1. Attempt to clone using PCRI documented dates 2/1/77.

2. At or shortly after the Miami Symposium, January 9-14, we received information from Herb Boyer via Mary Betlach that the plasmid PBR 322 had been approved as an EK2 vector. W.J. Rutter learned of this thirdhand at this time. With this news we elected to use the plasmid PBR 322 in our experiments.

3. Advantages of the use of PBR 322 were evident:
   (a) well characterized (restriction sites);
   (b) screening for recombinants is easy (2 resistant markers);
   (c) size is small;
   (d) Falkow had done experiments showing that transfer was lower than with the already approved plasmids PCRI and PSC101.
   (e) PBR 322 also has a much lower crossover. Thus, PBR 322 is a safer and more convenient vehicle. Convenience in this sense also has an element of safety, since less DNA is required to obtain a reasonable number of clones.

4. Experimentation with PBR 322 began. The first week in February a number of clones were obtained.

5. About two weeks after the initiation of experiments and after clones were obtained (February 5), Ullrich learned from Boyer that PBR 322 was not yet formally certified. Although approved in principle, no new transformation experiments were carried out after that date.

6. Goodman returned to the United States on February 10. For the first few days he was occupied with a site visit. Then reorientation with lab work occurred. He was told that PBR 322 was employed, but was unaware that it was not certified.

7. Use of the P3 facility has been approved for the general experiments (shotgun using islet mRNA preparations - P3 EK2). It was assumed throughout that PBR 322 was an acceptable alternative to PCRI.

8. At the Park City ICM-UCLA meetings, specifically on Tuesday, March 1, W. Cartland in answer to a question stated that the approved plasmids were PCRI and PSC101. Afterwards, he was asked the status of PBR 322 and he mentioned that the Committee had approved this plasmid in principle but additional data requested by Fredrickson had just arrived from Dr. Falkow, and had been discussed with the NIH Recombinant DNA Board via telephone. The decision had been made to mail the data before final action was taken. Certification within one week to ten days was anticipated.

9. Goodman learned on March 2 that an insulin clone (from sequence data) had been isolated from PBR 322.
10. On March 3, Goodman returned to the laboratory. He held a meeting with the laboratory personnel and halted all further work with the clones obtained from transformation with PBR 322.

11. Goodman told Ullrich (still in Utah) of this decision on March 4. Goodman attempted on March 3 to call Rutter who was in a meeting at Houston. Goodman reached him on March 4 and told him of this decision. Rutter concurred.

12. When Ullrich returned to San Francisco on Saturday, March 5, he destroyed the plasmid containing cells and kept only the purified DNA from the clones, frozen under isolated circumstances.

13. During the next 10 days no word was received from Washington. In a conversation with Falkow, Goodman asked about PBR 322. Falkow emphasized the superior characteristics of the plasmid compared with PCRI and PSC101, the approved plasmids. He mentioned other scientists were considering the possibility that PBR 322 might be approved as an E K3, and met EK2 requirements in normal E coli K12. Data on this matter was also reported at the Utah meetings in a workshop attended by Ullrich but not Goodman. In view of this, Falkow felt it acceptable to use PBR 322 now in cloning experiments.

14. On March 15, Goodman returned to San Francisco and telephoned Gartland's office. He spoke with Gartland's assistant, Dr. Kearney, because Gartland was out of the country. Goodman asked about the status of PBR plasmids. Kearney said they were in the process of putting the document together for Fredrickson's signature. She said it was approved by the Committee, but not formally certified. There was no question of certification, however she thought it might take 2-3 weeks for the administrative processing.

15. Consultation of the Guidelines themselves reveals no explicit statement concerning the dissemination of information concerning the plasmid vectors. The Guidelines specifically do not deal with the issue of approval versus certification by the Board and do not mention approval by Fredrickson.

**MATTERS OF JUDGMENT:**

On learning of the lack of certification of PBR 322, there were four possible courses of action:

1. Destroy all cloned DNAs.

2. Inform Gartland's office of the course of events and ask for advice.

3. Keep the cloned DNA since the experiments had already been performed and await certification before continued experiments.
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4. Consider that approval by the NIH Recombinant DNA Molecule Program Advisory Committee represented de facto approval of the plasmid, and to proceed with experiments.

We rejected 1. because the experiments had already been performed, thus the danger, if any, had passed. Furthermore the importance of the clones was obvious.

We rejected 2. largely because of the potentially explosive publicity that might follow the lack of strict compliance with the Guidelines, and the apparent willingness of some even within the scientific community to call for cessation of all recombinant DNA experiments on what seemed to us to be political rather than purely scientific grounds.

This would also enhance the tendency of various legislators to impress strongly restrictive laws concerning the research.

Thus, we concluded there would be pejorative effects based on a technicality rather than on the spirit of the Guidelines themselves.

Alternative 4 was rejected for the same general reasons expressed above in 2. We believed that we could not use PBR 322 until completely certified. Certainly if we were to report the experimental results publicly before formal certification by Fredrickson, it would have the same reaction described in 2.

We thus elected 3. We believed that further sequencing of the DNA clones was acceptable since the hypothetical danger, if any, is not with the DNA itself.

Howard Goodman

William J. Rutter