SOME TOPICS WITHIN BIOREACTION ENGINEERING.

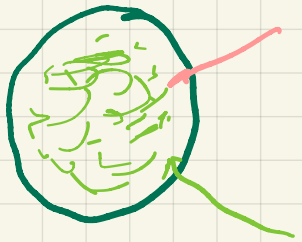
→ KINETICS OF ENZYME-CATALYZED REACTIONS

ELEMENTARY STEPS

STEADY-STATE APPROXIMATION

FITTING OF DATA TO NONLINEAR EXPRESSIONS...

→ IMMOBILIZED ENZYMES

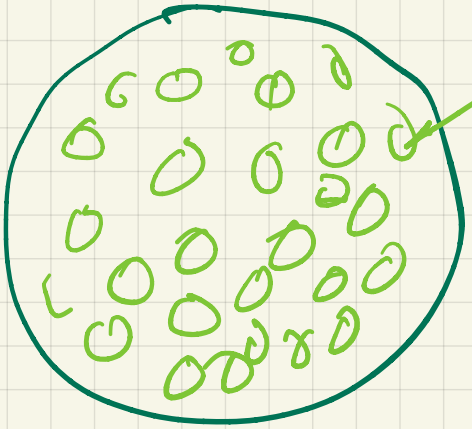


GEL MADE INTO BEAD

ENZYME DISPERSED INSIDE

⟹ THIELE MODULUS

PROBABLY NOT 1ST ORDER KINETICS

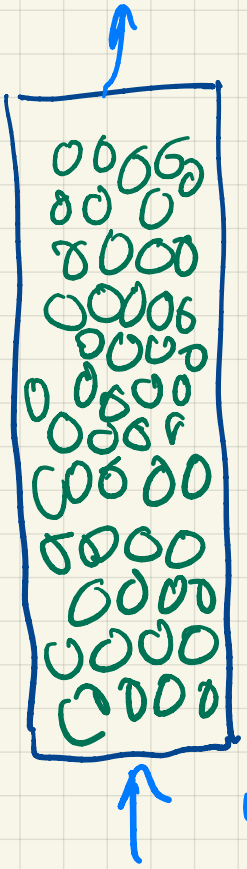


BACTERIA IMMOBILIZED IN A BEAD

THE BACTERIA WOULD BE USED FOR A SPECIFIC FUNCTION

= REMOVE NITRATES FROM GROUND WATER

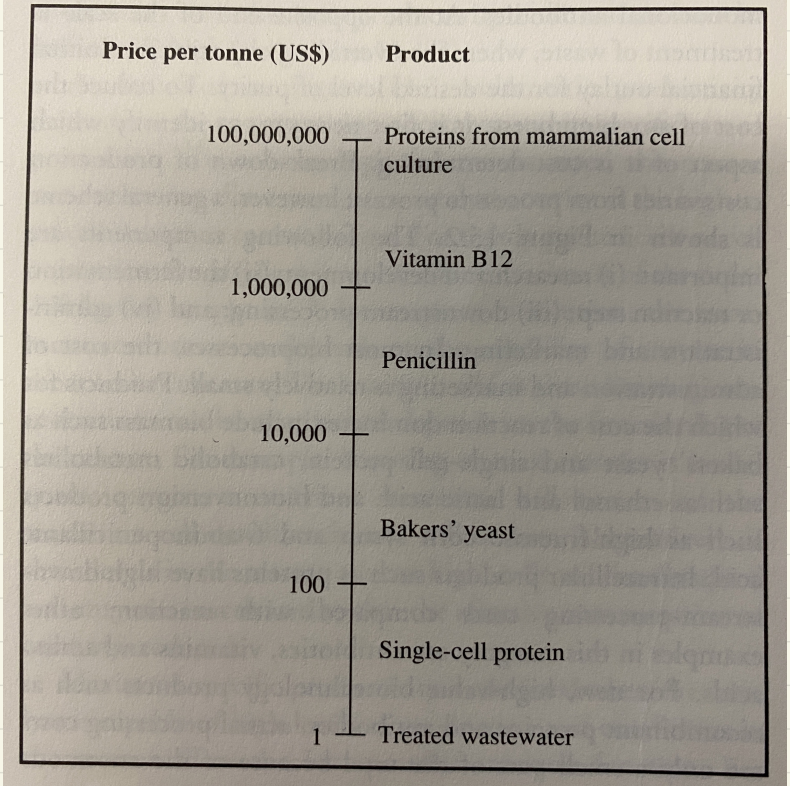
PACKED BED OF SUCH BEADS



WATER + O_2

BIOREACTORS ALMOST ALWAYS HAVE A GAS → LIQUID TRANSFER PROCESS

(From P.N. Royce, 1993, A discussion of recent developments in fermentation monitoring and control from a practical perspective. *Crit. Rev. Biotechnol.* 13, 117–149.)



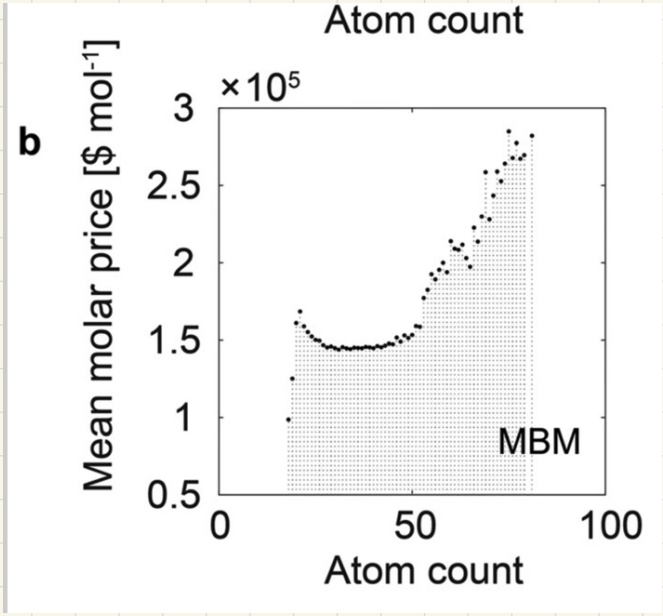
HOW MUCH "TROUBLE" YOU ARE WILLING TO GO THROUGH TO MAKE SOMETHING DEPENDS ON VALUE OF PRODUCT!!

FOR "CHEMICALS" RANGE IS NOT LARGE

STANDARD CHEMICALS & PHARMACEUTICALS FROM CHEMICAL PROCESSING

$\$ \sim$ M.W.

$\frac{\$}{\text{MOLE}}$



SCIENTIFIC REPORTS

OPEN

Molecular descriptor data explain market prices of a large commercial chemical compound library

Received: 06 April 2016
Accepted: 25 May 2016
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Jaroslaw Polanski[1], Urszula Kucia[1], Roksana Duszkiewicz[1], Agata Kurczyk[2], Tomasz Magdziarz[3] & Johann Gasteiger[4]

The relationship between the structure and a property of a chemical compound is an essential concept in chemistry guiding, for example, drug design. Actually, however, we need economic considerations to fully understand the fate of drugs on the market. We are performing here for the first time the exploration of quantitative structure-economy relationships (QSER) for a large dataset of a commercial

Figure 13.2 Contributions to total production cost in bioprocessing.

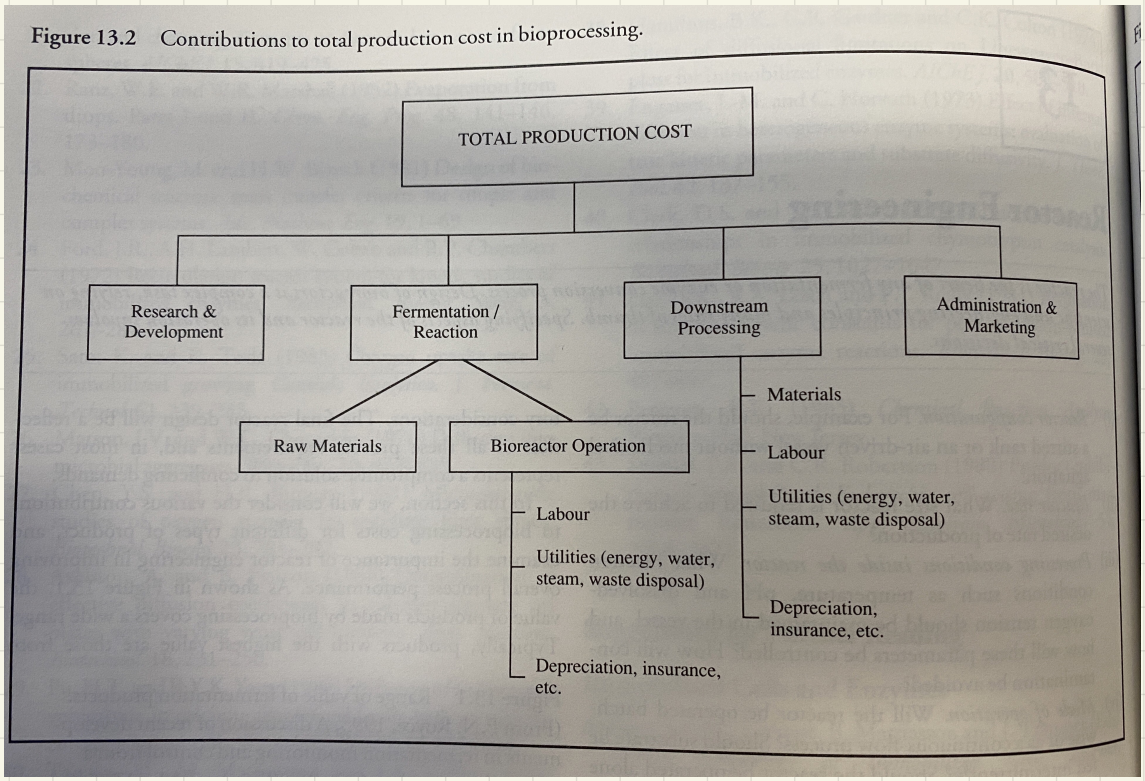
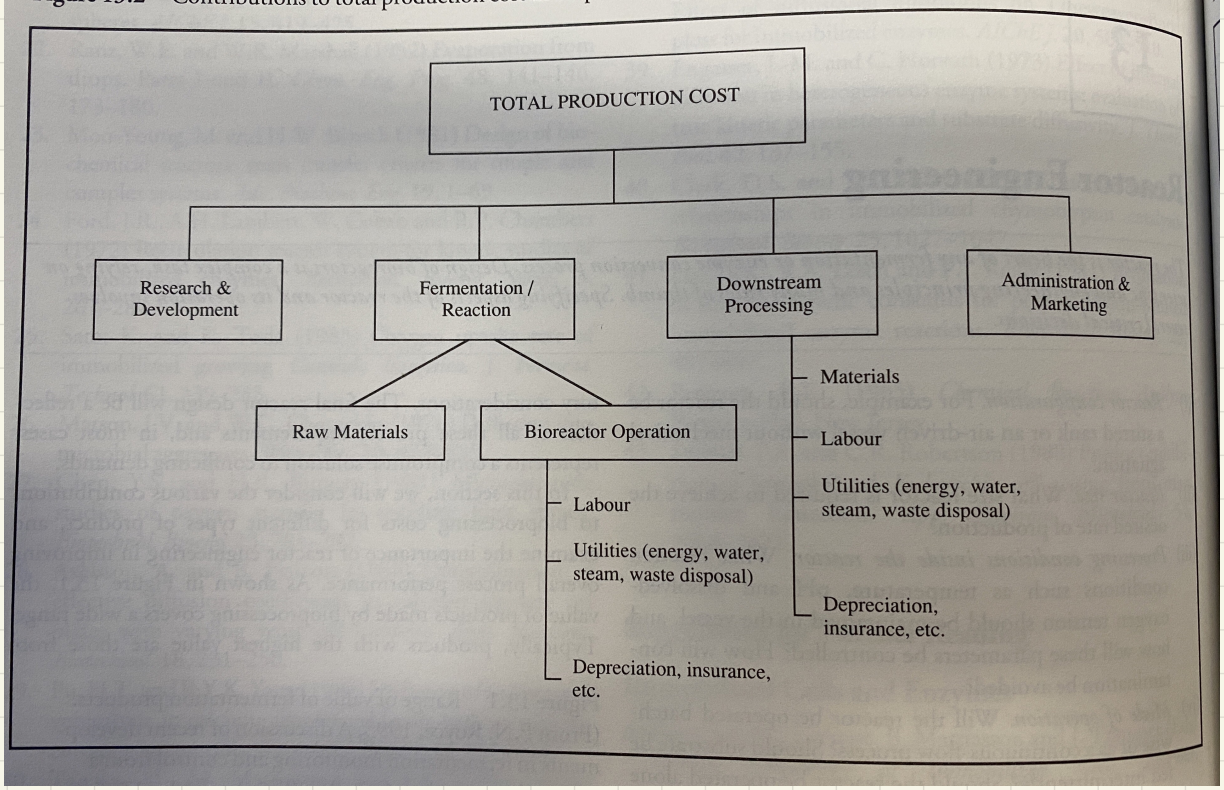


Figure 13.2 Contributions to total production cost in bioprocessing.



BIOREACTORS FOR CHEMICAL PRODUCTION

→ FERMENTER [Zymomonas mobilis]

GLUCOSE → ETHANOL

- COMMONLY BATCH

  BUT IF CSTR → "CHEMOSTAT"

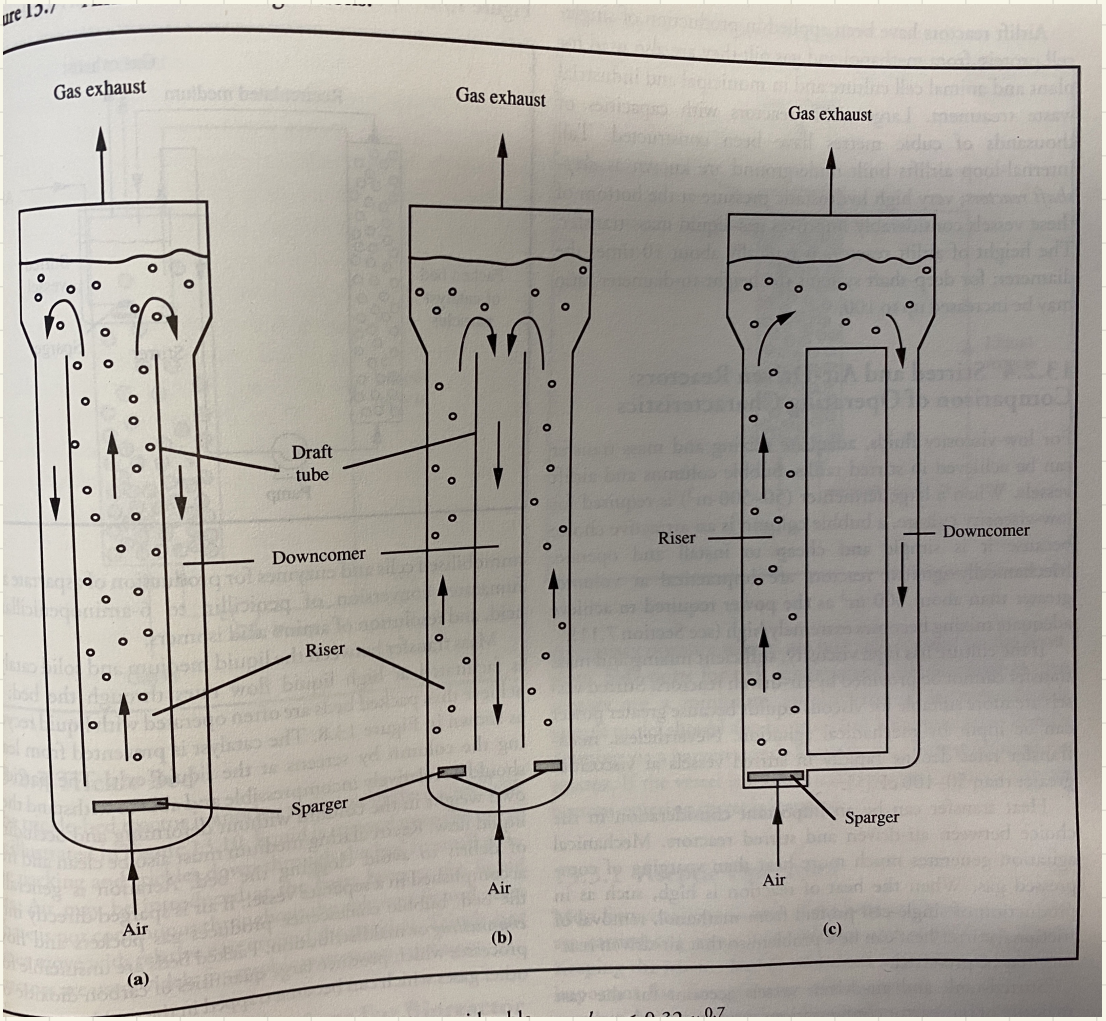
- HAVE TO KEEP CELLS ALIVE TO PRODUCE PRODUCT

- CELL MASS WON'T BE CONSTANT

→ AS MENTIONED ABOVE:

WILL HAVE GAS ABSORPTION

PROBABLY AIR



RECALL $\dot{W}_S = q \Delta P$

$q \rightarrow$ VERY LARGE

$\Delta P \rightarrow$ SIGNIFICANT FOR A BIG REACTOR

BUBBLE SIZE $\downarrow$ AS $\Delta P \uparrow$

FOR INJECTOR.

COULD USE A CSTR

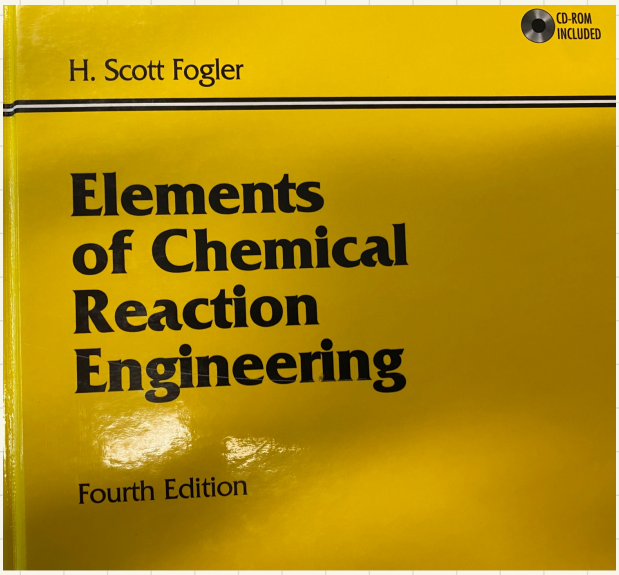
WITH IMMOBILIZED ENZYME

(SPHERICAL BEADS)

- ENZYME REMAINS IN REACTOR

- GROWING CELLS, HAVE TO WORRY ABOUT "WASHOUT"

A COMPLETELY DIFFERENT TOPIC IS PHYSIOLOGICAL OR PHARMACOLOGICAL MODELING.



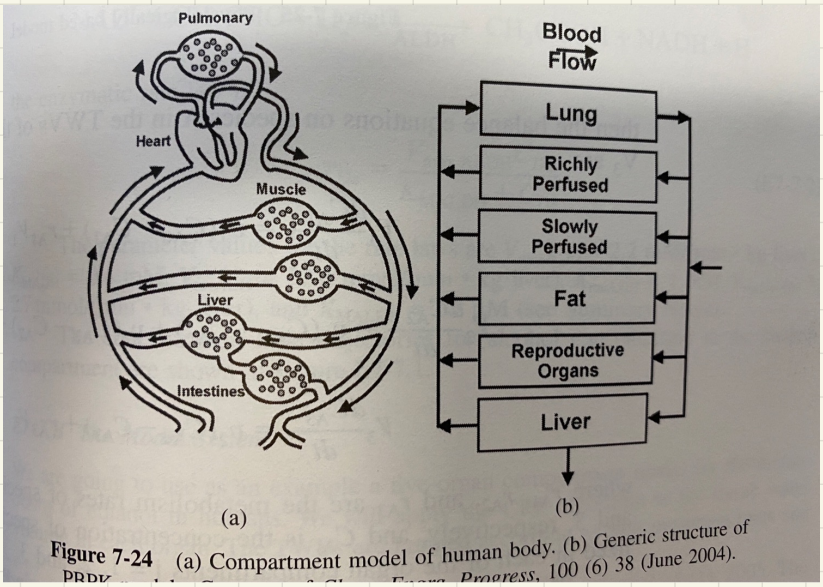


Figure 7-24 (a) Compartment model of human body. (b) Generic structure of PBPK ... *Progress*, 100 (6) 38 (June 2004).

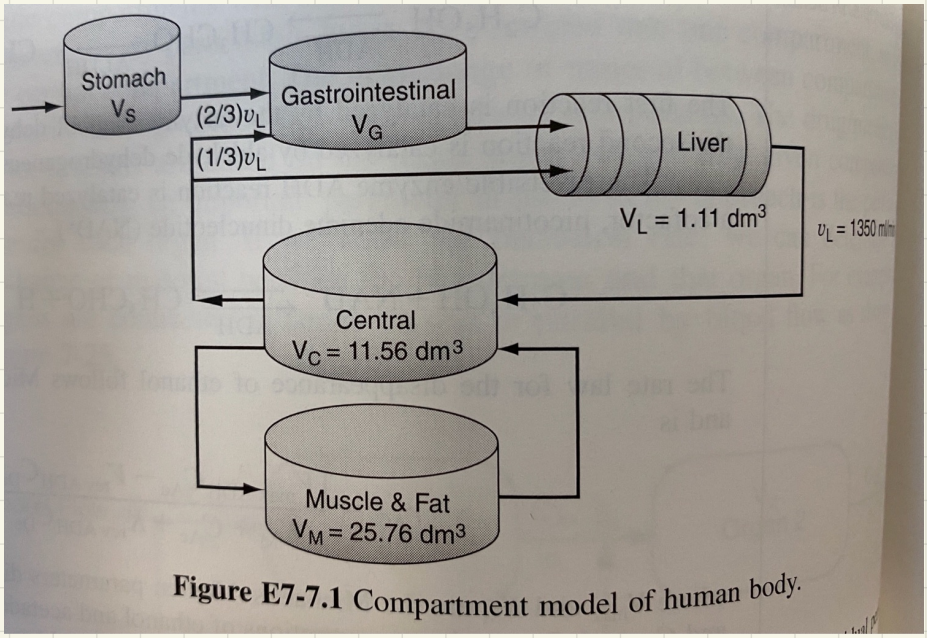


Figure E7-7.1 Compartment model of human body.

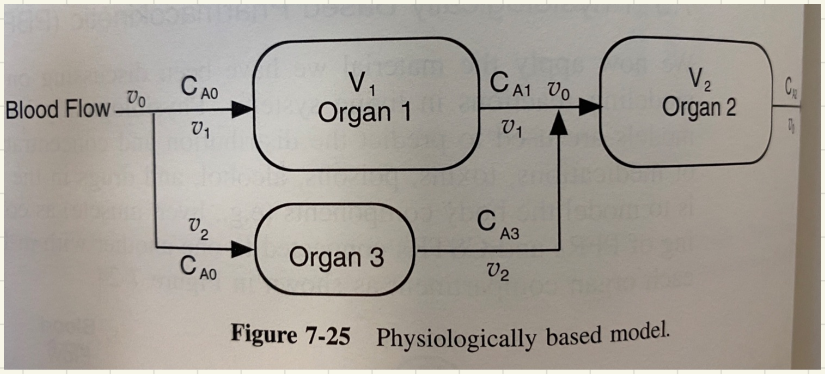


Figure 7-25 Physiologically based model.

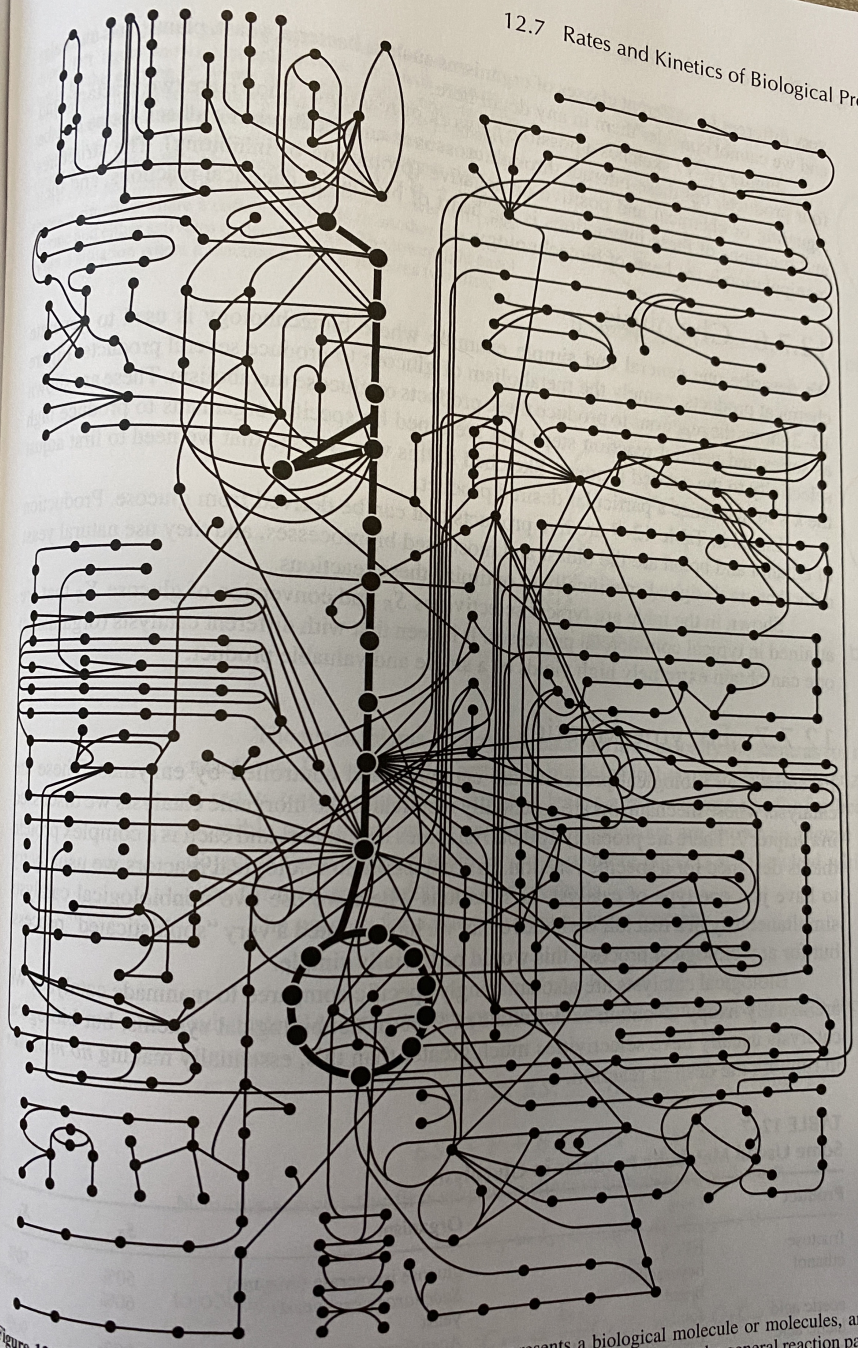
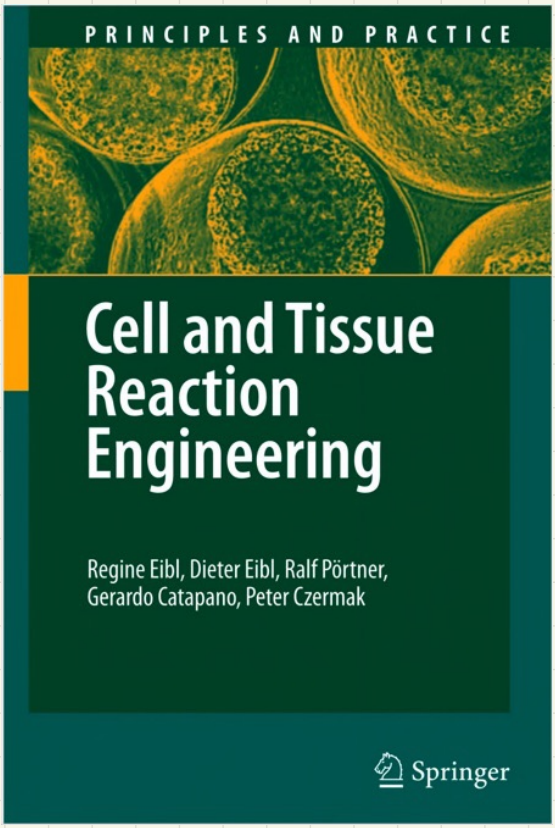


Figure 12–18 Generic metabolic pathway diagram. Each dot represents a biological molecule or molecules, and each line connecting them represents a reaction. This is a highly simplified pathway diagram, which approximates the general reaction pathways in all eukaryotic systems. The heavy line and circle are the glycolysis pathway of glucose to CO_2 which supplies the "engine" for all reactions.

USE OF MAMMALIAN CELLS TO PRODUCE "BIOLOGICAL" MOLECULES



CURRENT PRODUCTS

- VIRAL VACCINES
- MONOCLONAL ANTIBODIES
- INTERFERONS
- RECOMBINANT THERAPEUTIC PROTEINS

STILL EMERGING

TISSUE ENGINEERING

FOR REPLACEMENT OR THERAPEUTIC TESTING

GENE THERAPY

"MESSAGE" IS THAT WHILE THERE ARE BENEFITS TO KNOWING (SOME) MOLECULAR - CELLULAR BIOLOGY,

KEY DIFFICULTIES IN PROCESSES CAN BE OVERCOME WITH THE STANDARD TOOLS THAT ALL OF US CHEMICAL ENGINEERS POSESS!!

VIRAL VACCINES:

- HUMAN
  - POLIO, HEPATITIS B, MEASLES
  - MUMPS,
- VETERINARY
  - RUBELLA, RABIES,
  - FOOT & MOUTH DISEASE

PRODUCTS ARE PRODUCED IN "BIOREACTORS"

2 L ⟶ 20,000 L

SPECIFIC MANUFACTURING DIFFICULTIES!

→ GETTING APPROPRIATE CELLS TO START PROCESS

— SLOW GROWTH RATES
12 - 24 h DOUBLING TIMES

— LOW PRODUCTIVITY OF PRODUCTS

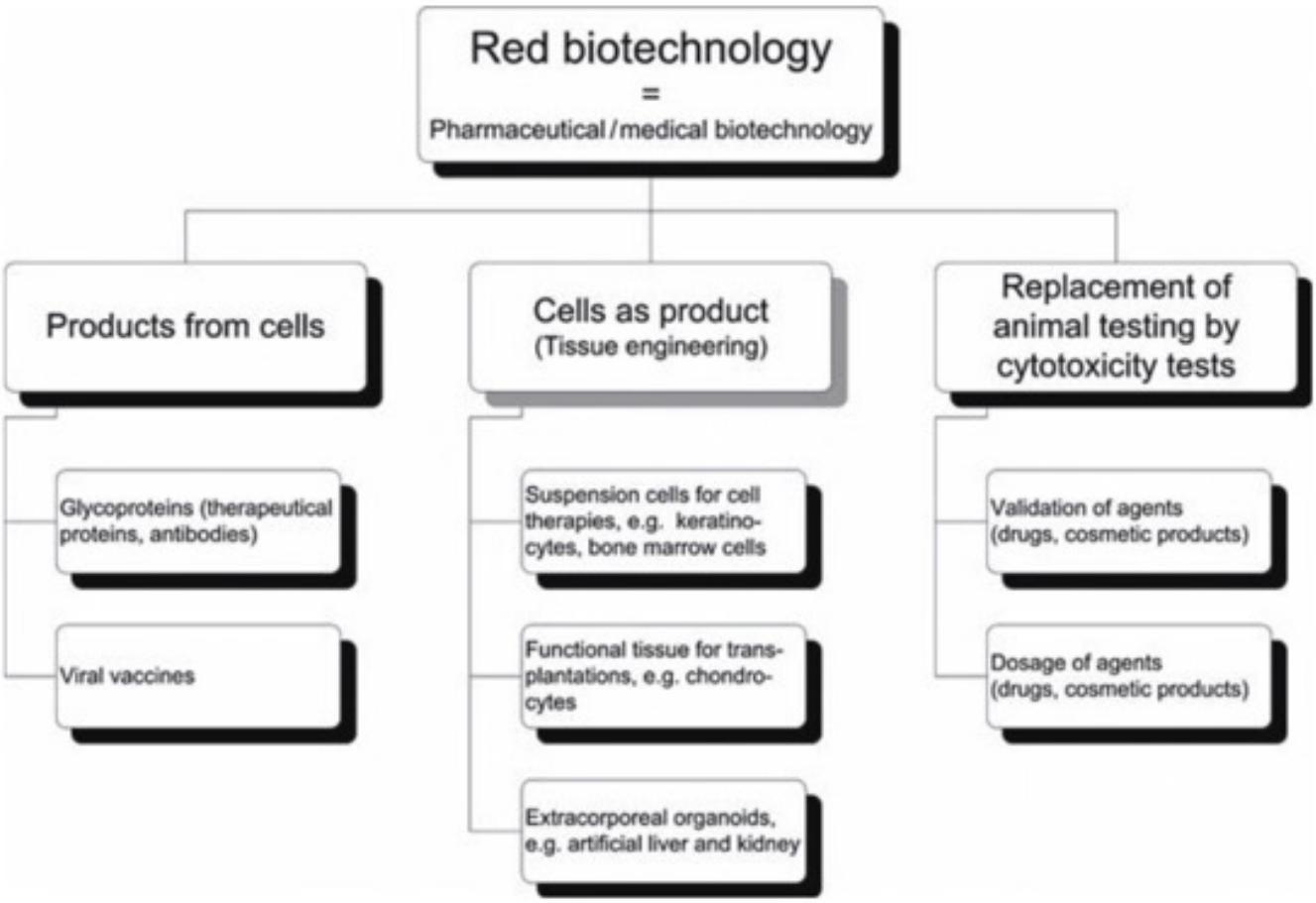
— SENSITIVITY TO SHEAR STRESS BECAUSE OF THE LACK OF A CELL WALL

WE KNOW A LOT ABOUT THIS!!!

— COMPLEX GROWTH MEDIUM

$!!!!!

— SOME KINDS NEED TO GROW ON A SOLID* SURFACE



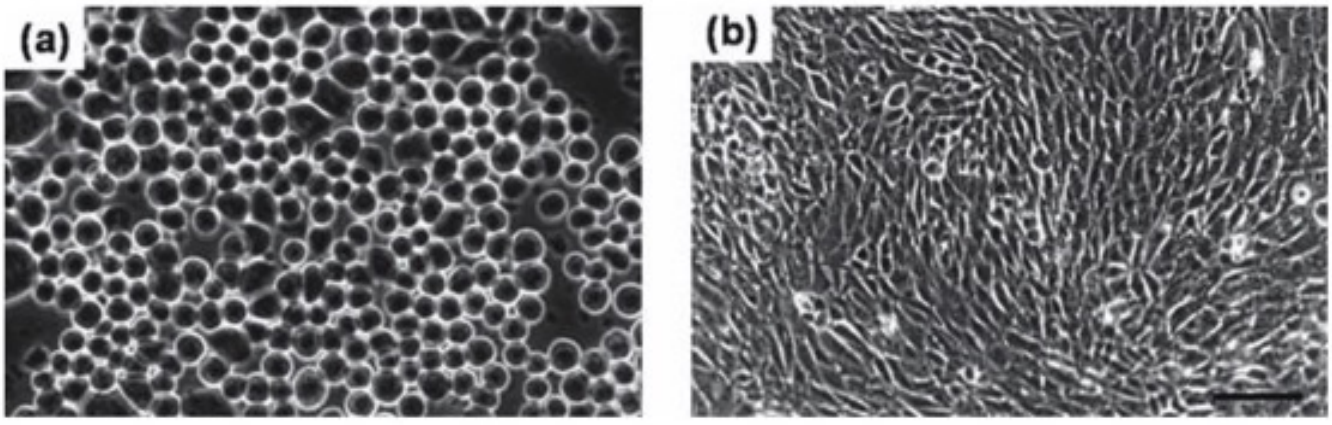


Fig. 1.2 Morphology of (**a**) suspendable and (**b**) adherent mammalian cells (bar approx. 30 µm)

Table 2.1 Culture characteristics (suspension) of microbial, plant cell and mammalian cell culture (t_d: doubling time, vvm: volume of gas per volume of liquid and minute)

Characteristic	Microbial culture	Plant cell culture	Mammalian cell culture
Size	2–10 µm	10–100 µm	10–30 µm
Individual cells	Often	Often aggregates	Sometimes adherent
Inoculation density	Low	High (10%)	High (5–10%)
Growth rates	Rapid (t_d = 1–2 h)	Slow (t_d = 2–7 d)	Slow (t_d = 20–50 h)
Shear sensitivity	Low	Moderate	High
Stability	Stable	Unstable	Unstable
Product accumulation	Intra-/extracellular	Mostly intracellular	Mostly extracellular
Culture medium	Often simple	Often complex	Complex
Temperature	26–36 °C	25–27 °C	29–37 °C
Aeration	Often high (1–2 vvm)	Low (0.1–0.3 vvm)	Low (~ 0.1 vvm)
Foaming	Often high	sometimes foaming	Sometimes foaming
pH-value	3–8	5–6	7.0–7.4
Cell density	(Very) high	Low	Low–middle
Scale-up	Easy	Difficult	Difficult

2.2.2 *Hybridom Cells for Production of Monoclonal Antibodies*

Table 2.2 Comparison of "normal" and "transformed" cells

Normal	Transformed
Diploid (46 chromosomes for human cells)	Abnormal number of chromosomes
Non-malignant	Malignant (form tumour in mice)
Finite life-span (50+−10 subcultures max.)	Infinite life-span
Anchorage-dependent (except blood cells)	Non-anchorage-dependent (i.e. suspension culture possible)
Mortal; finite number of divisions	Immortal or continuous cell lines
Contact inhibition; monolayer culture	No contact inhibition; multilayer cultures
Dependent on external growth factor signals for proliferation	May not need an external source of growth factors
Longer retention of differentiated cellular function	Typically loss of differentiated cellular function
Display typical cell surface receptors	Cell surface receptor display may be altered

nature biotechnology

Q&A | Published: 21 October 2020

COVID-19 antibodies on trial

Laura DeFrancesco ✉

In October, US President Donald Trump received Regeneron Pharmaceuticals' experimental monoclonal antibody (mAb) cocktail REGN-COV2 as part of his treatment for COVID-19. Buoyed by a positive response, both Regeneron and Eli Lilly have filed requests for Emergency Use Authorization from the US Food and Drug Administration, although Lilly had to pause clinical testing because the trial crossed a predetermined safety threshold. Lilly's product, LY-CoV555, is a cocktail of two human IgG1 mAbs targeting different spike (S) glycoprotein epitopes. These and 11 other experimental mAb treatments targeting the SARS-CoV-2 S protein are

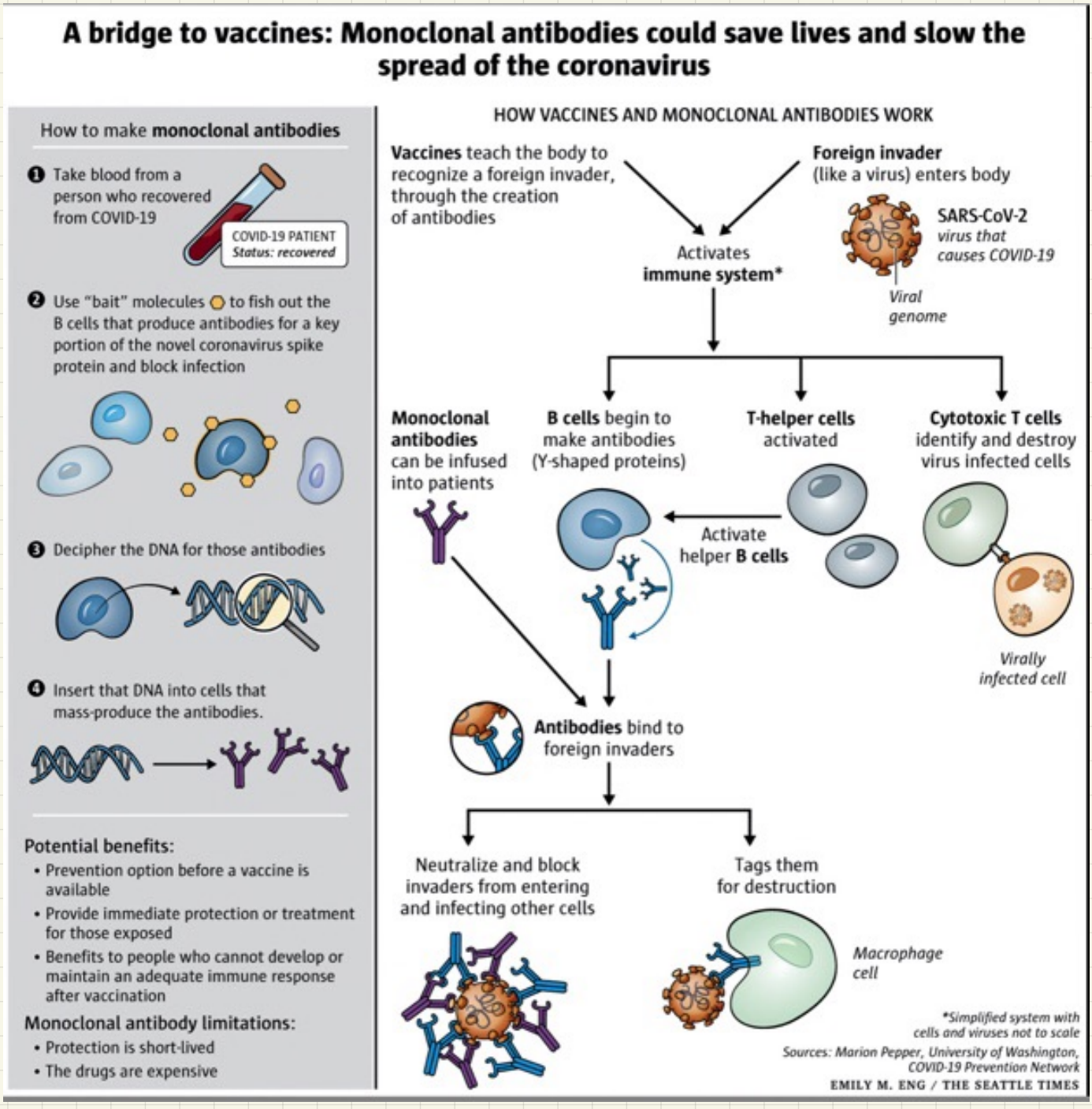
By Sandi Doughton
Seattle Times staff reporter

Monoclonal antibodies could fill the COVID-19 treatment gap until vaccines arrive — but at a cost

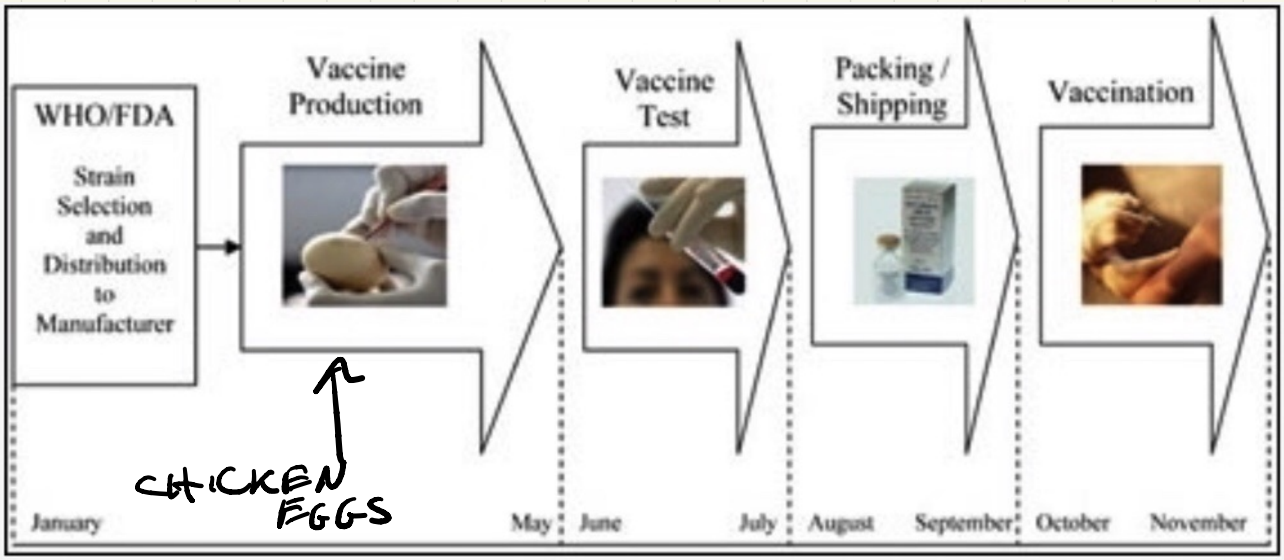
Oct. 2, 2020 at 6:00 am | *Updated Oct. 2, 2020 at 11:52 am*

Seven out of the top 10 best-selling drugs globally are monoclonal antibodies — including Humira for rheumatoid arthritis and Crohn's disease and Keytruda for melanoma and other types of cancer — and they're all expensive.

The median cost for a year of treatment ranges from $15,000 to more than $140,000, according to the report by the International AIDS Vaccine Initiative and the British philanthropy Wellcome.

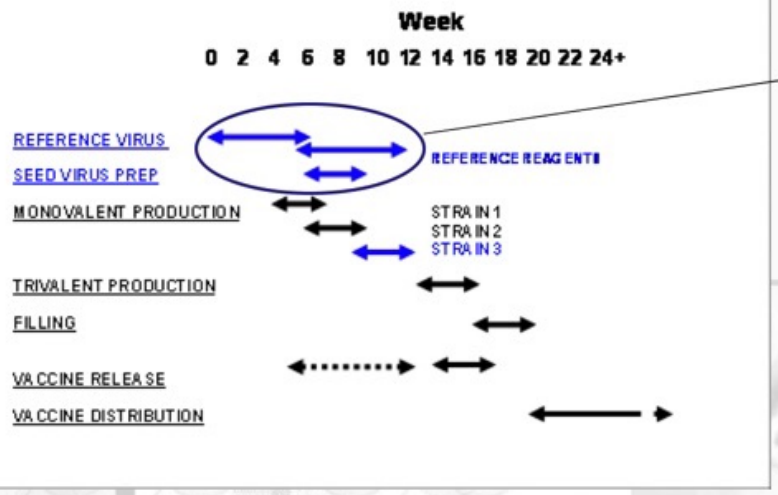


FLU "VACCINE" HAS LONG BEEN PRODUCED:



Egg-based Manufacturing
Current "Gold Standard"

Time to First Trivalent Vaccine Lot after Strain Change



less critical when using "gene to vaccine" technologies

From a presentation by Norman Baylor, US FDA/CBER

Examples of Influenza Vaccine products and manufacturing technologies

- **Products and Technologies requiring development of seed virus**
  - Egg-based manufacturing
    - Inactivated, split, purified subunit products
    - Live attenuated vaccines
  - Mammalian Cell-based manufacturing
    - Inactivated, split, purified subunit products
    - Live attenuated vaccines
- **Products which are manufactured from "gene to vaccine"**
  - Baculovirus
    - insect cell culture, whole larvae manufacturing
    - subunit versus VLP
  - Prokaryotic manufacturing (*E. coli*)
  - Recombinant Adenoviral-vectored influenza vaccines
  - Plant-based manufacturing (subunit versus VLP)
  - Peptide epitope products (computational vaccinology)