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Vaccine development within industry

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Over the last decade, new methodologies have generated significant progress in many fields of the biosciences (genetics, immunology, protein chemistry, etc.). New approaches to vaccine development have been formulated and experimented.

The new biotechnology industry as well as the "traditional" vaccine manufacturers were prompt to realize the potential of these technological and conceptual advances and embarked in new vaccine research and development programs as long as 8 years ago. One may then ask why the first vaccine for human use has yet to be made commercially available. In this paper I will try to summarize the different steps involved in driving an attractive new concept from the lab bench to the market place. A recombinant hepatitis B vaccine will be used as example.

The new approaches

Several new avenues of vaccine research are currently explored. Most of them rely largely on recombinant DNA technology:
- purified antigen produced by r-DNA
- attenuation by site directed mutations or recombinations (live vaccine),
- recombinant live carrier (vaccinia, shigella),
- synthetic peptides,
- anti-idiotypic antibodies.

These apply both to the improvement of existing vaccines as well as the development of new vaccines. Each of these approaches has its advantages and drawbacks. Each also has specific implications in terms of development into a product.

The production of a defined antigenic protein by r-DNA has received the most attention initially and this approach has reached, in a few cases, an advanced stage of development. The rest of the discussion will thus focus on this approach for which all the steps of development can be documented.

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Production of a purified antigen by r-DNA: the steps from laboratory to production

The road from the initial isolation of the gene for a (known or putative) protective antigen to the large scale manufacture of a vaccine is long. The main steps can be schematically summarized as follows:

A. Research phase

1. gene isolation,
2. gene characterization,
3. gene expression,
4. product isolation (analytical),
5. product characterization (biochemical and immunological).

B. Development phase

6. scale-up (pilot size),
7. development of process quality control,
8. product isolation (preparative),
9. product testing (safety, efficacy),
10. development of final product specifications and quality control procedures,
11. manufacture.

Obviously these steps are not strictly sequential. For instance, work on expression systems will continue during the development phase in order to improve yields, antigen presentation, facilitate purification, etc. Likewise product characterization and the development of quality control procedures will proceed simultaneously with the elaboration of the large scale purification process.

As the product moves along the research and development steps, increasing resources, both in terms of manpower and investment, will be required. Based on our own experience with a recombinant vaccine, the research phase can represent as little as 10% of resources needed to develop the product.

In terms of human resources only, a project like a recombinant hepatitis B vaccine involves hundreds of men × years.

The production process

The manufacturing of vaccines and other biological products rests on 3 key principles:

- *the seed lot system:* this ensures that each individual production run will be initiated with the same carefully controlled inoculum;
- *consistency of the process:* biological systems cannot be controlled like chemical ones; it is of crucial importance to ensure that each production run will perform within set limits;

Table 1. "Guidelines" documents

- "Standardization and control of the biological medicinal products of recombinant DNA and Hybridoma Technologies and of Products derived from aneuploid cells" from the National Institute of Biological Standards and Control of the United Kingdom.
- "Points to consider in the Production and Testing of new drugs and biologicals produced by recombinant DNA technology" issued by the Office of Biologics Research and Review, Center for Drugs and Biologics of the U.S.A.
- "Full text of notification on application data for Recombinant DNA drugs" from the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Japan.
- "Quality Control of biologicals produced by Recombinant DNA techniques" from W.H.O.
- "Production and Quality Control of polypeptide medicinal products derived from biotechnology". Position paper on the state-on-the-art of the European Federation of Pharmaceutical Industries Associations (Draft).

Further two draft documents regarding Hepatitis B vaccines have been edited:

- WHO: "Proposed requirements for the Standardization and control of Hepatitis B vaccines made by recombinant DNA techniques in yeast".
- National Control Authority of the Netherlands: "Standard Registration Document, Recombinant DNA Hepatitis B vaccine".

- *consistency of the product:* likewise, the final product should be fully characterized and tested (including clinically) after several successive production runs at industrial scale in order to ensure that the product will maintain its properties in future productions.

In the case of the antigens produced by r-DNA techniques, specific considerations apply:

- *Genetic stability of the host and the vector:* this is essential for the consistency of production.
- *Fidelity of expression:* it should be ensured that high level expression and large scale culture do not lead to translational errors or mutations in the coding sequence of interest.
- *Identity with the natural product:* whenever possible this should be demonstrated both in terms of primary as well as higher order structure.
- *Purity:* the highest possible degree of purity, compatible with economic feasibility should be achieved in order to minimize the potential risk associated with unknown contaminants from the hosts organisms used for expression. This may be especially true for products expressed in mammalian cells.
- *Efficacy:* in many instance, the efficacy of isolated antigens either purified from a virus or produced by r-DNA has been found to be lower than when kept in its original structure. This concern may be a determining factor in the choice of the expression system.

In view of the rapid progress and the activity in the field, several national and supra-national authorities decided to issue guidelines, "points to consider"

and "state-of-the-art" documents relating to r-DNA product standardization and control of biologicals produced by r-DNA. A list of documents can be found in Table 1.

Economical considerations

Several criteria will be taken into consideration at the onset of the development phase in order to determine the technical and economical feasibility of a project:

- growth requirements of the host and expression levels,
- complexity, scale-up potential and expected yield of the purification scheme,
- homogenicity of the product,
- expected dose needed (efficacy).

The choice of the host used for expression is crucial both in economic and qualitative terms: mammalian cells remain far more expensive to manipulate at large scale than microorganisms. However, in some instances, they may be required to produce an antigen of adequate efficacy. On average, expression levels reached in *E. coli* are higher than in yeast. But, fermentaion of the later can yield 5 to 10 fold more biomass.

The purification process is equally critical. The purity level that one has to achieve often requires many steps. It is worth noting that a 10 step process with a 80% yield at each step will result in a final yield of 10%.

The example of hepatitis B surface antigen

Hepatitis B surface antigen produced in yeast will be the first recombinant vaccine for human use to reach the market. Details on the strategy used for its production and the numerous tests carried on the process and the final product will be given in order to illustrate the consideration given above.