発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Kato T, Heike T, Okawa K, Haruyama M, Shiraishi K, YoshimotoM, Nagato M, Shibata M, Kumada T, Yamanaka Y, Hattori H, Nakahata T	A neurosphere-derived factor, Cystatin C, supports differentiation of ES cells into neural stem cells.	Proc.Natl.Acad. Sci.USA			2006 in press
Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, Nagai S, Fuji A, Yuasa T, Manki A, Sakurai Y, Nakajima M, Kobayashi H, Fujiwara I, Tsutsumi H, Utani A, Nishigori C, Heike T, Nakahata T, Miyachi Y.	Early-onset sarcoidosis and CARD15mutations with constitutive nuclear factor-kB activation: common genetic etiology with Blau syndrome	Blood	105	1195-1197	2005
Yasumi, T., Katamura, K., Okafuji, I., Yoshioka, T., Meguru, T., Nishikomori, R., Kusunoki, T., Heike, T. and Nakahata, T	Limited ability of antigen-specific Th1 responses to inhibit Th2 cell development in vivo.	J. Immunol.	174	1325-1331	2005
Nagato , Heike T., Kata T., Yamanaka Y., Yoshimoto M., Shimazaki T.,Okano H.,and Nakahata T.	Prospective characterization of neural stem cells by flow cytometry anakysis using a combination of surface markers.	J Neurosci Res	80	456-466	2005
T. Kusunoki, I. Okafuji, T. Yoshioka, M. Saito, R. Nisikomori, T. Heike, M. Sugai, A. Shimizu, T. Nakahata	SPRINK5 polymorphism is associated with disease severity and food allergy in children with atopic dermatitis	J Allergy Clin Immuno	115	636-638	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Kawamura T., Ono K., Morimoto T., Wada H., Hirai M., Hidaka K., Morisaki T., Heike T., Nakahata T., Kita T, and Hasegawa K	Acetylation of GATA-4 is involved in the differentiation of embryonic stem cells into cardiac myocytes.	J Boil Chem	280	19682-19688	2005
Yoshimoto M., Chang H., Shiota M., Kobayashi H., Umeda K., Kawakami A., Heike T., and Nakahata T	Two different roles of purified CD45+ c-kit+ Sca-1+ Lin- cells after transplantation in muscles	Stem Cells	23	610-618	2005
Saito,M., Fijisawa, A., Nishikomori, R., Kambe, N., Nakata-Hizume, M., Yoshimoto, M., Ohmori, K., Okafuji, I., Yoshioka, T., Kusunoki, T., Miyachi, Y., Heike, T., and Nakahata, T.	Somatic mosaicism of CIAS1 in a patient with chronic infantile neurogenic, cutaneous, articular syndrome	Arthritis & Rheumatism	52	3579-3585	2005
Kimura, S., Ito, C., Jyoko, N., Segawa, H., Kuroda, J., Okada, M., Adachi, S., Nakahata, T., Yuasa, T., Filho, V.C., Furukawa, H., Maekawa, T.:	Inhibition of leukemic cell growth by a novel anti-cancer drug (GUT-70) Calophyllim brasiliense that acts	by induction of apoptosis. Int J Cancer,	113(1)	158-165	2005
Matsumoto, S., Kimura, S., Segawa, H., Kuroda, J., Yuasa, T., Sato, K., Nogawa, M., Tanaka, F., Maekawa, T., Wada, H.	Efficacy of the third-generation bisphosphonate zoledronic acid alone and combined with anti-cancer agents against small cell lung cancer cell lines	Lung Cancer,	47(1)	31-39	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Kimura, S., Yurugi, K., Segawa, H., Kuroda, J., Sato, K., Nogawa, M., Yuasa, T., Egawa, H., Tanaka, K., Maekawa, T	Rapid quantitation of IgG antibodies specific for blood group antigens A and B by surface plasmon resonanse	Transfusion	45(1)	56-62	2005
Nogawa, M., Yuasa, T., Kimura, S., Kuroda, J., Sato, K., Segawa, H., Maekawa, T	Monitoring luciferase-labeled cancer cell growth and metastasis in different in vivo models	Cancer Lett,	217(2)	245-253	2005
Nogawa, M., Yuasa, T., Kimura, S., Kuroda, J., Segawa, H., Sato, K., Koizumi, M., Maekawa, T	Zoledronic acid mediates Ras-independent growth inhibition of prostate cancer cells	Oncol Res,	15(1)	1-9	2005
Sato, K., Kimura, S., Segawa, H., Yokota, A., Matsumoto, S., Kuroda, J., Nogawa, M., Yuasa. T., Kiyono, Y., Wada, H., Maekawa, T	Cytotoxic effects of gamma delta Tcells expanded ex vivo by a third generation bisphosphonate for cancer immunotherapy	Int J Cancer	116(1)	94-99	2005
Maekawa ,T., Kimura, S., Kasai, Y	Development of novel advanced cell and gene therapy and GMP-controlled cell processing	JMAJ	48(2)	1-4	2005
Yuasa, T., Tsuji, H., Kimura, S., Niwa, N., Yurugi, K., Egawa, H., Tanaka, K., Maruya, E., Saji, H., Asano, H., Maekawa, T	HLA in Japanese patients with biliary atresia - a retrospective analysis in the patients with living donor liver transplantation	Hum Immunl	66(3)	290-295	2005
Segawa, H., Kimura, S., Kuroda, J., Sato, K., Nogawa, M., Yuasa, T., Yokota, A., Hodohara, K., Fujiyama, Y., Maekawa, T	The anti-leukemic efficacy of the third generation bisphosphonate ONO5920/YM529	Leuk Res	29(4)	451-457	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Nogawa, M., Yuasa, T., Kimura, S., Tanaka, M., Kuroda, J., Sato, K., Yokota, A,,Segawa, S., Toda, Y., Kageyama, S., Yoshiki, T., Okada, Y., Maekawa, T	Intravesical administration of small interfering RNA targeting PLK-1 successfully prevents the growth of bladder cancer	J Clin Invest,	115(4)	978-985	2005
Maekawa, T	Establishment of institutional GMP is mandatory for the development of translational research in cell therapy.	J Pharmacol Sci	97	20	2005
Yuasa, T., Nogawa, M., Kimura, S., Yokota, A., Sato, K., Segawa, H., Kuroda, J., Maekawa, T	A third generation bisphosphonate minodronic acid (YM529), augments the interferon a/b-mediated inhibition of renal cell cancer cell growth both in vitro and in vivo	Clin Cancer Res	11 (2 Pt 1)	853-859	2005
Yuasa, T., Niwa, N., Kimura, S., Yurugi, K., Tsuji, H., Egawa, H., Tanaka, K., Asano, H., Maekawa, T	Intraoperative blood loss during living related liver transplantation analysis of 635 cases at a single center.	Transfusion	45(6)	879-884	2005
Matsumoto, S., Okitsu, T., Iwanaga, Y., Noguchi, H., Nagata, H., Yonekawa, Y., Yamada, Y., Fukuda, K., Tsukiyama, K., Suzuki, H., Kawasaki, Y., Shimodaira, M., Matsuoka, K., Shibata, T., Kasai, Y., Maekawa, T., Shapiro, A.M.J., Tanaka, K	Insulin independence after living-donor distal pancreatectomy and islet allo-transplantation	Lancet	365 (9471)	1642-1644	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Segawa, H., Kimura, S., Kuroda, J., Sato, K., Yokota, A., Kawata, E., Kamitsuji, Y., Ashihara, E., Yuasa, T., Fujiyama, Y., Ottmann, O.G., Maekawa, T	Zoledronate synergizes with imatinib mesylate to inhibit Ph+ primary leukaemic cell growth	Br J Haematol	130	558-560	2005
Kimura, S., Naito, H., Segawa, H., Kuroda, J., Yuasa, T., Sato, K., Yokota, A., Kamitsuji, Y., Kawata, E., Ashihara, E., Nakaya, Y., Naruoka, H., Wakayama, T., Nasu, K., Asaki, T., Niwa, T., Hirabayashi, K., Maekawa, T.	NS-187, a potent and selective dual Bcr-Abl/Lyn tyrosine kinase inhibitor, is a novel agent for imatinib-resistant leukemia	Blood	106(12)	3948-3954	2005
Okitsu, T., Matsumoto. S., Iwanaga, Y,. Noguchi, H., Nagata, H., Yonekawa, Y., Maekawa, T., Tanaka, K	Kyoto islet isolation method: the optimized one for non-heart-beating donors with highly efficient islet retrieval	Transplant Proc	37	3391-3392	2005
Matsumoto, S., Okitsu, T., Iwanaga, Y., Noguchi, H., Yonekawa, Y., Nagata, H., Yamada, Y., Fukuda, K., Seino, Y., Shibata, T., Kasai, Y., Maekawa, T., Tanaka, K	Successful islet transplantation from non-heart-beating donor pancreata using modified Ricordi islet isolation method.	Transplantation, in press			
Horie, N., Murata, H., Nishigaki, T., Segawa, H., Yuasa, T., Kimura, S, Maekawa, T., Fushiki, S., Kubo, T.	The third-generation bisphosphonates inhibit tumor proliferation and induce apoptosis in murine osteosarcoma in vitro.	Cancer Lett, in press			

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Kimura, S., Maekawa, T	Stem cell transplantation for Ph+ leukemias in the imatinib and post-imatinib eras *In,* "Bone Marrow Transplantation New Research.	Nova Science Publishers, Inc. review, in press,			2005
Naito, H., Kimura, S., Nakaya, Y., Naruoka, H., Kimura, S., Ito, S., Wakayama, T., Maekawa, T. and Hirabayashi, K.	*In vivo* inhibitory effect of NS-187, a dual Bcr-Abl/Lyn tyrosine kinase inhibitor, on the proliferation of leukemic cells harbouring Abl kinase domain mutations	Leuk Res, in press			2006
Kimura, S., Niwa, T., Hirabayashi, K., Maekawa, T	Development of NS-187, a potent and selective dual Bcr-Abl/Lyn tyrosine kinase inhibitor	Cancer Chemo Pharmacol in press,			2006
木村晋也、黒田純也、前川　平	Ras 関連蛋白質シグナルを標的とした造血器腫瘍の分子標的治療 Annual Review　血液 2005（高久史麿、溝口秀昭、坂田洋一、金倉　譲、小島勢二　編集）	中外医学社、東京		179-189	2005
木村晋也、黒田純也、前川　平	Ras superfamily シグナル伝達経路を標的とした白血病治療分子標的療法の基礎と臨床（鶴尾　隆 監修）	篠原出版社, 東京		175-184	2005
木村晋也、前川　平	細胞内シグナル伝達系を阻害する薬剤 3. Ras 阻害剤、2) Zoledronate. 分子標的治療薬—作用機序と臨床—.（元吉和夫、大野竜三編）	メディカル・レビュー社, 東京		143-151	2005
辻　博昭、湯浅　健、前川　平	消化管出血の輸血療法消化器疾患診療実践ガイド（千葉勉、井廻道夫 編）	文光堂、東京		266-269	2005
湯浅　健、木村晋也、前川　平	RNA を標的としたがん治療の可能性臨床腫瘍内科学入門（金倉譲　編著）	永井書店、大阪		117-121	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
前川　平	輸血療法の基礎と実際三輪血液病学（浅野茂隆、池田康夫、内山 卓 監修）	文光堂、東京		672-733	2005
木村晋也、前川　平	イマチニブ以後の白血病に対する分子標的療法薬. Annual Review　血液 2006（高久史麿、溝口秀昭、坂田洋一、金倉譲、小島勢二　編集）	中外医学社、東京		99-113	2006
湯浅　健、野河正輝、木村晋也、前川平	膀胱癌、遺伝子医学 MOOK（中村義一編）	メディカル ドゥ			
前川　平	輸血・成分輸血、内科学（第九版）.（矢崎義雄、小俣正男、水野美邦 監修）	朝倉書店、東京（印刷中）			
湯浅　健、木村晋也、前川　平	Bisphosphonate の抗腫瘍作用	Cancer Frontier	7	70-76	2005
笠井泰成、前川　平	これからの臨床検査技師教育を考える—期待される活動領域と技師教育	高度先進医療部門. 臨床検査	49(8)	872-873	2005
万木紀美子、前川　平	ABO 血液型不適合移植と輸血—臓器移植看護を理解するためのキーワード—	看護技術（臨時増刊号「臓器移植看護の現在」）	51(12)	15-19	2005
万木紀美子、木村晋也、前川　平	抗A，抗B抗体価測定法の検討—表面プラズモン共鳴を応用した新規測定法—	日本臨床検査医学会誌	53(11)	1011-1018	2005
Maekawa, T	Establishment of institutional GMP is mandatory for the development of translational research in cell therapy	J Pharmacol Sci	97	20	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
前川　平	RNA 干渉—その基礎と臨床応用—	Front Wave in Hematology	15	4-7	2005
木村晋也、上辻由里、前川　平	急性リンパ性白血病	癌治療と宿主	18(1)	69-80	2005
湯浅　健、丹羽紀実、辻　博昭、万木紀美子、江川裕人、田中紘一、木村晋也、前川　平	外科医のための輸血医学講座—肝移植における輸血—	外科	67(5)	555-558	2005
河田英里、芦原英司、木村晋也、前川平	GVHD と腎障害	腎と透析	59（6）	970-976	2005
芦原英司、前川　平	結腸がん細胞に対する Vγ9Vδ2T 細胞の腫瘍細胞認識機構	分子細胞治療	5(2)	98-100	2006
木村晋也、黒田純也、前川　平	Abl 点突然変異	血液・腫瘍科（印刷中）			
黒田純也、木村晋也、前川　平	ビスフォスフォネート製剤の抗腫瘍作用	感染免疫腫瘍（印刷中）			
木村晋也、芦原英司、前川　平	新規 dual Bcr-Abl/Lyn kinase inhibitor	血液・腫瘍科、2006 印刷中			
Oritani K, Kanakura Y.	IFN-zeta/ limitin: a member of type I IFN with mild lympho-myelosuppression.	J Cell Mol Med	9	244-254	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Kashiwagi H, Shiraga M, Kato H, Kamae T, Yamamoto N, Tadokoro S, Kurata Y, Tomiyama Y, Kanakura Y.	Negative regulation of platelet function by a secreted cell repulsive protein, semaphorin 3A.	Blood	106	913-921	2005
Shiraga M, Miyata S, Kato H, Kashiwagi H, Honda S, Kurata Y, Tomiyama Y, Kanakura Y.	Impaired platelet function in a patient with P2Y12 deficiency caused by a mutation in the translation initiation codon.	J Thromb Haemost	3	2315-2323	2005
Ishida N, Oritani K, Shiraga M, Yoshida H, Kawamoto S, Ujiie H, Masaie H, Ichii M, Tomiyama Y, Kanakura Y.	Differential effects of a novel IFN-zeta/limitin and IFN-alpha on signals for Daxx induction and Crk phosphorylation that couple with growth control of megakaryocytes.	Exp Hematol	33	495-503	2005
Tanaka H, Matsumura I, Kanakura Y.	Cell cycle regulation in hematopoietic stem/progenitor cells.	J Biol Sci	5	50-60	2005
Ezoe S, Matsumura I, Gale K, Satoh Y, Ishikawa J, Mizuki M, Takahashi S, Minegishi N, Nakajima K, Yamamoto M, Enver T, Kanakura Y.	GATA transcription factors inhibit cytokine-dependent growth and survival of a hematopoietic cell line through the inhibition of STAT3 activity.	J Biol Chem	280	13163-13170	2005
Ishiko J, Mizuki M, Matsumura I, Shibayama H, Sugahara H, Scholz G, Serve H, Kanakura Y,	Roles of tyrosine residues 845, 892 and 922 in constitutive activation of murine FLT3 kinase domain mutant.	Oncogene	24	8144-8153	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Ishiko E, Matsumura I, Ezoe S, Gale K, Ishiko J, Satoh Y, Tanaka H, Shibayama H, Mizuki M, Era T, Enver T, and Kanakura Y.	Notch signals inhibit the development of erythroid/megakaryocytic cells by suppressing GATA-1 activity through the induction of HES1.	J. Biol.Chem.	280(6)	4929-39	2005
Sakane-Ishikawa E, Nakatsuka S, Tomita Y, Fujita S, Nakamichi I, Takakuwa T, Sugiyama H, Fukuhara S, Hino M, Kanamaru A, Soma T, Tsukaguchi M, Igarashi K, Kanakura Y, Aozasa K.	Prognostic Significance of BACH2 Expression in Diffuse Large B-Cell Lymphoma: A Study of the Osaka Lymphoma Study Group.	J Clin Oncol	23	8012-8017	2005
Kabutomori O, Kanakura Y, Iwatani Y.	Inflammation markers and liver dysfunction.	Ann Hematol	84	136	2005
Nojima J, Kuratsune H, Suehisa E, Iwatani Y, Kanakura Y.	Acquired activated protein C resistance associated with IgG antibodies against beta2-glycoprotein I and prothrombin as a strong risk factor for venous thromboembolism.	Clin Chem	51	545-552	2005
Nishimoto N, Kanakura Y, Aozasa K, Johkoh T, Nakamura M, Nakano S, Nakano N, Ikeda Y, Sasaki T, Nishioka K, Hara M, Taguchi H, Kimura Y, Kato Y, Asaoku H, Kumagai S, Komada F, Nakahara H, Hagihara K, Yoshizaki K, Kishimoto T.	Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease.	Blood	106	2627-2632	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
Koma Y, Ito A, Watabe K, Hirata T, Mizuki M, Yokozaki H, Kitamura T, Kanakura Y, Kitamura Y.	Distinct role for c-kit receptor tyrosine kinase and SgIGSF adhesion molecule in attachment of mast cells to fibroblasts.	Lab Invest	85	426-35	2005
金倉　譲	悪性リンパ腫 up-to-date—混沌よりあらたなエビデンスを求めて　はじめに	医学のあゆみ	212	291	2005
金倉　譲	CLL の新たな予後推定因子 ZAP-70. Annual Review 血液 2005（高久文磨，溝口秀昭，坂田洋一，金倉　譲，小島勢二編）	中外医学社, 東京		190-199	2005
金倉　譲	臨床血液学—進歩の軌跡と今後の展望—.	綜合臨牀	54	1723-1724	2005
金倉　譲，水木満佐央	悪性リンパ腫に対する化学療法. インフォームド・コンセント-その理論と書式実例（前田正一編）	医学書院，東京		152-158	2005
松村　到	Hyper eosinophic syndrome (HES)の病態と新たな治療：Imatinib 療法と抗 IL-5 抗体療法. Annual Review 血液 2005（高久文磨，溝口秀昭，坂田洋一，金倉　譲，小島勢二編）	中外医学社, 東京		151-162	2005
松村　到，金倉　譲	ファルネシル化阻害剤	血液・腫瘍科	50	42-52	2005
松村　到，金倉　譲	ファルネシル化阻害剤	Mebio	22	74-80	2005
松村　到	新たな分子標的療法剤	総合臨床	54	1799-1804	2005
松村　到	JunB 欠損マウスに発症する CML 様病態における白血病幹細胞の起源	分子細胞治療	4	98-99	2005
松村　到，金倉　譲	造血細胞における転写因子：総論. 医学のあゆみ　血液疾患 Ver.3（坂田洋一，小澤敬也編）	医歯薬出版株式会社，東京		48-51	2005
松村　到，金倉　譲	ファルネシルトランスフェラーゼ阻害剤. 臨床腫瘍内科学入門（金倉　譲編）	永井書店，大阪		60-63	2005
松村　到	プロテアソーム阻害剤. 臨床腫瘍内科学入門（金倉　譲編）	永井書店，大阪		64-66	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
松村　到，金倉　譲	Farnesyl transferase 阻害剤．分子標的治療薬（元吉和夫，大野竜三編）	メデイカルレビュー社，東京		133-142	2005
松村　到，金倉　譲	細胞周期の制御機構．三輪血液病学（浅野茂隆，池田康夫，内山　卓監修）	文光堂，東京		99-103	2005
松村　到，金倉　譲	好酸球，好塩基球および肥満細胞の異常．三輪血液病学（浅野茂隆，池田康夫，内山　卓監修）	文光堂，東京		1308-1320	2005
松村　到，金倉　譲	急性白血病の分類(FAB 分類と WHO 分類)　三輪血液病学（浅野茂隆，池田康夫，内山　卓監修）	文光堂，東京		1374-1408	2005
松村　到，金倉　譲	白血病	内科	96	1028-1036	2005
松村　到	Hyper eosinophic syndrome (HES)の病態と新たな治療：Imatinib 療法と抗 IL-5 抗体療法．Annual Review 血液 2005（高久文磨，溝口秀昭，坂田洋一，金倉　譲，小島勢二編）	中外医学社，東京		151-162	2005
松村　到，金倉　譲	サイトカイン mimetics の臨床応用．実験医学増刊 Vol.23 No.20（宮島　篤，北村俊雄編）	羊土社，東京		182-187	2005
水木満佐央，金倉　譲	シグナル伝達阻害分子による白血病の治療．分子標的療法の基礎と臨床（鶴尾　隆監修，今村雅寛，金倉　譲，井上勝一編）	篠原出版新社，東京	22	15-28	2005
水木満佐央，金倉　譲	ファルネシル化酵素阻害剤．	今日の移植	18	520-525	2005
水木満佐央，金倉　譲	c-Kit と急性白血病．医学のあゆみ　血液疾患 Ver.3（坂田洋一，小澤敬也編）	医歯薬出版株式会社，東京		222-226	2005
織谷健司，金倉　譲	新たなⅠ型インターフェロン:IFN-z/limitin とＢリンパ球．	臨床免疫	43	535-541	2005
田中宏和，伊藤仁也	臍帯造血幹細胞の体外増幅	血液・腫瘍科	51	148-153	2005

発表者氏名	論文タイトル	発表誌名	巻名	ページ	出版年
伊藤 仁也, 中畑 龍俊	臍帯血造血幹細胞の ex vivo 増幅細胞		36	48-51	2004
廣瀬　弥保、田中　聡、伊藤　仁也	Ex vivo 増幅培養にともなう臍帯血造血幹細胞の FACS 解析	Cytometry Research	15(1)	1-6	2005
伊藤仁也、中畑龍俊	ex vivo 増幅造血幹細胞を用いた臍帯血移植	実験医学	24(2)	274-285	2006
伊藤　仁也	活性化 T 細胞の造血細胞移植への臨床応用　血液成分治療	医薬ジャーナル社		145-158	
伊藤　仁也	臍帯血造血幹細胞の体外増幅と臨床応用　臍帯血移植	新興医学出版社（分担執筆）			

VI. 研究成果の刊行物・印刷物

Guidance for Industry

INDs — Approaches to Complying with CGMP During Phase 1

Draft Guidance

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Monica Caphart at 301-827-9047 or (CBER) Christopher Joneckis at 301-435-5681.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2006
CGMP

G:\6164dft.doc
1/9/2006

Guidance for Industry

INDs — Approaches to Complying with CGMP During Phase 1

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2006
CGMP

G:\6164dft.doc
1/9/2006

Contains Nonbinding Recommendations

Draft Not for Implementation

TABLE OF CONTENTS

Guidance for Industry
INDs — Approaches to Complying with CGMP During Phase 1[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist persons producing drug and biological products (investigational drugs) for use during phase 1 development (21 CFR 312.21(a)) in complying with relevant current good manufacturing practice as required by § 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Controls for producing an investigational new drug for use in a phase 1 study are primarily aimed at ensuring subject safety. The Agency believes that applying quality control (QC) principles to the production of investigational products (i.e., interpreting and implementing CGMPs consistent with good scientific methodology) will facilitate the initiation of investigational studies in humans and protect study subjects. When finalized, this guidance will replace the *1991 Guideline on the Preparation of Investigational New Drug Products (Human and Animal)* for the production of IND products for phase 1 clinical trials described in the Scope section of this guidance.

This guidance is being issued concurrently with a direct final rule (and companion proposed rule), which specifies that the particular requirements in Part 211 (21 CFR 211) need not be met for most investigational drugs manufactured for use during phase 1 development. Instead, the Agency recommends the approaches outlined in this guidance for complying with § 501(a)(2)(B) of the FD&C Act.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by an Agency working group with representatives from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA), at the Food and Drug Adminstration.

II. BACKGROUND

The FD&C Act specifies that drugs must be manufactured, processed, packed, and held in accordance with current good manufacturing practice (CGMP), or they are deemed to be adulterated. In September 1978, FDA implemented revised CGMP regulations for drug and biological products (see 21 CFR Parts 210 and 211). These regulations were written primarily with commercial manufacturing in mind. Although the Agency stated at the time that the regulations applied to all types of pharmaceutical production,[2] we indicated in the preamble to the regulations that we were considering proposing additional regulations governing drugs used in investigational clinical studies.

In 1991, the Agency issued the *Guideline on the Preparation of Investigational New Drug Products (Human and Animal).* However, the 1991 document did not discuss all manufacturing situations, including, for example, small- or laboratory-scale production of investigational new drugs. In addition, the 1991 document did not address fully the Agency's expectation that an ***incremental approach*** to manufacturing controls would be taken during investigational drug development, which for most products includes a change in production scale.

This guidance (once finalized) and the regulation it complements, once finalized, will represent the Agency's effort to proceed with its plans to formally describe an approach to aide manufacturers in implementing manufacturing controls that are appropriate for the stage of development. The use of this approach recognizes that some controls and the extent of controls needed to achieve appropriate product quality differ not only between investigational and commercial manufacture, but also among the various phases of clinical studies. Consistent with the Agency's CGMP for the 21 Century initiative,[3] where applicable, manufacturers are also expected to implement controls that reflect product and production considerations, evolving process and product knowledge, and manufacturing experience.[4]

This guidance describes FDA's current thinking regarding controls for special production situations (e.g., a laboratory setting, exploratory studies, multi-product and multi-batch testing) and specific types (e.g., biological/biotechnology products, aseptically processed products) of investigational new drug (IND) products manufactured for use during phase 1 clinical trials as described in the Scope section of this guidance. As the new rule specifies, the particular requirements in Parts 211 (21 CFR 211) need not be met for certain exploratory products manufactured for use during phase 1 clinical trials.

---

[2] Preamble to the CGMP 1978, comment #49. "The Commissioner finds that, as stated in 211.1, these CGMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages. It is appropriate that the process by which a drug product is manufactured in the development phase be well documented and controlled in order to assure the reproducibility of the product for further testing and for ultimate commercial production. The Commissioner is considering proposing additional CGMP regulations specifically designed to cover drugs in research stages."

[3] See http://www.fda.gov/cder/gmp/21stcenturysummary.htm.

[4] We are considering issuing additional guidance and/or regulations to clarify the Agency's expectations with regard to fulfilling the CGMP requirements when producing investigational drugs for phase 2 and phase 3 clinical studies.

When finalized, this guidance will replace the *1991 Guideline on the Preparation of Investigational New Drug Products (Human and Animal)* for the production of IND products for phase 1 clinical trials described in the Scope section of this guidance. Phase 2 and 3 production will continue to be subject to those portions of 210 and 211 that are applicable.

III. SCOPE

This guidance applies to the following:

> Investigational new human drug and biological products (including finished dosage forms used as placebos) intended for human use during phase 1 development, including, for example, investigational recombinant and nonrecombinant therapeutic products, vaccine products, allergenic products, in vivo diagnostics, plasma derivative products, blood and blood components, gene therapy products, and somatic cellular therapy products (including xenotransplantation products) that are subject to CGMP requirements of § 501(a)(2)(B) of the FD&C Act.

The guidance applies to investigational products whether they are produced in small- or large-scale environments because such studies are typically designed to assess tolerability or feasibility for further development of a specific drug or biological product. However, if an investigational drug has already been manufactured by an IND sponsor for use during phase 2 or phase 3 studies or has been lawfully marketed, manufacture of such a drug must comply with the appropriate sections of 21 CFR Part 211 for the drug to be used in any subsequent phase 1 investigational studies, irrespective of the trial size or duration of dosing.

This guidance does ***not*** apply to the following:

- Human cell or tissue products regulated solely under Section 361 of the PHS Act
- Clinical trials for products subject to the device approval or clearance provisions of the Food, Drug, and cosmetic Act
- Investigational new drugs manufactured for phase 2 and 3 studies
- Already approved products that are being used during phase 1 studies (e.g., for a new indication)

If clarification on applicability of this guidance to a specific clinical study is needed, please contact the appropriate center with responsibility for review of the IND.

We recommend that this guidance be used as a companion to other guidances describing the chemistry, manufacturing, and control (CMC) information submitted and reviewed in an IND application for phase 1 studies (References 1, 2, 3). At this stage of development, in many cases, manufacture of the active ingredient and the final investigational product will be accomplished through a series of steps within a single facility. Producers of new active pharmaceutical