Among the geeky shows with a target audience of science and engineering nerds, the Science Channel’s “How It’s Made” is a standout. In continuous production since 2001 this show has produced hundreds of episodes documenting the manufacture of the most humble household appliance (think toilets) to esoteric medical instruments such as MRI scanners. The long running appeal of this show must resonate with the universal human curiosity about how things are put together. In this article I hope to connect to that common interest.

Not exactly with a “How It’s Made” perspective on plasma derivatives since readers of this magazine already have at least a general understanding of plasma derivative manufacture but rather an examination of a “Why They are Made this Way”. The focus will be on some of the unique factors associated with the production of these therapeutic agents and how these factors shape our approach to modern manufacturing.

As pharmaceutical agents the most unique feature of human plasma derivatives is the obvious. The production raw material is human plasma. To the casual observer, the medical use of whole blood or plasma feels reasonably obvious and natural, remove blood from one individual, transfuse it into another. However the concept that one could take multiple units of plasma, pool them and purify individual plasma components and that the isolated components would have more medical value than the component plasma is not immediately obvious. The fact that plasma derivatives first came into being and perhaps exist at all is arguably an unlikely accident. Their origin arose out of the confluence of medical need in a global conflict, developments in protein biochemistry and the presence of a
few individuals such as Edwin Cohn who had the knowledge, passion, and influence necessary to provide the leadership for plasma derivative development. To get a flavor of just how improbable these products are, try imagining the challenges one would face today in constructing a business plan for the de novo development of these agents. A consideration of the associated legal and liability issues alone would likely doom any funding of plasma derivative development.

Fortunately for humanity and our industry, there was a “black swan” event. Plasma derivatives were developed and these products have provided life sustaining and lifesaving medical benefit to millions. While many factors come into play when companies contemplate the manufacture of any class of therapeutics, for plasma derivatives the complexity that underlies their manufacture is undoubtedly a major deterrent. To illustrate how the complexity of these products impacts manufacturing I will utilize conventional synthetic drugs as a comparator. These products make up the majority of prescription medicines. For these “typical” pharmaceutical products, a production run is initiated with one to a few lots of starting material. Acquisition and release of these raw materials as “suitable for further manufacture” requires qualification of a limited number of suppliers and the performance of small number of incoming release tests. The release testing is often just visual inspection of a container, review of a supplier certificate of analysis, and the performance of a single test to confirm identity. Compare this situation to that which occurs in the production of a single lot of a plasma derivative such as intravenous immunoglobulin (IVIG). A lot size of 50 Kg IVIG requires the collection, testing, and release of approximately 16,000 to 60,000 lots of the raw material, a unit of plasma (the variation is driven by the unit volume of the plasma type, source, -880 ml, or recovered, -240 ml, used). Each supplier of the plasma (otherwise known as the donor) must also be individually qualified. Taken together, these activities approximately 200 information inputs per unit, each production run requires generating, evaluating and storing ~3,000,000 to 12,000,000 raw material data points.

Obviously this is a staggering amount of information to manage and preserve. Current Good Manufacturing Procedures (cGMP) for pharmaceuticals require that manufacturers not only perform qualification of the raw materials but also be able to forward and reverse track the raw materials, throughout the production process and ultimately to all recipients. This means that the manufacturers need credible systems which can track forward and back each unit of plasma from the vein of the donor to the vein of all recipients. The data analysis required for a task of this magnitude helps explain why over the preceding decades commercial manufacturers have dramatically increased the size and capabilities of their computerized manufacturing networks. The systems necessary to manage this data intensive environment have significant economies of scale. Simply put, computers scale efficiently, humans don’t. Small scale manufacturers have great difficulty amortizing the cost of automated systems over small production volumes.

Raw material tracking is, of course, far from the only complex and demanding area of plasma derivative manufacture. These therapeutics also have three other general features which tend to differentiate them from traditional pharmaceuticals. The first and most important is the moral/financial penalties associated with raw material loss. Every donation of plasma is voluntary and waste through inefficiency is, simply put, an abuse of the trust donors place in manufacturers. Fundamentally avoidable waste or low yield processes are in a sense unethical. With both
under-diagnosis in the developed world and under-treatment in the developing world, there is currently a patient for every product vial produced and inefficiency means some patient unnecessarily is deprived of the benefit of these therapeutics. Fortunately, economic factors reinforce this ethical dimension. Conventional pharmaceuticals typically have a cost structure in which raw materials represent a small percentage of the total cost of manufacture. For simple therapeutic solutions, the raw material cost is often less than the cost of the final product container. For plasma derivatives the situation is quite different, plasma costs account for 57% of the cost of manufacture as pictured. This raw material cost is magnified by the 60 day plasma hold (no just-in-time delivery for plasma) which increases inventory costs. The relatively high raw material costs account for the production process in the form of Work-in Progress (WiP) inventory costs. These costs are further amplified by the relatively long, typically months, of production time from plasma collection to final product. In summary, for cost effective production, plasma loss in manufacture must be driven to as low a level as possible.

The second differentiating feature of plasma derivatives is the inherent complexity and mutability of the raw material and intermediates. Plasma is sometimes characterized as a living material. This is, of course, not true however plasma does share some characteristics of living systems. Plasma has a complex composition. Most of the components show biochemical activities and can react with themselves and/or other components. Multiple environmental factors, such as temperature, pH, ionic strength, material surfaces, etc. will cause compositional changes usually in a non-linear fashion (small change big impact). Like a living system, plasma is also extremely sensitive to microbial contamination. All of these features were, of course, well understood by Cohn and coworkers. The success of their foundational work was owed as much too rigorous process control as to scientific expertise.

When dealing with complex systems, there is a truism in manufacturing that complexity is best offset by simplicity. As far as possible, you reduce allowable operating ranges, variations in procedures, process hold times, etc. The intent is to simplify the available options at any step. Obviously this requires substantive expertise and investment in process design and development. Properly implemented, this reduction in variation reproducibly leads to higher yields and improved quality. In short, since you can’t change the nature of your starting material, you obtain repeatable results by consistent, strict control of the manufacturing materials, processes, and environment. This stringent management naturally comes with a substantive and continuing investment in staff training, process development, and facilities. Again, operational scale greatly enhances the return on this investment.
The third differentiating factor arises from a combination of the above two. In an environment with significant material and production costs and lengthy production runs, efficient manufacturing requires high facility capacity utilization. Many production areas in plasma derivative manufacturing facilities commonly run at even higher utilization than conventional pharmaceutical manufacturing, where 65% to 75% capacity utilization is the norm. The benefits of very high facility utilization, working your assets hard, while intuitively obvious are not simple to attain. Ideally, your manufacturing facility is optimally designed so that all available production slots are utilized, raw material and WIP inventory is minimized, and production targets are met. The ability to achieve this sweet spot requires a sophisticated management of ancillary manufacturing activities such as production planning, logistics, process monitoring, and maintenance. The necessity for wide ranging capabilities in these areas in turn favors larger production plants. Large organizations can afford to maintain the expertise breadth to provide comprehensive support services in these areas. With high levels of facility utilization, manufacturers also derive substantive immediate benefit from the implementation of new technologies or processes which introduce additional efficiencies. If you are operating at 65% capacity and the introduction of a new technology allows you to provide the same output at 60% facility utilization the advantages of change are limited. In contrast, in a 100% utilization setting, getting 5% more product from the same facility (in an environment where every vial has a customer) provides significant advantage.

In summary, the current realities in the manufacture of plasma derivatives favor large manufacturing networks with plasma throughputs in the millions of liters per year. Operating in competitive markets with professional independent regulation, these large entities produce plasma derivatives with the highest quality and the lowest possible production cost. Despite the organic pressures which favor large production entities with independent oversight, there are those who advocate a national self-sufficiency program in which governmental entities would produce plasma derivatives required for their region.

In the introduction to this report, the authors layout the rationales for their belief in the desirability of self-sufficiency. In this discussion one point which was made that would give rise to little disagreement is the view that “...blood and blood products are a precious national resource that will remain limited by nature.”

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that national governments have not demonstrated that are inherently better able than any other entity to sustainably manage any national resource. In fact, a fair reading of history would suggest that the state producers often have the unchecked ability to mismanage a resource while utilizing the considerable power of the state to deflect or discourage criticism. This situation where the state polices itself, often devolves into crony regulation. These factors tend to make a government organization the least fit approach for efficient, sustainable resource utilization. Even assuming that one believed that for plasma derivatives, state manufacturing organizations were philosophically preferable, given that healthcare dollars are globally a scarce and limited resource, this approach to production means that resources will be inefficiently used. With limited available funding, governments will have to short-change patients in one area to support inefficient provision of plasma derived therapeutics in another. Potentially even more problematic for patients, will be that self-sufficiency becomes in practice not what the market needs but what can be produced by a government monopoly in a closed marketplace.

Does this mean that there is no desirable role for the state in plasma derivative production? Certainly activities by countries to encourage blood and plasma donation are of value. Public/private partnerships in which countries enter into relationships with experienced fractionators to produce plasma derivatives (toll fractionation, joint facilities etc.) provide a potentially useful mechanism for expanding plasma derivative supply. So long as markets remain open, and regulation is credibly independent, the provision of sufficient high quality products is supported.

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Sources:
1. In this article plasma derivatives will be defined as therapeutic substances derived from plasma and processed so as to provide a defined therapeutic composition.
2. A black swan event is a high-impact, hard to predict, and rare event that is beyond the realm of normal expectations.
3. Depending on the country regulatory agencies require that donor information be retained for up to 30 years.
4. In this discussion the concept of “cost” will be treated somewhat simplistically essentially plasma cost will be considered as the free market spot purchase cost.