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March 31, 2021

Rebecca C. Potts
12601 Twinbrook Parkway
Rockville, MD 20852-1790, USA

Reference to Correspondence Number – C271195
Proposed <1042> Cell Banking Practices for Recombinant Biologics – USP PF 47(1)

Dear Ms. Potts:

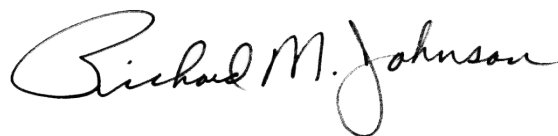
PDA is pleased to have the opportunity to provide comments on the proposed USP Informational Chapter <1042>, released for public comment on January 31, 2021. We recognize that the purpose of the proposed chapter is to provide practical guidelines for the derivation, production, storage, characterization, and qualification of recombinant cell banks used in the manufacture of biological drug products.

Our comments were prepared by a group of expert volunteers with experience in cell banking and recombinant biologics product regulation, development, and manufacturing. The following pages present some concerns with the proposed chapter. The specific technical comments are organized by the draft's section headings.

PDA is a non-profit, international, professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. These comments were prepared by a committee of experts with experience in the practice of pharmacy and pharmaceutical manufacturing including members representing our Board of Directors and our Advanced Therapy Medicinal Products Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President, PDA

CC: Glenn Wright, PDA; Joshua Eaton, PDA

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General Comments

General Comments	Rationale

Specific Comments to the Text

Item #	Section	Current Text	Proposed Change	Rationale
1	Scope	The bank can be released before it is fully tested to start drug substance manufacturing	The bank can be conditionally released before it is fully tested to start drug substance manufacturing	Clarity
2	GENERAL PROCESSES AND CONSIDERATIONS OF CELL BANKING	The source, origin, generation, propagation, and selection of the cell line must be documented and described in detail	Clarify where this should be documented.	Guidance for end users
3	GENERAL PROCESSES AND CONSIDERATIONS OF CELL BANKING	"RCBs are usually generated under non-GMP conditions, whereas MCBs and WCBs are required to be produced in GMP facilities."	Figure 1 outlines the general practices and considerations of cell banking processes and how they evolve through development into GMP manufacturing. The bar at right side of figure indicated "Use of Good Manufacturing Practices" starts from "selection of host cell line/strain and expression construct". It seems it should start from "culture premaster research cell bank (pmRCB) into Master Cell Bank (MCB)". In addition, Figure 1 is also not consistent with Figure 2 in regard to GMP requirement.	Assure consistency between text and figures

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Item #	Section	Current Text	Proposed Change	Rationale
4	GENERAL PROCESSES AND CONSIDERATIONS OF CELL BANKING	The RCBs chosen for the production cell lines/strains and backup cell lines/strains are sometimes referred to as premaster research cell banks (pmRCB), which need to go through purity testing prior to the production of MCBs and subsequent WCBs	Clarify or refer to the purity testing for pmRCB (if described below)	Ensure completeness of guidance
5	GENERAL PROCESSES AND CONSIDERATIONS OF CELL BANKING - Figure 2.	Expression construct stability (if not tested in MCB)	Clarify how stability should be tested	Expression construct stability is tested in comparison to MCB (MCB and EOP from WCB)
6	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs	non-secreting (NS0) mouse myeloma cells	non-IgG secreting (NS0) mouse myeloma cells	clarity
7	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs (General information)	6. CHO cells are amenable to genetic manipulation, which allows for easy introduction of recombinant DNA resulting in expression/secretion of large quantities of the desired protein.	Clarify the benefit of CHO cell use	Clarify if Number 6 is more about the ability to integrate DNA to generate stable recombinant protein expressing cell lines.

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Item #	Section	Current Text	Proposed Change	Rationale
8	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs (Table 1)	Table 1	Make the information more cell banking focused	This table is focused on the properties that are important for choosing one expression system over another. It does not offer much information that is relevant to cell banking.
9	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs (Table 1)	Secreted recombinant proteins are properly folded and are identical in primary, secondary, and tertiary structure to the natural human protein	Secreted recombinant proteins are properly folded and are identical in primary, secondary, tertiary, and quaternary structure to the natural human protein	This would apply for antibodies
10	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs	New chromosomal structures, known as homogeneously staining regions (HSRs), can be found in the metaphase of MTX-selected CHO cells.	New chromosomal structures, known as homogeneously staining regions (HSRs), can be found in the metaphase chromosomes of MTX-selected CHO cells.	Clarity
11	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs	Selection markers such as DHFR or GS for recombinant cell line selection	Addition of antibiotic resistance genes that are sometimes used for CHO cells, e.g., neomycin, bleomycin	Completeness

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Item #	Section	Current Text	Proposed Change	Rationale
12	<p>3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs</p>	<p>Although the overexpressed or knocked out genes do not encode sequences for the final therapeutic protein, they play critical roles in the productivity and quality of the expressed therapeutic proteins. Therefore, evaluation of the integrity and stability of those genes for the intended purposes should be included as a part of the cell substrate characterization.</p>	<p>Clarify characterization process as to whether the knock-in or knock-out has to be characterized in every cell line made using that host or just once for the host cell line.</p>	<p>CHO cell lines with gene knock-outs have been used for decades, for example the selectable markers DHFR and GS, and loss of expression should only need characterization in the host cell line. CHO host cell lines with overexpressed gene knock-ins most likely need to be characterized in all derivative cell lines as the gain of function is presumably required for appropriate expression or modification of the therapeutic biologic. Additionally, the knocked-in gene would present a Host Cell Protein (HCP) risk and may need demonstration of clearance during the purification process by means of an impurity assay.</p>

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Item #	Section	Current Text	Proposed Change	Rationale
13	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs	For large-scale therapeutic protein production, an optimal copy number should be identified because too few gene copies may result in low levels of mRNA leading to low protein productivity while too many copies may impose metabolic burdens on cells. In addition, high-copy-number plasmids have been shown to possess higher segregation instability, especially in the absence of selective markers. This can lead to the overgrowth of plasmid-free cells, resulting in a significant loss of protein productivity. Therefore, it is usually not desirable to use high-copy-number plasmids, and it is critical to monitor plasmid retention during large-scale production.	Clarify copy number considerations regarding stability	It seems the copy number would play a role in production stability and this would be important for cell banking consideration - as is the case for mammalian cells.

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Item #	Section	Current Text	Proposed Change	Rationale
14	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.1 Common Cell Line Types and Associated Expression Constructs	Selection markers, usually antibiotic-resistant genes such as TetR, are included in the plasmid to determine the growth of plasmid-free cells. Therefore, antibiotics are usually included in the growth media. Some common examples include neomycin, polymyxin B, streptomycin, and gentamicin. However, the use of antibiotics in clinical manufacturing can lead to adverse events in some patients and raises concerns over the development of drug-resistant pathogens, so it is desirable to develop antibiotic-free plasmid systems, if possible.	Clarify antibiotic use	Antibiotics are removed during expansion when using mammalian cells. If microbial production processes also remove antibiotics, clarify this in the context of cell banking with antibiotics and removal during production.
15	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.2 Production Cell Lines/Strains and Recommended Documentation (DESCRIPTION OF EXPRESSION CONSTRUCT)	The steps in the GOI assembly from the original sources to the final expression plasmid should be described in detail and are often summarized using a flow diagram. In addition, the source and function of all genetic components carried by the expression plasmid should be provided. The components include:	Clarify components referenced	Components can be listed, detailed in a "Table of Components" so abbreviations can be used on plasmid map.

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Item #	Section	Current Text	Proposed Change	Rationale
16	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.2 Production Cell Lines/Strains and Recommended Documentation (GENERATION AND CONSIDERATIONS OF RCB/PMRCB)	pmRCBs from mammalian cell lines should, at minimum, be tested and found sterile for contaminants and negative for mycoplasma before transfer to a GMP facility for the generation of the MCB. For an E. coli-derived pmRCB, testing for purity, identity, and bacteriophages should be performed before entry to a GMP facility. In addition, post-banking evaluation of the pmRCB for growth, viability, and viable cell density should be provided to aid MCB production and characterization	Clarify when and how pmRCB testing can be accomplished	The pmRCB post-banking evaluation can be done in Development labs and included as part of the Tech Transfer to GMP
17	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.2 Production Cell Lines/Strains and Recommended Documentation (GENERATION AND CONSIDERATIONS OF RCB/PMRCB)	Typically, the cells are carefully mixed with a low concentration of dimethyl sulfoxide (DMSO) in cell culture media and/or other ingredients appropriate for that specific cell strain.	Clarify DMSO use and hold-time determination	DMSO hold times are usually controlled in MFG and should be assessed in development prior to Tech Transfer.

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Item #	Section	Current Text	Proposed Change	Rationale
18	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.2 Production Cell Lines/Strains and Recommended Documentation (GENERATION AND CONSIDERATIONS OF RCB/PMRCB)	the carefully controlled freezing process, the new cell bank is moved to appropriate storage conditions.	Clarify "appropriate storage conditions"	It seems some guidance on use of liquid nitrogen at this stage would be useful.
19	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.2 Production Cell Lines/Strains and Recommended Documentation (GENERATION AND CONSIDERATIONS OF RCB/PMRCB)	Figure 4 shows an example of a cell process for a mammalian (CHO) cell bank.	Figure 4 shows an example of a cell banking process for a mammalian (CHO) cell bank.	Proper terminology
20	Figure 4. Example of mammalian (CHO) cell bank process.	Appropriate Cleanroom Quality Control Procedures	Clarify procedures	This should be more general to indicate that validated cleaning procedures should be in place prior to banking and appropriate environmental (microbiological) controls are in use during banking. It is not clear who is doing the streaking nor when it is occurring.

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Item #	Section	Current Text	Proposed Change	Rationale
21	Figure 4. Example of mammalian (CHO) cell bank process.	Fill freezing containers to appropriate volume	Fill freezing containers to appropriate volume and cell density	Inclusion of important parameter
22	Figure 4. Example of mammalian (CHO) cell bank process.	Characterize the cell bank ↔ Specification Analysis	Clarify the distinction between these two activities	The distinction between cell bank characterization tests and those tests that are required for cell bank release (based on Specification) is paramount in this kind of guidance document. This part of the figure is not clarifying. For example, copy number is not typically a release specification for the MCB but can be done for characterization, although many companies wait to compare MCB to EOP during genetic characterization.

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Item #	Section	Current Text	Proposed Change	Rationale
23	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.2 Production Cell Lines/Strains and Recommended Documentation (GENERATION AND CONSIDERATIONS OF RCB/PMRCB)	To avoid any unexpected loss of the cell bank, the containers are typically kept in at least two different geographical locations.	Add reference to mammalian cell banks	Mammalian cell banks should also be split into two locations - I did not see that above.

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Item #	Section	Current Text	Proposed Change	Rationale
24	3. PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION 3.2 Production Cell Lines/Strains and Recommended Documentation (ADDITIONAL CONSIDERATIONS)	During development, the production strains/cell lines used for manufacturing clinical materials usually continue to evolve to meet the commercial manufacturing needs.	During development, the production strains/cell lines used for manufacturing clinical materials may continue to evolve to meet the commercial manufacturing needs.	This type of change is not typical at many companies and may not be appropriate to be stated as "usually" because, at least for mammalian cells, this represents a significant effort to show product comparability in regulatory filings. It is the case that many companies improve their processes but keep the same cell line, and even these changes would require regulatory amendments. This section makes it seem like changing cell lines can be done easily and all that is need is linkage between plasmids and parental cells.
25	4. CLONALITY 4.1 Overview	These practices include limited dilution, fluorescence-activated cell sorting	These practices include limiting dilution, fluorescence-activated cell sorting	Proper grammar

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Item #	Section	Current Text	Proposed Change	Rationale
26	4.2 Methodology LIMITING DILUTION CLONING	Two rounds of LDC provide an approximately 99% probability that the cell line will be monoclonal. However, it is a time-consuming process and can take up to 12 months to complete.	Include seeding density considerations	It is important to include the expected seeding density as part of this probability calculation. Regarding seeding density - it seems regulatory agencies are only OK with determining seed density prior to plating and probability calculations cannot be made from well occupancy (outgrowth) numbers which are usually much lower than seed density targets. It would be good to provide some guidance in this section.
27	4.2 Methodology SINGLE-ROUND LDC WITH IMAGING	After LDC, the stained cells are deposited into imaging-quality well plates where day 0 images are acquired in both fluorescence and brightfield imaging.	Clarify use of fluorescence imaging the process.	Many production cells do not express fluorescent markers. Typically, fluorescent markers are used to validate imagers, then brightfield images are used for identifying single cells for production cell lines.

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Item #	Section	Current Text	Proposed Change	Rationale
28	4.2 Methodology FLUORESCENCE-ACTIVATED CELL SORTING	If antibodies are used in the selection process, they should be tested for adventitious agents.	Any reagent used in the selection process should be tested for adventitious agents.	Any reagent used as part of FACS should have appropriate documentation (e.g., produced without using animal-origin products).
29	4.2 Methodology AUTOMATED CLONE PICKING FROM SEMISOLID MEDIUM	The process can be completed in as little as 7 days, with the identification of stable clones by 4 weeks.	Recommend deletion	The timelines presented here and above are subjective. It does not add to the point of the guidance (cell banking) to include information such as this which may be misinterpreted.

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30	4.2 Methodology OTHER AUTOMATED CLONE SELECTION TECHNOLOGY	Entire sub-section	Revise to exclude single cell printing.	The overview mentioned single cell printing, which is becoming more widespread in the industry. This section and the Table 2 do not mention it. Also, this technology is highly experimental and not really focused on cloning. It is more about clone selection based on expression. The rationale is not clear of how to go from this technology to cell banking as stated at end of paragraph.
31	4.3 Assurance of Clonality	Images, especially day 0 and over time; genetic data; and consistent process data and product quality	Remove "consistent process and PQ"	The "consistent process and PQ" doesn't seem to fit in this section. Imaging and genetics may help ensure consistent product.

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Item #	Section	Current Text	Proposed Change	Rationale
32	4.3 Assurance of Clonality GENETIC SUPPORT	For clones with random (non-site-specific) integration, genetic information supporting the location of the integration site — such as integration site analysis by Southern blot and fluorescence in situ hybridization (FISH) — provides evidence that the cell line was clonal.	Remove reference to Southern blotting	Southern blot does not provide much information on clonality, especially for a single cell bank (banding patterns from MCB to EOP can show consistency). FISH does if enough single cell chromosome spreads are analyzed.
33	5. CELL BANK CHARACTERIZATION	Introduction paragraph	Revise to focus on banking and not the biological process	This section seems to conflate the banking process with the biological process. For CHO cells, it may not be best to characterize banking as inherently variable. The production processes can be quite variable. This production process variability is what leads to changes in CQAs, as described. It seems important to focus on cell banking in this section.

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34	5. CELL BANK CHARACTERIZATION 5.1 Genetic Characterization	The most common methodologies for the assessment of gross structure of the expression construct are restriction endonuclease (RE) mapping analysis and DNA sequencing (NGS).	Revise to exclude NGS	More guidance is needed pertaining to NGS. It should not be included with the Southern blotting, which is an established method with clear specifications. If included, it should have its own section and cover several applications. Specific guidance on what NGS data is submitted, or comparisons that are made, would be helpful. Recommend a reference to PDA Technical Report 71 Emerging Methods for Virus Detection.
35	5. CELL BANK CHARACTERIZATION 5.1 Genetic Characterization	The most common methodologies for the assessment of gross structure of the expression construct are restriction endonuclease (RE) mapping analysis and DNA sequencing (NGS).	Include that NGS should occur on cells at a representative cell age from a representative commercial process.	Better guidance on consistent processes. Recommend a reference to PDA Technical Report 71 Emerging Methods for Virus Detection.

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Item #	Section	Current Text	Proposed Change	Rationale
36	5. CELL BANK CHARACTERIZATION 5.1 Genetic Characterization	It is recommended that LIVCA be determined based on the cell age of the EOP cells for a defined duration beyond the routine commercial drug substance manufacturing process.	Clarify what qualifies as the EOP cells to be analyzed.	End of production (EOP) can vary depending on the validated number of passages - providing a worst-case scenario may be helpful
37	5. CELL BANK CHARACTERIZATION 5.1 Genetic Characterization	DNA sequencing (NGS)	Next generation sequencing (NGS) of DNA	Improper application of acronym
38	5. CELL BANK CHARACTERIZATION 5.1 Genetic Characterization	The most common methodologies for the assessment of gross structure of the expression construct are restriction endonuclease (RE) mapping analysis and DNA sequencing (NGS).	Consider referencing <i>PDA Technical Report 71 Emerging Methods for Virus Detection</i>	Although not specific to mammalian cells, describes NGS techniques and considerations
39	5. CELL BANK CHARACTERIZATION 5.1 Genetic Characterization	The most common methodology for the evaluation of GOI copy number is quantitative PCR (qPCR). GOI-specific qPCR assays and a normalizer qPCR assay targeting a host genome region are usually applied. ... New DNA sequencing technology such as NGS may further enhance the capability for genetic characterization.	Revise for clarity	This paragraph is hard to follow. Copy number is required as shown above, point #4. The third through last sentence do not add to or support the use of qPCR for copy # determination.

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Item #	Section	Current Text	Proposed Change	Rationale
40	Table 4. Mammalian Cell Bank Characterization (CHO cells)	Sterility: USP/European Pharmacopoeia /ICH requirements	Addition of further guidances	Guidance for Mycoplasma inhibition and Sterility test suitability are presented in USP <63> and USP <71>, respectively. These qualification assays are routinely performed during cell bank testing and seem appropriate to mentioned in the UPS <1042> guidance.
41	Table 4. Mammalian Cell Bank Characterization (CHO cells)	“In vitro assay” row “-“ for WCB column	Change to “+”	Practically speaking, WCB is made before EOP. The guidance seems to be more supportive of in vitro and in vivo testing on WCB.
42	Table 4. Mammalian Cell Bank Characterization (CHO cells) Footnotes	d Species-specific viruses present in rodent cell lines may be detected by mouse, rat, or hamster antibody production tests (MAP, RAP, or HAP).	Remove RAP	This Table Title states it is specific for CHO - so it should reflect the CHO based test (e.g., HAP and MAP, not RAP)

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Item #	Section	Current Text	Proposed Change	Rationale
43	Table 4. Mammalian Cell Bank Characterization (CHO cells)	Bovine and porcine virus in vitro assay (9 CFR [17])	Revise to include requirements for serum-free media	These tests are recommended for cells grown in serum. As many host cells are now adapted to grow without serum, this test is not required for MCB release, provided the host cell line has been tested.
44	Table 4. Mammalian Cell Bank Characterization (CHO cells)	Identity Tests Nucleic acid fingerprinting or other: “-“ in the MCB column	Change to “+”	It is common practice to perform Identity test on MCB.
45	Table 4. Mammalian Cell Bank Characterization (CHO cells) Footnotes	d Species-specific viruses present in rodent cell lines may be detected by mouse, rat, or hamster antibody production tests (MAP, RAP, or HAP).	Remove RAP	This Table Title states it is specific for CHO - so it should reflect the CHO based test (eg HAP and MAP, not RAP)
46	Table 4. Mammalian Cell Bank Characterization (CHO cells) Footnotes	e Selection of viruses to be screened should take into account cell lines that are known to have been infected by such agents and the source from which the cell line was derived.	Add reference to MMV and possibly Vesivirus	For CHO, this would include MMV (some are pushing Vesivirus)

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Item #	Section	Current Text	Proposed Change	Rationale
47	5.5 Other General Considerations for Cell Banks CELL BANK STORAGE STABILITY AND MONITORING	Data for WCB stability monitoring may also include data from appropriately documented scale-down or pilot-scale processes, such as those performed during process characterization and validation studies. WCB stability should be periodically monitored unless the bank is no longer in use for commercial production or the product has been removed from the market.	Add considerations for vial tracking	The number of vials made, used and remaining needs to be tracked
48	REFERENCES	11. Berting A, Kreil T, Biotechnology, Bioengineering. Vol. 106, 598–607; March 26, 2010.	Berting, Farcet and Kreil	Incorrect author attribution