Standardization of apheresis collections for consistent cell product manufacturing

*by*ALEXEY BERSENEV*on JANUARY 30, 2016  in*[CELL PRODUCT](http://stemcellassays.com/category/cell-product/), [CLINICAL LAB](http://stemcellassays.com/category/clinical/), [CONFERENCES](http://stemcellassays.com/category/conferences/)

With success and increasing interest to immunocellular therapies, apheresis became the most frequent incoming raw material for product manufacturing.  Everyone, who is involved in day-to-day processing of immunocellular therapy products, very familiar with a big variability of  apheresis collections. But, until now, professionals have not discussed openly manufacturing risks and potential solutions, related to variability of apheresis products. Speakers from two conferences that I’ve attended this week (see [here](http://www.bioleaders-forum.com/) and [here](https://www.ibbr.umd.edu/NISTCART)), brought up these issues in relation to manufacturing of CAR T-cell products.

While product manufacturing process becomes more and more defined, impact of external factors, such as incoming donor material and storage/ delivery (post-manufacturing logistics) are still poorly validated and standardized. These external factors, which have nothing to do with manufacturing, could totally kill your product.

Why this issue is coming up more and more right now? While immunocellular therapy is developed in academic institution, the most (if not all) apheresis products get processed. However, significant fraction of patients with hematological malignancies have hugely abnormal hematopoiesis and peripheral blood profile. For example, apheresis product from CLL patient, contained 100 billion cells, could be composed of 99% leukemic blasts. This is extremely hard product to work with if you need to get very pure population of T-cells on day 0 of culture. To resolve apheresis collection variability problem, academics usually develop multiple processing pathways. Nonetheless, some products still may fail manufacturing due to “hard to work” composition of incoming apheresis material. The problem is greatly amplified in commercialization of T-cell therapies and technology transfer. Industry doesn’t want to take a risk of manufacturing failures, related to apheresis product. The trigger of public discussion was a progress of T-cell therapy to multicenter and multinational trials.

Tim Oldham from Cell Therapies (Australia) gave 2 talks during Phacilitate Cell Gene Therapy meeting on a problem of managing apheresis for CAR T-cell products manufacturing. He said that the most variable and the most critical process in the whole auto- product manufacturing exercise is incoming donor material. The major issues, which developers facing with variable apheresis products are the following:

* insufficient collection (low volume/ low cell number)
* unmanageable contamination by unwanted cell populations (leukemic blasts, granulocytes, red blood cells)
* unplanned 2-days collection (mostly applicable to mobilized HPC(A) products)

Potential sources of apheresis product variability:

1. Donor (patient in auto- settings) – the most important single variability factor!
2. Collection device (apheresis machine)
3. Device operator (apheresis nurse)
4. Facility’s internal policies, scheduling and logistics

Unfortunately, it is impossible to fully solve this problem by standardization, because you cannot standardize the patients. Every patient with the same disease could differ from another by chemotherapy regimen (some chemo- drugs kill T-cells), history of previous stem cell transplants and relapses, tumor burden, co-morbidities, immune system status and so on.

There are 2 groups of potential reasons for manufacturing failure, related to incoming apheresis products:

* number of targeted cell population is too low to begin with (example: absolute lymphocyte count close to zero in immunodepleted patient);
* new process, validated on normal donors does not work for patient with hugely abnormal blood.

Now, how can we solve or minimize the problem of apheresis product variability? One way to go is to standardize it by setting apheresis specs. As of now “minimal manufacturability requirements” largely unknown or “in the making”.

**Device/ operation/ protocol specs.** Even though, apheresis collection parameters are standardized within one institution (by using the same program on the same device with the same operator’s protocol) from device and operation stand point, there is no harmonization between multiple collection centers. Will company-sponsor require such harmonization? As Oldham says, changing the current well established practice of particular collection facility in favor of CAR T-cell product manufacturing, is not trivial exercise. Ideally, collection outcome could be predicted by peripheral blood cell count (as it’s done in stem cell transplant by CD34+ cells), but it will require a lot of work. Most commercial developers keep them as a secret.

**Product specs.** Another option, is to let collection centers to operate as per their SOPs, but set minimal specs for the products, which will go to manufacturing. For example, if absolute lymphocyte count in peripheral blood pre-collection or in apheresis below the limit, the risk of manufacturing failure is too high to collect/ accept product for processing. Unfortunately, based on these specs, some patients will be rejected by not meeting “criteria of manufacturability”.

**Multiple processing pathways.** Finally, sponsor/ manufacturing facility could decide to not set strict collection specs, but accommodate all patients/ products. In this case, multiple manufacturing pathways should be developed, based on cell number and composition of incoming apheresis. Cell Therapies did exactly this and ended up with 5 different processing pathways. Unfortunately, for industry, this option means increase of complexity (and related risks). Multiple processing pathways may require more facility equipment (multiple devices), prolonged personnel training (know how to triage products for different pathways), less options for automation of entire process and more complex regulation.

Oldham called for industry collaboration in data collection of apheresis products variability. Some sort of database could be created and publicly shared. He acknowledged that companies may not invest in setting of pre-collection specs or if the do, may not be willing to share the data. He says that this kind of data usually is not proprietary and sharing could greatly advance the field. Another hurdle is potential tension between company-sponsor, physicians, collection facility and manufacturing facility in the common decision making.

Working with many apheresis products, I know the problem very well. I wish the developers can share some data on it and come up with recommendations.