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**FDA Critical Path Initiative**  
**Docket No. 2004-N-0181**

**1. Hurdle Identification.**

Methods for blinding tableted research medications.

The two most widely used methods are over-encapsulation (38%) and the Double-Dummy design (62%). Both methods have shortcomings that make them less than ideal in practice.

For both placebo and comparative studies, blinding by over-encapsulation allows a trial design that is simple and relatively inexpensive. However, over-encapsulation can raise concerns about bioequivalence. In addition, many tablets are too large to fit into gelatin capsules. In such cases, tablets must be broken or crushed, or the alternative double-dummy design must be used.

In double-dummy designs, the production of placebos is relatively expensive and time-consuming. The additional packaging, shipping, labeling, QA, and significant amounts of data for inclusion in Regulatory Submissions also add to the time and cost of the double-dummy designs. In addition, the requirement that patients take two or more doses at each time point can reduce patient compliance.

According to the 2003 PhRMA annual membership survey, U.S pharmaceutical companies spend \$9.3 billion in 2001 conducting Phase I/II/III clinical studies. With 10-20% of this total cost devoted to research medications, significant savings are possible by improving the design and conduct of research trials. A tool which eliminated the use of placebos for comparators in research with tableted products would significantly reduce the cost and time required to produce clinical materials.

**2. Type of Drug Involved**

Any type of tableted, oral medication.

**4. Diseases Affected**

Any disease treatable with tableted, oral medications.

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## 5. Nature of the Solution

The CapTab capsule is identical to standard, two-piece gelatin capsules, except it has the shape of a tablet. With a diameter of 0.500 inch and a height of 0.295 inch, the CapTab capsule can be used to over-encapsulate approximately 97% of tablets currently on the market in the U.S.

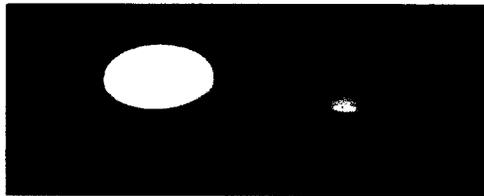


Fig. 1: Open CapTab capsule with large tablet inserted in capsule body.

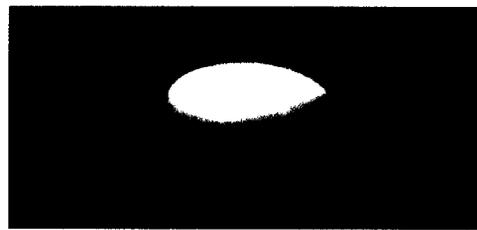


Fig. 2: Closed CapTab capsule.

It is anticipated that the availability of the CapTab capsules will increase the percentage of trials that use over-encapsulation for blinding. The potential benefits include:

- Simplified trial designs that will reduce administrative costs for sponsors
- Faster and less expensive manufacture of research medications (reduces need to manufacture placebo tablets).
- Fewer tablets per day for patients to consume compared to Double-Dummy methods, resulting in improved patient compliance

## 6. Time to Market

CapTab capsules have been manufactured on a pilot scale. It is anticipated that the product will be launched to the research market by May 2005.

## 7. Role of the FDA

In consultation with clinical scientists in academia and industry, FDA should attempt to define best practices in medication blinding by addressing the following issues:

- What improvements in current blinding methods would produce the most critical benefits in terms of public health?

- Is one current method of blinding clearly superior in terms of quality of data generated, patient compliance, and cost to sponsors?
- Should FDA support adoption of standardized blinding methods as a means of improving clinical trial outcomes?
- Will a registry of products with approved overencapsulation dissolution and/or bioavailability characteristics speed the development of clinical supplies by eliminate the need for multiple companies to study the same drugs overencapsulation characteristics.

#### **8. Factors to Consider in Setting Priorities**

FDA should consider the time needed to implement suggested solutions and their potential impact on multiple therapeutic areas. Highest priority should be assigned to solutions that can be implemented for immediate benefit to patients and sponsors.