activity, was effectively rendered

inoperative and defunct, more or less as other independent advisory committees during recent years.

Finally, a word needs to be said about the international scene. Regulatory practices in the U.S. have been closely followed on the international scene and, in many cases, adopted more or less in their totality as a result of U.S. advice. This is an especially serious problem. There is no question but that if the global smallpox eradication program had been dependent on vaccine produced in laboratories meeting U.S. GMP standards, eradication would never have gotten off the ground. All vaccine used in the program came to be independently tested by WHO collaborating laboratories and had to meet established criteria of potency, stability and purity but it is certain that none would have begun to meet the most elementary GMP standards of today. Risks had to be acknowledged but the overwhelming benefits tipped the balance. As time has passed and more rigid standards for production adopted, higher costs of product have been inevitable. How costly these incremental standards may be is suggested by the fact that smallpox vaccine was able to be purchased for two to nine cents per dose as late as 1975. In 1975 At that time, costs for production were specifically assessed in one industrialized country laboratory, taking into full account costs of plant and depreciation. The cost was just under ten cents per dose. In part, this was due to the fact that smallpox vaccine could only be packaged in containers of 100 doses, an obvious saving over the need to produce vaccines in single dose vials. Recent purchases of vaccine for the national stockpile require nearly two dollars per dose.

A little recognized problem is the assumption internationally that U.S. regulatory practices are the "gold standard" and that, for any country, to adopt less than these standards is to accept a sub-standard product. Indeed, certain of the large commercial manufacturers encourage this view and, in fact, do not protest more stringent GMP standards, in part because they have come to recognize that such standards serve to obstruct new entrants into the vaccine production field.

Are we in need of a more effective and intelligent, balanced approach to examining benefits, risks, ethical values and vaccine costs? Desperately so but unless there are expectations of full and frank discussions as to why we have the dysfunctional system we have today, little more is apt to be accomplished than has been achieved over recent decades.