CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

To: Members of the CIRM Facilities Working Group

From: Marie Csete MD PhD, Chief Scientific Officer

RE: GMP facilities for CIRM grantees

Date: February 23, 2009

CIRM's 2006 Strategic Plan anticipated the need for current Good Manufacturing Practices (GMP) facilities to produce clinical-grade cell products for administration to patients. CIRM conducted research on GMP facilities in California in order to inform a plan of action around how we can best use our resources to facilitate CIRM grantee access to GMP facilities, as the translational research programs mature. The research consisted of :

1. Literature searches
2. Site visits to several facilities by CIRM staff
3. A day-long intensive workshop on GMP with domain experts from around the country, in November 2008, organized by the Science Office
4. Hiring a consultant (Biologics Consulting Group) to generate a report focused on GMP capacity in the state

The enclosed materials include:

1. The CIRM GMP Workshop report including summary recommendations that arose from the workshop discussions
2. BCG consultation by Darin Weber PhD. Note: Since this report, another major contract GMP facility was identified (Bio-Matrix Scientific Group in San Diego). California Stem Cells also has room for contract work, per a discussion with their director. Further, the report is not comprehensive, in that biotech-managed GMP facilities are not catalogued, and so the BCG report underestimates GMP capacity in the state. Even with this underestimation, CIRM grantees have adequate options and access for GMP cell manufacturing.
3. A 2003 report from Japan that provides a simple summary of the technical issues in cell manufacture (Maekawa, Education Program 6)

From these reports, the Science Office came to the following major conclusions and recommendations:

1. Current and anticipated (5 year) needs for GMP by CIRM grantees can be adequately met by established academic and commercial facilities in the state.

2. Both academic and commercial GMP facilities are interested in working with CIRM grantees as contract organizations as needed, obviating the need for CIRM to buy or manage a GMP facility.
3. CIRM could further access to GMP facilities by working with an NIH-funded consortium (Production Assistance for Cellular Therapies, PACT), by making an investment in a California-based expansion of these facilities into one of the academic GMP facilities in the state. The Science Office is currently exploring this option with NHLBI managers of the PACT program and interested California applicants to the PACT program.
4. CIRM should develop a training program to educate a technical training force for California biotechnology-based GMP facilities, as a critical lack of appropriately trained manpower was universally acknowledged in the workshop. As a result of this recommendation, the next Bridges (undergraduate) Training Awards should include a focus to help train a key technical personnel in this area.
5. The opportunity for developing and optimizing strategies for cell manufacture is enormous. For this reason, CIRM will continue to solicit basic and translational research into optimal isolation and manufacturing methods for GMP as part of its RFAs.
6. FDA has not provided precise regulatory requirements for manufacture of pluripotent cell-based therapeutic products although FDA has recently approved a clinical trial for Geron Corp. CIRM will try to work with FDA to promote development and publication of regulatory standards for stem cell manufacture.

CIRM GMP Workshop Summary—Csete—November 12, 2008

On November 3, 2008 CIRM held a workshop with several goals:

1. Review state of the art of GMP for cell manufacture
2. Educate CIRM staff about variety and scale of facilities in California potentially available for CIRM grantee research (and ultimately clinical) processing needs.
3. The most important goal was to gather opinion from assembled experts about the best use of CIRM's remaining $35M in facilities funding to optimally support necessary GMP for CIRM grantee's funded research.

Note: Research opportunities highlighted in red

Major areas covered in the meeting:

Elements of GMP(from D. Weber): Each element requiring enormous expertise and independent regulatory consideration

a. Facility design to control operations
b. Documentation and record keeping
c. Production and process controls
d. Quality control/assurances
e. Validation
f. Equipment calibration and qualification
g. Personnel training and certification
h. Environmental monitoring

Academic capacity in CA was represented by City of Hope, UC Davis, and CHORI

a. CHORI and UC Davis to date are planning use only by their own faculty. CHORI has no current production of hESC, concentrating on marrow- cord blood-, and placental-derived adult stem cells for local clinical use.
b. UC Davis has six suites and is in process manufacturing hESC-derived progenitors for eventual Phase I trials (neural progenitors and others). Has experienced GMP manager, with considerable training experience.
c. COH has excess capacity and currently >50% of work is contract for outside academic institutions (including USC), and others including foreign agencies. Can manufacture 6 products simultaneously, adaptability for many cell products.
d. COH model is to offer 'affordable' contracts to investigators to facilitate translation and they pick contracts based on science. Have much more capacity for CIRM grantees.
e. With 40 employees and not full capacity, cost of running facility is $1.7M/year
f. Expanding considerably to meet needs of other academic institutions (capacity will double by 2011).

g. Important product they can offer: Consultation on product development for academics, which makes ultimate GMP expansion easier. (Another RFP research opportunity)
h. Cord blood capacity (Lubin) limited in California (financial limitation). Note: Cord blood banks can become profitable but require substantial initial investment (~$20M)
i. Systematic search of academic capacity was not done at the meeting.

2. Ability to expand hESC-derived cell products under GMP conditions

a. General need for RESEARCH in this area since the processes have not been optimized and currently NO MECHANISM for funding this kind of research.
b. Geron estimated that a single product development from hESC requires 40 people with 12 involved in manufacturing and 3 senior experts in GMP.
c. General estimate (dose and application-dependent) for scaling up to a master bank for one hESC product >$100M (but very dependent on differentiation process, dosing schedule, other issues)
d. FACS sorting (incorporated in facility at Davis, not at COH) if needed for manufacturing increases costs, difficulty
e. Derivation of hESC lines under GMP conditions still being optimized. FDA has no regulation on IVF embryo cultures, so no real guidelines in this area. Note also: IVF cultures not even necessarily xeno-free.
f. Another research opportunity: RFP to derive lines under GMP conditions for distribution and use by CIRM grantees—Use the lines for research that will ultimately be used for clinical application.
g. Intermediate progenitors (NSC) can be maintained and expanded for much longer in culture when derived from hESC than from fetal sources (Zeng)—Not a surprise but magnitude was impressive, highlighting need to optimize GMP methods for hESC-derived cell products

3. **NIH Support for GMP—successful non-commercial model**

a. 3 university based GMP centers (Baylor, Minnesota, Penn) with 5 year funding, now ?renewal
b. Resulted in 45 products processed, 20 IND applications (17 clinical, 3 translational) and 6 approved INDs, 4 products withdrawn
c. Major effort in developing SOPs
d. Contracts for manufacture extremely time-consuming and difficult
e. Transfer of materials to non-local GMP facilities: FDA has not weighed in
f. Indemnification must be done case-by-case
g. Consortium model worked because 3 centers had different expertise and emphases, and because projects were reviewed by center directors to choose best ones

h. Each facility holds own master file of SOP and has the obligation to maintain it, though IND is with the PI.
i. Documentation daunting with multiple different contractors.
j. Can support out of state, NIH-funded investigators

4. **Translational pitfalls** where forward thinking around GMP issues can help:
   a. Though GMP for Phase I has FDA guidelines, pre-clincial and clinical manufacturing processes should have overlap from the beginning of the research processes, in order to speed work through regulatory hurdles. Manufacturing variations have to be set through the clinical trials continuum.
   b. GMP expectations during development—applies to both facility and process
   c. Expect controls to increase as product moves from one phase to next

5. **Commercial contract organizations**—Several models

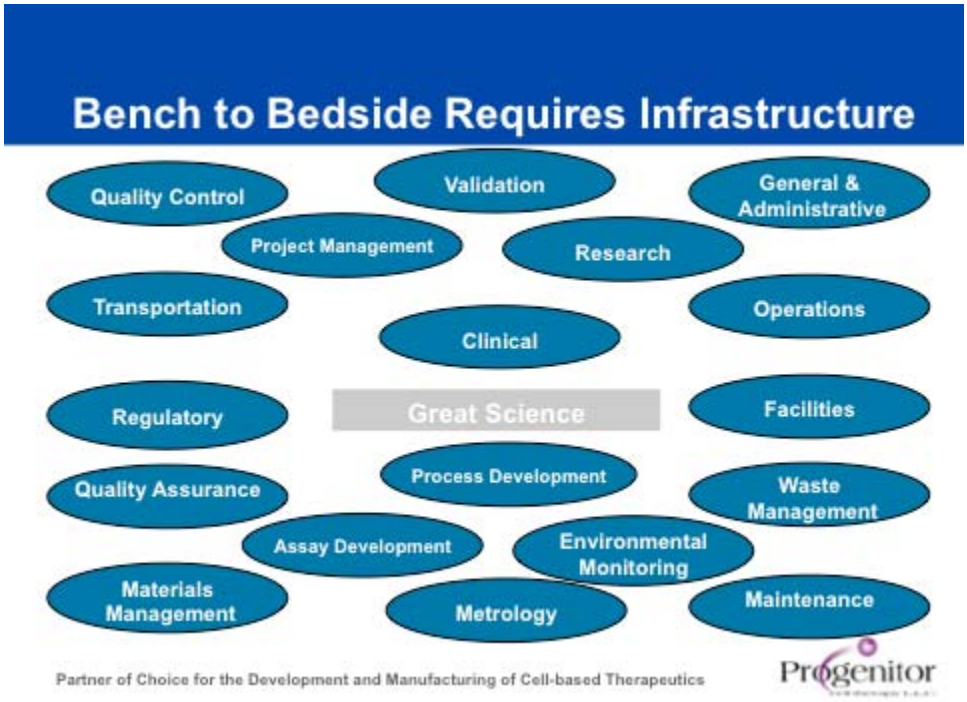
a. From Preti – successful GMP facility has major challenges and not many people know how to do it.

§Conversion of great science into technical feasibility
§Proving scientific basis
§Demonstrating clinical relevancy
§Product characterization and potency
§Comparability
§Clinical trial design, execution & duration
§Economics, logistics and feasibility of manufacture
§Intellectual property
§Evolving regulatory frameworks
§Ethics and financing

b. Progenitor is a model for large traditional GMP facility with multiple suites (one facility in CA) and with their scale, they are profitable but enormous resources required. Cognate also presented, similar large scale capacity with California facilities.

c. Systematic calculation of California commercial capacity was not done but all industry representatives agreed that current capacity is sufficient for any number of Phase I and Phase II cell therapies (because major scale-up not necessary and many varied facilities are operating).

d. Complexity of manufacturing highlighted by slide below.



e. Other model (Pacific GMP) using mostly disposables instead of traditional free-standing facility

-Advantages in cleaning, sterilization and cost but some limits in scalability

-Both models can decompress CIRM need for GMP resources

f. Bottom line for manufacture: The product is the process

g. Tension between development (inherently associated with change) and manufacturing (does not embrace change)

h. Overall: Commercial GMP = building a rational approach to product development

i. Dearth of technicians: CIRM could help industry greatly by education programs

-On site training requires minimum 6 months, generally 2 years for ability to fully execute SOP

RECOMMENDATIONS—From the general discussion

1. **CIRM could and should fund research** in this area, as no other research dollars are available for optimizing processes, especially for hESC therapies. Areas of research (highlighted in red) included undergraduate level Bridges-type program focused on GMP to build work force; methods to expand hESC in suspension; qualification and optimization of culture reagents to meet safety requirements; methods to scale-up AND reduce costs; derivation of hESC/iPS lines under GMP conditions; methods for product development in the context of academic labs. Industry representatives expressed interest in

responding to research and training RFAs, especially as a trained work force now represents a bottleneck in industry.

Overall: Considerable consensus that directed research and education programs would be a major contribution to CIRM grantees and facilitate their research and translational needs (and push the field as a whole forward).

2. General agreement that **CIRM should not be in the business of building or operating GMP facilities**. Reasons: Would be distracting, unnecessary and huge effort to do this right. More value to funding research alone or supporting a consortium model (below).

3. If CIRM funds not designated for research, another model for facilitating CIRM grantee access to GMP also received universal endorsement: **A PACT-like model with existing California facilities could be made into a consortium** (through RFP).

Basics of this model:

-Competitive application to consortium (through GWG?) to determine translational potential of the product.

-Consortium manufacturing costs can be off-set by CIRM in competitive process of RFAs and/or through contractual arrangements.

- Academic programs generally don't have the money for scale-up so most of consortium would be commercial, but public (CIRM)-private partnerships may be ideally suited to this consortium

-Biggest saving for all CIRM grantees would be in the standardization that comes with the consortium arrangement

-A single facility cannot deal with surge capacity, so if multiple CIRM successes in proceeding through regulatory requirements, consortium can handle.

-Capacity in state may be able to handle currently but deserves further documentation.

Identification of Cellular Therapy GMP Manufacturing Facilities in California

December 6, 2008

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Executive Summary

The state of California possesses significant expertise in the manufacturing of cellular therapies in compliance with good manufacturing practices (GMP). Ten institutions in California have been identified with direct experience in the clinical manufacturing of cellular therapies in compliance with FDA quality standards. Combined, these facilities represent a total of 25,680 ft^2 of potential clean room space for manufacturing of cellular therapy products. This includes a combined twenty ISO 8 (class 100,000) and forty-one ISO 7 (class 10,000) clean rooms.

There are an additional 18 institutions in California with facilities for hematopoietic stem cell transplants (HSCT). These facilities are required to comply with good tissue practices (GTPs), which significantly overlap with GMP principles. It is estimated that collectively these GTP facilities represent an additional 9,000 ft^2 of clean room space that could be suitable for cell therapy manufacturing processes.

It is recommended that CIRM work closely with these existing cell therapy manufacturing facilities, which are primarily located in academic institutions and thus are in close proximity to most CIRM grantees. These facilities could conceivably play an important role in GTP/GMP education and provide hands on training for CIRM grantees in clinical manufacturing of cellular therapies.

Scope

The California Institute for Regenerative Medicine (CIRM) is in the process of assessing how best to support grantee access to GMP facilities for their research needs and ultimately for clinical applications. Currently, information is incomplete with regards to the extent of experience within the state of California for the manufacturing of cellular therapy products in compliance with necessary quality standards, such as good tissue practice (GTP) and good manufacturing practice (GMP).

The availability of such information should enhance CIRM's ability to objectively evaluate the potential need for additional investments in either GTP/GMP education and training, and/or the development of new manufacturing facilities to meet anticipated grantee needs.

The intent of this report is to identify and catalog existing cell therapy GTP/GMP manufacturing facilities within California that may be suitable for use by CIRM grantees.

Findings

Cell Therapy GMP Manufacturing Facilities in California

As tabulated below, 10 institutions in California have been identified with direct experience in the manufacturing of cellular therapies in compliance with GMPs. Combined, these facilities represent a total of 25,680 ft^2 of potential clean room space for manufacturing of cellular therapy products. This includes a combined 20 ISO 8 (class 100,000) and 41 ISO 7 (class 10,000) clean rooms. To my knowledge, this is the largest concentration of clean room space in the U.S.

Since most cell therapy products cannot be terminally sterilized with out destroying the activity of the cells, they must be manufactured under aseptic processing conditions to prevent the introduction of adventitious microbial agents (bacteria, fungi, virus, mycoplasma). This typically requires that manufacturing of cell therapies be done in ISO 7 certified clean rooms and that any open manipulations, such as cell passaging, be done within a certified ISO 5 (class 100) biological safety cabinet. Thus, providing CIRM grantees access to ISO 7 clean room facilities will be critical. However, it is worth pointing out that there is a trend in cell therapy manufacturing to utilize 'closed' manufacturing systems, which can allow the utilization of less stringent clean room environments, such as ISO 8. This has the potential for significant cost savings, since operation expenses for ISO 7 clean rooms

are high. Thus, for some cell therapy manufacturing processes it may be feasible to utilize available ISO 8 clean rooms instead of ISO 7 clean rooms.

Of the 10 facilities, 3 are commercial contract manufacturing organizations (CMO). Two of these CMOs, Cognate Bioservices and Progenitor Cell Therapy, are devoted to GMP manufacturing of cell therapies and have significant experience with manufacturing Phase I through Phase III cell therapy products. Pacific GMP has less experience with cell therapy products, but has experience with other biologics.

Table 1. Cell Therapy GMP Facilities in California

Facility Name	Location	Clean Rooms			Types of cell therapies	Specific Examples	INDs Supported	Contract Manufacture
		~Square feet	ISO 8	ISO 7				
Cognate Bioservices	Sunnyvale	2,000	1	2	Autologous, Allogeneic	tumor vaccines, myeloid progenitor cells	Multiple INDs; Phase I, Phase II, Phase III	Academic, non-profit, industry
PacificGMP	San Diego	1,500	2	1	gene-modified	donor leukocytes	N= 12 (6 active); Phase I, Phase II	Academic, non-profit, industry
Progenitor Cell Therapy	Mountain View	1,500		5	Autologous, Allogeneic	Dendritic, neural stem cells, MSCs, encapsulated cells	Multiple INDs; Phase I, Phase II, Phase III	Academic, non-profit, industry
Children's Hospital Los Angeles Clinical Gene and Cell Therapy Laboratory	Los Angeles	1,250		2	Allogeneic, gene-modified	CD3+ T cells, CD34+ cells from matched unrelated or haplo-identical donors; Gene-corrected CD34+ cells from SCID and AIDS patients	N=4; Phase I, Phase II	Academic only
City of Hope Center for Biomedicine and Genetics	Duarte	10,000	6	15	Autologous, Allogeneic, gene-modified	T-cell, CD34+; Neural Stem cells, Islet cells	N=40 (20 COH+ 20 third party); Phase I, Phase II	Academic, non-profit, industry
Hoag Cancer Center	Newport Beach	unknown	?	?	Autologous	tumor vaccines	N=2; Phase I	No
Stanford Cellular Therapeutics & Transplantation Laboratory	Palo Alto	2,000	4		Autologous, Allogeneic	HPC, TC-D, TC-T (CIK cells)	N=2, Phase I, HCT/P	No
UC Davis CIRM Institute for Regenerative Cures Stem Cell Program GMP Facility **(under construction)**	Sacramento	5,000	3	6	Autologous, Allogeneic, gene-modified	Adult and embryonic stem cells and derived therapeutic cell typs; HCT/Ps	Anticipating Phase I, Phase II; possibly Phase III	Academic, non-profit, industry
UC Los Angeles Jonsson Cancer Center GMP facility	Los Angeles	1,431	1	6	Autologous, Allogeneic, gene-modified	HSC, T-cells Dendritic, ESC	N=4; Phase I, Phase II	No
UC San Francisco Islet and Cellular Transplantation cGMP Facility	San Francisco	1,000	3	4	Autologous, Allogeneic	islet cells	N=2; Phase I, Phase II	No
	Total =	**25,681 sq. feet of clean room space**	**20 ISO 8**	**41 ISO 7**	Notes: ISO 8 = class 100,00 air quality	ISO 7 = class 10,000 air quality		

There are 7 academic institutions with varying degrees of experience in GMP manufacturing of cell therapies. The City of Hope has a very large program in biologics. It currently has 15 ISO 7 (class 10,000) clean rooms and an additional 10 ISO 7 rooms under construction, which are ideal for manufacturing of cell therapies. It has experience in manufacturing of cell therapy products, including islet cells and neural stem cells. The City of Hope facility has also supported 40 IND submissions to the FDA, suggesting a strong track record of translation to the clinic.

The UC Davis GMP facility is currently under construction, but when complete has the potential to become one of the larger academic GMP facilities in California primarily focused on stem cell derived cell therapies, with ~5,000 ft^2 of clean room space.

The remaining academic institutions generally have smaller GMP facilities, but all reportedly have supported FDA compliant manufacturing for IND submissions. It must be noted that most of the academic programs are supporting early Phase I/II INDs and thus would not likely be considered fully compliant with GMP. The FDA does not require full GMP compliance until late in development (Phase III/BLA). Of note, 80% of these cell therapy GMP facilities are registered with the FDA as establishments manufacturing human cell, tissue, and cellular and tissue-based products (HCT/P).

Hematopoietic Stem Cell Transplant (HSCT) Programs in California

In the course of identifying cell therapy GMP manufacturing facilities, it became increasingly apparent that California has a large number of high caliber hematopoietic stem cell transplant facilities. As tabulated below, 18 such facilities were identified. In a number of instances these HSCT facilities coexist at institutions that also have cell therapy GMP facilities. This includes programs at City of Hope, Children's Hospital of Los Angeles, UCLA, UC Davis, UCSF and Stanford. It is significant to note that all but one (94%) of the HSCT programs are FACT accredited and most (89%) are also registered with the FDA as HCT/P establishments. As such, most of these facilities are compliant with the FDA's good tissue practice (GTP) regulations, which has the same core principles as GMPs, albeit with a different emphasis. The individuals working within these facilities are likely well trained in quality manufacturing of clinical products and represent an important potential resource for education and training of CIRM grantees in GTP principles, which significantly overlap with GMP principles. Additionally, it is likely many of the HSCT programs have at least one clean room that could be classified as ISO 8 or ISO 7. If one were to conservatively estimate that each HSCT program has one clean room of ~500 ft^2, which is an average size, then collectively the 18 identified facilities potentially represent an additional 9,000 ft^2 of clean room space that could potentially be used by CIRM grantees.

Table 2. HSCT Facilities in California

Hematopoietic Stem Cell Transplant Facilities in California					
Facility Name	Location	Accreditation			FDA Registered
		AABB	FACT	NMDP	
Alta Bates Summit Blood and Marrow Transplant Program	Berkeley		X		X
City of Hope Hematopoietic Cell Transplantation Program	Duarte	X	X	X	X
Scripps Blood and Marrow Transplant Program	La Jolla		X	X	
Loma Linda University Blood and Marrow Transplant Program	Loma Linda		X	X	X
Cedars-Sinai's Samuel Oschin Comprehensive Cancer Institute Blood and Marrow Transplant Program	Los Angeles		X	X	X
Hematopoietic Stem Cell Transplant Program at Children's Hospital Los Angeles	Los Angeles	X	X	X	
UCLA Hematopoietic Stem Cell Transplant Program	Los Angeles		X	X	X
USC Norris Cancer Hospital	Los Angeles		X		X
Children's Hospital & Research Center at Oakland Blood & Marrow Transplantation Program	Oakland		X	X	X
St. Joseph Hospital HPCT Program Orange, California	Orange		X		X
Children's Hospital of Orange County Blood and Marrow Transplant Program	Orange		X	X	X
UCI Medical Center Bone Marrow Transplant Laboratory	Orange				X
UC Davis Combined Adult and Pediatric Stem Cell Transplant Program	Sacramento		X	X	X
Sutter Medical Center, Sacramento, Blood and Marrow Transplant Program	Sacramento		X		X
The Blood and Marrow Transplant Program of UCSD/Sharp LLC and Rady Children's Hospital of San Diego	San Diego	X	X	X	X
UCSF Medical Center Adult Bone Marrow Transplant Program	San Francisco	X	X	X	X
University of California, San Francisco Children's Hospital Pediatric Bone Marrow Transplant Program	San Francisco		X		X
Stanford University Medical Center Blood and Marrow Transplant Program	Palo Alto		X	X	X
Estimated Additional Clean Space in California (sqft): =		**9,000**			
Assumption: Each HSC facility has a single clean room of 500 sqft (18 rooms x 500 sqft)					

Discussion and Recommendations

The state of California has a significant number of institutions with cell therapy GTP/GMP manufacturing experience, located primarily at academic institutions and thus likely to be in close proximity to CIRM grantees. CIRM should give serious consideration to accessing the existing knowledge in quality manufacturing that resides in these manufacturing facilities as a potential mechanism for 'grass roots' training of CIRM grantees in GTP and GMP principles. It is likely that many of the identified facilities, even those not considered fully GMP compliant, would serve as a valuable hands on training resource.

An important caveat with such an approach would be the need to develop a uniform curriculum consistent across all participating institutions. It is recommended that elements of such a curriculum include the following:

- General education on clinical product development, including implementation of "good development practices" in R&D to facilitate technology transfer and translation to GMP.
- A clear distinction must be made between scientific research and clinical manufacturing
- The concept of a 'quality' mindset should be instilled early to ensure product development and process improvement occurs in a regulatory compliant manner.
- In general, academic manufacturing facilities are understaffed, particularly with regards to experienced quality and regulatory personnel.
    - CIRM should consider offering CIRM grantees early access to experienced quality and regulatory experts to evaluate product development plans and identify strategies for making rapid progress to clinical trials.
    - CIRM should establish and enforce baseline quality standard to be in place when IND enabling preclinical animal efficacy and safety studies are underway. This should include external verification by or on behalf of CIRM to ensure compliance standards are met.

Most importantly, CIRM should establish and/or facilitate participation of CIRM grantees in educational forums where 'lessons learned' in product development and interactions with regulatory authorities are openly shared to identify best practices.

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Appendix I – Resources Used

The table below indicates the variety of publically available information sources that were used to identify cell therapy GTP/GMP manufacturing facilities within the state of California.

Source	Additional Information
US FDA Human Cell and Tissue Establishment Registration (HCTERS) Database	http://www.fda.gov/cber/tissue/tissregdata.htm
National Center for Education Statistics	http://nces.ed.gov/collegenavigator/
National Marrow Donor Program (NMDP)	
Foundation for Accreditation of Cellular Therapies (FACT)	http://www.factwebsite.org/default.aspx
American Association of Blood Banks (AABB)	http://www.aabb.org/Content
International Society for Cell Therapy (ISCT) Membership Directory	http://www.celltherapysociety.org
Internet Search Engines	Search terms used: o California (used for all searches) o Cell Therapy o GMP facility o good manufacturing practices o cell processing o cell laboratory o manufacturing o bone marrow transplant
GMP Facility Survey	Sent to selected cell therapy GMP facilities to obtain specific information on clean rooms and cell therapy products

It was usually possible to cross-check information obtained from one source against another source to verify accuracy.

US FDA Human Cell and Tissue Establishment Registration (HCTERS) Database

Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P. On January 19, 2001, the Food and Drug Administration published a registration and listing final rule that requires human cells, tissue, and cellular and tissue-based product establishments to register with the agency and list their human cells, tissues, and cellular and tissue-based products (HCT/Ps).

HCT/P establishments that only manufacture HCT/Ps currently under IND or IDE do not

need to register and list their HCT/Ps until the investigational HCT/P is approved through a Biologics License Application (BLA), however most HCT/P establishments with ongoing INDs voluntarily register since it requires minimal effort

In the state of California there are 261 establishments currently registered with the FDA as manufacturers of human cell, tissue, and cellular and tissue-based products (HCT/P). Of those, there are ~ 23 facilities (9%) in California that process, manufacture or otherwise handle cellular therapeutics. Most of these facilities (70%) are involved in hematopoietic stem cell transplantation, such as bone marrow transplants. The remaining 30% of FDA registered establishments (n=7) have direct experience in manufacturing of cellular therapy products under good manufacturing practice (GMP) conditions. There are several cell therapy manufacturing facilities in California that are not registered with the FDA, since they are not required to do so until the cell therapy product is approved (BLA).

National Center for Education Statistics

This entity has an online database of all institutions of higher education in the U.S. It was utilized to proactively identify institutions of higher education located in the state of California. Using this database, 161 institutions of higher learning in California were identified. 58 of those institutions grant doctoral degrees, indicating likelihood of active research programs. Each of these institution's websites were individually searched to determine if any are involved in cell therapy GMP manufacturing.

National Marrow Donor Program (NMDP)

The National Marrow Donor Program (NMDP) maintains basic guidelines for organizations to facilitate bone marrow and cord blood transplants. Key guidelines are defined within the NMDP Standards and include specific requirements that must be met by the partnering facility, its personnel, and its policies and procedures. 12 of the 18 (67%) identified HSCT Programs in California are in the NMDP transplant network.

Foundation for Accreditation of Cellular Therapies (FACT)

Founded in 1996, FACT establishes standards for high quality medical and laboratory practice in cellular therapies. FACT is a non-profit corporation co-founded by the International Society for Cellular Therapy (ISCT) and the American Society of Blood and Marrow Transplantation (ASBMT) for the purposes of voluntary inspection and accreditation in the field of cellular therapy. The major objective of FACT is to promote high quality patient care and laboratory performance in the belief that a valid accreditation must assess both clinical and laboratory aspects.

Accreditation is awarded after successful documentation of compliance with the current standards. Compliance is determined by evaluation of written documents provided by the facility and by on-site inspection. In the state of California there are 12 FACT accredited cell therapy GTP/GMP manufacturing facilities

American Association of Blood Banks (AABB)

Celebrating 60 years of operation in 2007. AABB is an international association representing individuals and institutions involved in activities related to transfusion and cellular therapies, including transplantation medicine. Note: Despite the name, AABB has issues specific standards for procurement, manufacturing, labeling and distribution of cellular therapy products.

The AABB Accreditation Program assesses the quality and operational systems in place within the facility. The basis for assessment includes compliance with Standards, Code of Federal Regulations and federal guidance documents.

This independent assessment of a facility's operations helps the facility to prepare for other inspections and serves as a valuable tool to improve both compliance and operations. Accreditation is granted for collection, processing, testing, distribution, and administration of blood and blood components; hematopoietic progenitor cell activities; cord blood activities; perioperative activities. In the state of California there are 4 AABB accredited cell therapy facilities.

International Society for Cell Therapy (ISCT) Membership Directory

ISCT was established in 1992 and is the main professional organization for those working or interested in cell-based therapies. It seemed logical that the ISCT membership directory could potentially identify individuals from California institutions that have cellular therapy manufacturing facilities. 91 individual ISCT members are located in California. This proved useful in cross referencing their institutional affiliation to determine if their institution had been previously identified as having an existing cell therapy GMP facility or hematopoietic stem cell transplant program.

Internet Search Engines

General internet searches using search engines such as Google were employed to initially identify potential cell therapy manufacturing facilities in California. Additionally each of the websites of each of the 58 institutions identified from the National Center for Education Statistics database were searched to identify those with experience in cell therapy manufacturing. This proved to be tedious and time consuming due to inconsistent use of nomenclature for describing activities associated with the manufacturing of cell therapies. For example, many academic institutions refer to their manufacturing facilities, as laboratories. Some refer to FDA compliance rather than GMP. Most do not have websites providing specific details on their cell therapy manufacturing operations.

GMP Facility Survey

Due to the dearth of specific information about a given institutions cell therapy manufacturing operations, a simple survey was created to elicit specific information on the number of GMP clean rooms in use at an institution's facility as well as information related to the types of cell therapy products manufactured. This survey was sent to the following institutions:

- Children's Hospital of Los Angeles
- City of Hope
- Pacific GMP
- Stanford
- UCSD
- UCLA
- UCSF

Responses to the survey were returned by all institutions with the exception of UCSD. Sufficient information was available from the websites and other sources for Cognate Bioservices and Progenitor Cell Therapy, such that a sending the survey form was not necessary.

Appendix II – GMP Facility Survey Form

CIRM Project: Cell Therapy GMP Manufacturing Facilities in California

Instructions: Provide requested information by filling in gray form boxes. Select "yes" boxes if applicable and provide examples if possible. Return form to dweber@bcg-usa.com

Questions		Responses	
1. Facility Name and Address:		Input name & address here: If applicable, please provide: California Food & Drug Branch license US FDA FEI:	
2. Website URL:		http://	
3. cGMP Facility footprint (approximate ft^2):		~ ft^2	
4. Clean room foot print (approximate ft^2):		~ ft^2	
5. Number and Type of clean rooms:			
	ISO 8 (class 100,000)	# of rooms	
	ISO 7 (Class 10,000)	# of rooms	
6. Types of cell-based products manufactured			
	Autologous	Yes ☐	Examples:
	Allogeneic	Yes ☐	Examples:
	Xenogeneic	Yes ☐	Examples:
	Ex vivo gene therapy (gene-modified cells)	Yes ☐	Examples:
	Other (specify)	Yes ☐	Examples:
7. Approximate numbers of IND/IDEs supported:		# of INDs/IDEs	
8. Has GMP Manufactured Cell-based Therapies for:			
	Phase I studies	Yes ☐	
	Phase II studies	Yes ☐	
	Phase III studies	Yes ☐	
	FDA approved	Yes ☐	
	361 HCT/Ps (minimal manipulated cells/tissue)	Yes ☐	
9. Is the GMP Facility Accredited by:			
	AABB	Yes ☐	
	FACT	Yes ☐	
10. Does the GMP facility offer manufacturing for external parties (contract manufacturing)			
	Academic (external to your organization)	Yes ☐	
	Non-profit	Yes ☐	
	Industry (for profit)	Yes ☐	

Education Program 6

Current good manufacturing practices (cGMP) controlled cell processing for the development of novel advanced cell and gene therapy

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Translational research requires high scientific and ethical standards throughout the manufacturing of clinical trial material according to ICH-GCP guidelines. Advanced cell therapy development such as cell transplantation, adoptive immunotherapy, gene therapy and regenerative therapy mandate cGMP (current good manufacturing practices) grade cell processing to assure the safety and quality of manipulated cell products. One of the first steps in cGMP conversion from the bench to the clinic is the design of a facility for the preparation of clinical material for use in human trials. The establishment of regulatory guidelines is clearly needed. Considerations important for the development of cGMP graded cell processing are discussed.

1. Introduction

Improved understanding of the molecular basis of disease has resulted in the development of novel cell and gene therapeutic strategies. These strategies may revolutionize therapy for many life-threatening human diseases including cancer, cardiovascular disease, diabetes, and HIV. Cell therapy involves the replacement of abnormally functioning cells with cells that function normally. Cell therapies can be used to treat malignant diseases and may improve degenerative disorders of many organs including bone, muscle, nerve, retina, skin, pancreatic islets, and blood vessels. The combination of cell and gene therapy is likely to be particularly potent. However, after identification of an appropriate clinical target, establishment of a novel cell or gene based therapeutic approach, and completion of pre-clinical studies, transformation of these research breakthroughs into new therapies for treating human disease is often difficult.

Successful clinical cell therapy requires transformation of laboratory based techniques into individualized, cell production processes with regulatory safety and efficacy standards similar to those established for pharmaceutical therapeutics. To transfer research progress to clinical settings (translational research), qualified clinical grade cell and gene products must be manufactured in well-controlled cell processing laboratories using current good manufacturing practices (cGMP). Manufacturers should be keenly aware that poor cGMP conditions at a manufacturing facility can ultimately pose lifethreatening health risks to patients.[1] Academic researchers, scientists, and clinician-investigators will hopefully understand the importance of cell processing and play a pivotal role in establishing cGMP cell processing.

2. Status quo in Japan

As cell and gene-based therapies grow more complex and widely used, advanced cell engineering laboratories must also become increasingly sophisticated and well-controlled. More extensive and prolonged laboratory processes involve greater risk of complications (with potential adverse events for patients), and so the need for control in the processing laboratory is correspondingly

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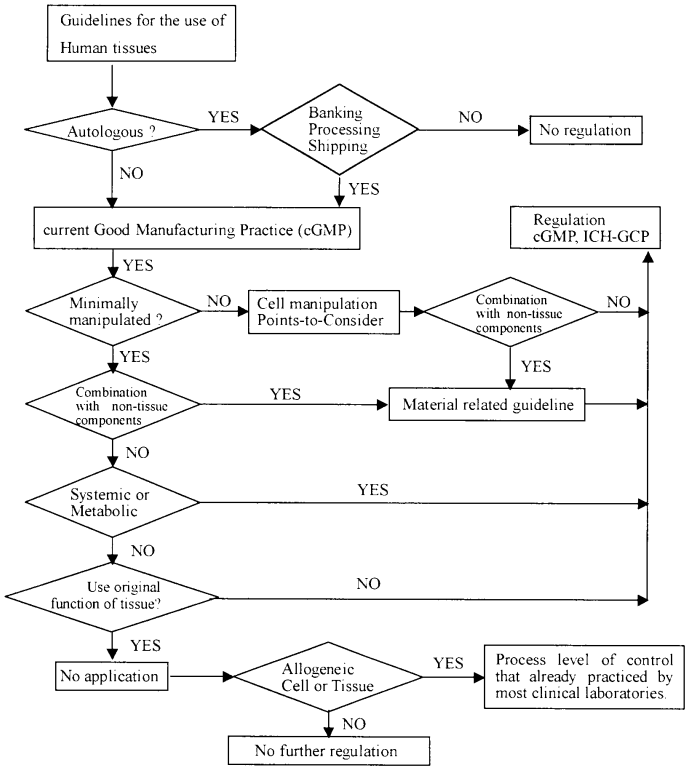

Figure 1. Regulatory requirements associated with the proposed flow chart of cell and tissue based processing.

greater. Proposed regulations should define the design of cell-processing laboratories, procedures according to the degree of manipulation involved and, correspondingly, the risk of adverse processing-related events.[1,2] Minimal manipulation, such as cryopreservation of autologous peripheral blood and bone marrow stem cells, may be performed using a level of control already practiced by most clinical laboratories. More-than-minimal manipulation, however, requires cGMP (Figure 1), or a higher degree of process control and laboratory sophistication. At present, more-than-minimal manipulation includes gene transduction, *ex vivo* expansion, activation, combination with non-tissue components, use for other than the tissue's normal function, and transplantation of unrelated allogeneic cells and tissues. Consequently, growing numbers of medical centers active in cell and gene therapy are designing and building clinical laboratories capable of performing cell engineering and vector production using cGMP.

Unlike in the States, however, definite and detailed rules of cGMP-grade cell processing using human cells and tissues for advanced cell and gene therapy have not been issued in Japan[3,4], although rough concepts have recently been reported. In addition, few architects and engineers have sophisticated knowledge of how to appropriately design facilities for production of advanced cell and gene therapeutics. Of course, Japanese pharmaceutical companies employ such knowledge, but for GMP grade manufacturing of tablets or drugs. Cell processing for advanced cell therapy using human tissues, is, however, quite different from the production of conventional pharmaceutical drugs. Moreover, as mentioned below, most advanced cell and gene therapies are going to be developed in academic institutions with inadequate

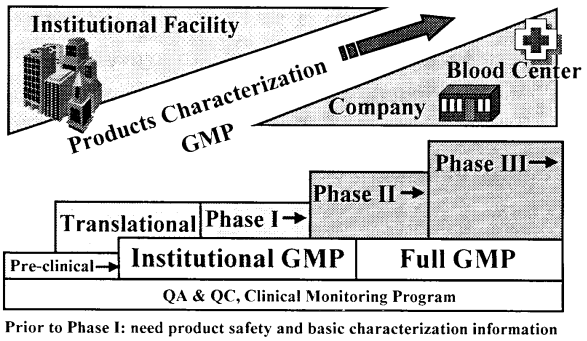

Figure 2. Stepwise approach: regulatory requirements increase with product development. Institutional GMP should be established to advance translational research in academia. Please refer to the color pages at the end of this book.

staff sizes. Establishment of institutional cGMP in academia is urgently needed for the development of novel cell and gene therapeutics in Japan (Figure 2).

3. What is cGMP?

cGMP is defined as, "methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of cell and gene products to assure that such products meet the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess". cGMP may be divided into ten elements:

1. Facilities and equipment
2. Production and process controls
3. Personnel management
4. Record-keeping
5. Calibration
6. Validation
7. Error management
8. Standard operating procedures (SOPs)
9. Labeling
10. Quality control and auditing

The unifying concept underlying all aspects of cGMP, however, is *control*. The well-controlled laboratory has systems in place to ensure control over each aspect of cGMP, and to document that ontrol. cGMP is most productively understood as a process, or unified group of processes. The facility, while the most obvious and tangible aspect of cGMP, must support this process, and therefore, the systems necessary for cGMP should be developed. While process control comes to mind quickly when considering cGMP cell engineering, the concept of control must pervade every aspect of the cGMP laboratory. For example, if the laboratory instruments are well-controlled – calibrated, validated, maintained and monitored – then the process they measure or carry out, and the products of those processes, are more likely to be satisfactory.

4. Facility design and development process in academic institutions

One of the first steps in cGMP conversion from research to manufacturing is design of an initial manufacturing facility for preparation of clinical trial material.[5] Most cGMP cell engineering laboratories currently support translational research and/or Phase I/II clinical trials, many of which enroll very small numbers of patients. At the same time, cell engineering laboratories, particularly at academic institutions, are often called upon to support multiple clinical trials. Also, more adaptable laboratories are likely to remain useful for longer – a very relevant concern considering the costs associated with building and operating these facilities. A clinical cGMP cell-engineering laboratory in an academic institution, therefore, must be designed with flexibility and varied applications in mind.

While most discussions about cGMP laboratory design have dealt with biopharmaceutical issues, advanced clinical cell engineering presents unique issues in laboratory design and operation. Perhaps the most fundamentally different characteristic of cGMP cell processing is what could be called its "boutique" quality. Unlike biopharmaceutical processing, an advanced cell engineering laboratory in an academic institution often produces an extensively processed cell product for a single patient.[6]

5. Design layout and process flow - an example

One possible design for a laboratory performing gene transduction and cell engineering (Figure 3) is based on the current design of the Center for Cell and Molecular Therapy (CCMT) at Kyoto University Hospital. Many designs are, of course, possible; this example illustrates options for cGMP laboratory design and operation. The facility in Figure 3 is approximately 200 m^2 wide and can be used for gene transduction and cell engineering. Air quality throughout is specified at class 10,000 (defined as class B in EU-GMP) based on the frequency of air changes. A single-pass air-handling system with high-efficiency particle air (HEPA) filters would be appropriate, providing air with <10,000 measurable particles/ft^3 of air. Production and manufacturing rooms would be constructed with epoxy liquid flooring with a covered base, reinforced resinous wall surfacing, and an epoxy-painted veneer plaster ceiling.

One positive-pressure Biosafety Level 2 (BL-2) room with negative-pressure airlocked anterooms would be available for cell engineering and expansion, and two negative-pressure (one minus) BL-2 rooms with negative-pressure (two minus) airlocked anterooms for gene transduction. The open and closed arrows in Figure 3 indicate personnel and air flow, respectively. Whenever

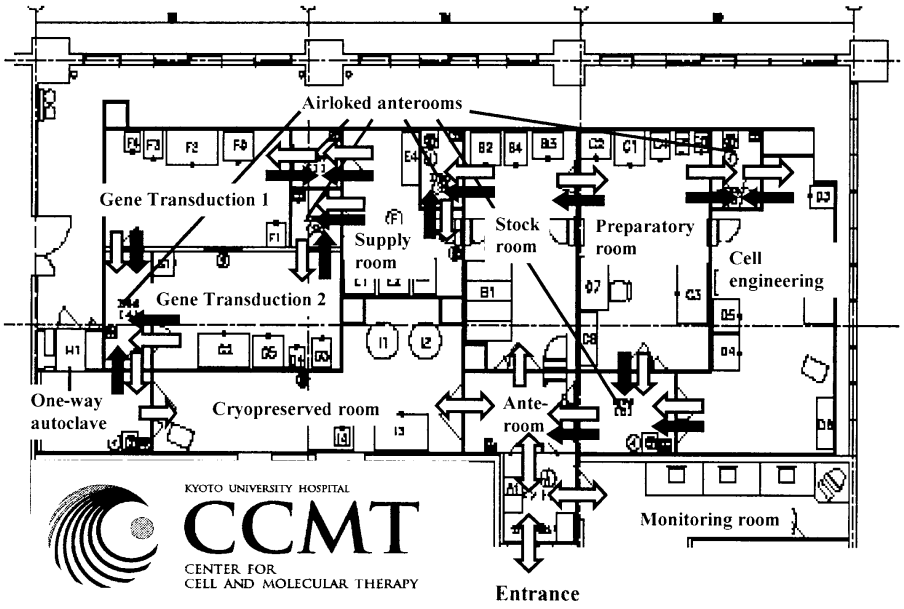

Figure 3. Floor design of the Center of Cell and Molecular Therapy (CCMT) of Kyoto University Hospital. Permitted personnel movement is indicated by open arrows. Monitored and controlled pressurization levels in manufacturing rooms ensure that air flows in the directions indicated by closed arrows when a door is opened.

possible, personnel and material flows should be designed to be unidirectional. Preventing contamination and mix-up of material begins with the layout of work areas and planned flow of people and materials through the facility. Process-flow diagrams are used to plan movements of materials and facility personnel, and to develop the facility Validation Master Plan (VMP), regulatory submissions and standard operating procedures (SOPs). After determining room and equipment layout, flow diagrams should be developed specifying movements of personnel, materials and supplies, equipment, waste, products in process, and final products. Access to the facility and to areas within the facility, should be limited and documented. Electronic card-key systems are helpful and simplify record-keeping.

6. Aseptic processing areas

The aseptic processing area laboratory is the region most directly used for cell engineering, including vector production, gene transduction, cell expansion and unusual cell isolation processes[1]. This area is also the most vulnerable to cross-contamination, which can arise from aerosols, spills, contaminated equipment, or individuals passing through multiple production rooms. Processes listed below, therefore, should be isolated as much as possible to reduce risk of contamination in processing and to ensure process control.

- Floors, walls, and ceilings made of smooth, hard surfaces that are easily cleaned.
- Temperature and humidity controls.
- An air supply filtered through HEPA filters under positive pressure, regardless of whether flow is laminar or non-laminar.
- A system for monitoring environmental conditions.
- A system for cleaning and disinfecting the room and equipment used to control aseptic conditions.

The aseptic processing area by definition should be easily cleaned and should be designed to minimize the possibility of contamination. For ease of cleaning, as well as to increase flexibility of the workspace, permanent equipment should not be installed. A bare room of smooth surfaces is far easier to sanitize than one filled with immovable equipment. Processing equipment can be brought into the aseptic processing area and removed when no longer needed, making the facility more adaptable for varied processes.

The aseptic processing area should be stringently isolated, with limited and documented access. The aseptic area should be entered through airlock double doors enclosing an anteroom for gowning. The airlock minimizes airborne contamination of the aseptic processing area and maintains differential air pressures between rooms. From the gowning area a staging room can be conveniently entered, which should house appropriate

supplies and reagents, to ensure that the actual processing room is stocked with appropriate equipment and supplies once the procedure is begun. The aseptic processing room should have a separate exit to a de-gowning anteroom also enclosed by a double door airlock.

Supplies of liquid nitrogen and CO_2 may be piped into the room, to avoid the potential contamination associated with supply cylinders. Main supply cylinders can be located near an outside wall adjoining the aseptic processing room. Running water must be excluded from the area. Hand-washing sinks may be located outside the gowning airlock, and waterless antimicrobial lotions can be made available in the processing area. If water is necessary in processing, to reconstitute a reagent for example, then water for injection (WFI) must be used.[7]

Transduction and expansion is generally carried out at BL-2 to help ensure purity of the cell product.[8] Processing is performed in an isolated, limited-access aseptic processing room by gowned and gloved personnel. Room air quality should be Class 10,000 or cleaner. The air-handling system may recirculate air, but single-pass, non-recruited air is preferable. If recirculated air is used, potential sources of cross-contamination should be considered. Open procedures, in which aerosols may be generated, should be carried out in biological safety cabinets, which provide Class 100 air. Rooms used for BL-2 transduction and expansion should be maintained at positive air pressure to further minimize risk of contamination.

Due to the space available, other important aspects including monitoring[9], release-criteria, sanitation/mainte-nance, validation, and the cost of constructing and running the facility, etc., cannot be discussed in this paper. Given the high cost of constructing and operating a cGMP cell engineering laboratory, financial factors acquire considerable importance, particularly for academic institutions. It is far too easy to decide to construct a cGMP laboratory based on the perception that advanced academic institutions should have one. Some centers undoubtedly do require cGMP processing on-site. Others, however, may find collaboration with an existing cGMP laboratory more cost-effective.

7. Conclusion

To establish and operate an effective cell processing facility, positive and close collaborations with medical doctors and researchers, technicians, pharmacists, engineers, GMP consultants, and government officers are mandatory. Since participants come from different scientific, medical, technological, and political backgrounds, each must try to understand the other's point of view and work with the same purpose of producing novel cell and gene therapies for many patients with incurable diseases. Advanced cell and gene therapies cannot be developed without effective and well thought-out cell processing.

The basic concepts of cGMP cell processing are similar to those of blood transfusion therapy.[10] Conventional blood transfusion technologies should be evaluated for appropriateness for sophisticated cell processing laboratories.

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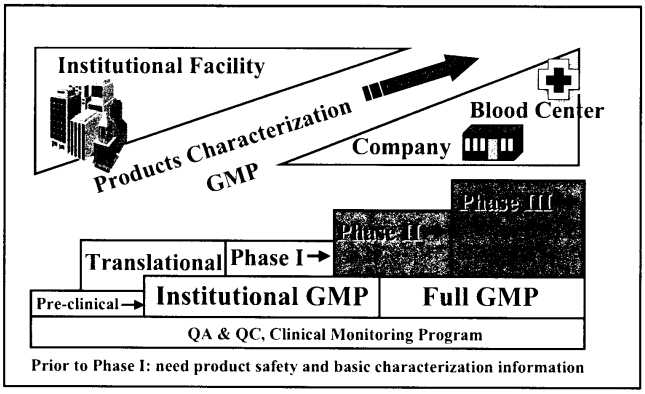

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