ReedSmith

William J. McNichol, Jr. • 215.241.7950 • wmcnichol@reedsmith.com

October 16, 2001

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Mail Stop HFA-305
Rockville, MD 20852

Re: Docket No. 01P-0428/CP 1

Supplemental Citizen Petition Regarding Proposed Generic Cefuroxime Axetil Products

Dear Sir or Madam:

SUPPLEMENTAL CITZEN PETITION

We write to supplement the Citizen's Petition filed on September 19, 2001 by Professional Detailing, Inc. and its wholly-owned affiliate LifeCycle Ventures (collectively, "PDI"), the exclusive distributor of CEFTIN® Tablets (cefuroxime axetil tablets) and CEFTIN® for Oral Suspension (cefuroxime axetil powder for oral suspension) in the United States. In its Petition, Docket No. 01P-0428/CP 1, PDI has requested that the Food and Drug Administration ("FDA"):

1. Decline to approve any Abbreviated New Drug Application ("ANDA") that seeks approval for a generic product containing a mixture of amorphous and crystalline cefuroxime axetil.

2. Decline to approve the pending ANDA submitted by Ranbaxy Laboratories, Inc. ("Ranbaxy"), in which Ranbaxy proposes to market a drug containing a mixture of amorphous and crystalline

01P-0428 SUP 1

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Delaware
New Jersey
New York
Pennsylvania
United Kingdom
Virginia
Washington, DC

cefuroxime axetil as a generic substitute for CEFTIN®, which contains wholly amorphous cefuroxime axetil.

3. Decline to make effective any approval of the pending ANDA submitted by Ranbaxy or the pending ANDA submitted by Apotex, Inc. ("Apotex") for a generic drug containing a mixture of amorphous and crystalline cefuroxime axetil until either (a) thirty months from the date on which Glaxo commenced a patent infringement action against that applicant, or (b) the date on which a court enters a final order or judgment declaring Glaxo's U.S. Patent No. 4,562,181 to be invalid and/or not infringed by that applicant's ANDA.

4. Issue a regulation to set uniform standards for new drug applications in which the applicants seek approval for drugs that contain a different form of an active ingredient that is contained in a reference listed drug.

Major international pharmacopoeias provide further support for PDI's Citizen's Petition, and are appended to this supplement for FDA's review and consideration. Appended hereto as Exhibits 19, 20 and 21, respectively, are copies of the European Pharmacopoeia, British Pharmacopoeia and Chinese Pharmacopoeia monographs for cefuroxime axetil. Each of these monographs requires that, for drugs containing cefuroxime axetil, the cefuroxime axetil must be in amorphous form and must have a specified isomeric mixture. None of these pharmacopoeial authorities permits the inclusion of crystalline material to this drug substance.

These pharmacopoeia references are significant for two reasons. First, as a matter of science, they show a lack of support in the international scientific community for the proposition that crystalline cefuroxime axetil may be considered "the same as" amorphous cefuroxime axetil, as ANDA applicants have asserted to FDA. On the contrary, as these pharmacopoeia references and the other authority cited in PDI's Citizen's Petition all demonstrate, there is widespread consensus in the international scientific

community that the two forms of cefuroxime axetil are significantly different, and that only the amorphous form of cefuroxime axetil should be used as an active ingredient in drug products.

Second, these pharmacopoeias highlight a serious policy problem that would arise if FDA were to approve generic drugs containing both crystalline and amorphous cefuroxime axetil as active ingredients. Approval of such drugs would be contrary to the goal of international harmonization to which FDA is committed. It would give rise to many of the problems that harmonization is intended to prevent.

FDA is committed to working with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") to set uniform international standards for regulating drug substances and drug products. Those efforts include collaboration with the international Pharmacopoeial authorities, establishment of international standards for good manufacturing practices, and setting of uniform specifications for drug substances and products. *See, e.g.,* ICH Topics and Guidelines, "Quality Topics" (appended hereto as Exhibit 22 and incorporated herein by reference); *see also, e.g.,* Draft ICH Guidance, "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances," 62 Fed. Reg. 62,890 (Nov. 25, 1997) (attachment D to Citizen's Petition filed by Glaxo Wellcome Inc., now GlaxoSmithKline, filed September 29, 2000, Docket No. 00P-1550); FDA Guidance for Industry, "Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (August 2001) (endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2000) (appended hereto as Exhibit 23 and incorporated herein by reference).

If FDA were to approve a generic drug containing both crystalline and amorphous cefuroxime axetil as active ingredients, it would allow into the United States market a drug product that likely would not be approved by other international regulatory authorities. Such action would give rise to precisely the sort of conflicting standards and confusion regarding which drugs may be sold in which markets that ICH has been working to eliminate.

There is no basis in public policy, science or law to warrant approving a generic cefuroxime axetil drug that does not comport with international standards. Such an approval would create disharmony and confusion in the global pharmaceutical market, with no offsetting benefit to the American or international public.

These pharmacopoeias highlight the seriousness of the scientific and policy issues presented by ANDAs that are directed to different crystalline forms of a listed drug. Issues of this magnitude should not be resolved *ex parte* or on an *ad hoc* basis. The Agency should deal with them in a thoughtful, open manner with the benefit of the best science available, taking into account the views of all interested parties. This can only be accomplished by the rulemaking previously requested by PDI.

There is no shortage of amorphous cefuroxime axetil. All consumer needs for cefuroxime axetil drug products can readily be met with drugs containing wholly amorphous cefuroxime axetil – the only cefuroxime axetil drug substance that has been fully investigated by FDA, and the only cefuroxime axetil drug substance that is recognized by the European, British and Chinese Pharmacopoeial authorities.[1]

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1 The international pharmacopoeia references cited herein provide compelling evidence that there is no consensus in the global scientific community to justify approval of drugs containing both crystalline and amorphous cefuroxime axetil. Even if these pharmacopoeia references were to be amended to conform with the recently amended United States Pharmacopoeia monograph for cefuroxime axetil, however, the proposed new generic drugs containing cefuroxime axetil still cannot be approved through the ANDA process, for the reasons set forth in PDI's Citizen's Petition.

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Accordingly, PDI renews its request that FDA take the action described above, for all the reasons set forth in PDI's Citizen's Petition and this supplement thereto.

Respectfully submitted,

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Enclosures

cc: Ms. Jane A. Axelrad (w/encs.) (via overnight mail)
Mr. Gary J. Buehler (w/encs.) (via overnight mail)

Exhibits to October 16, 2001 Supplemental Citizen Petition of Professional Detailing, Inc. and LifeCycle Ventures Regarding Proposed Generic Cefuroxime Axetil Products

INDEX OF EXHIBITS[1]

[1] The exhibits to PDI's Citizen Petition (filed September 19, 2001) are numbered 1-18; accordingly, the exhibits to PDI's Supplemental Citizen Petition begin with number 19.

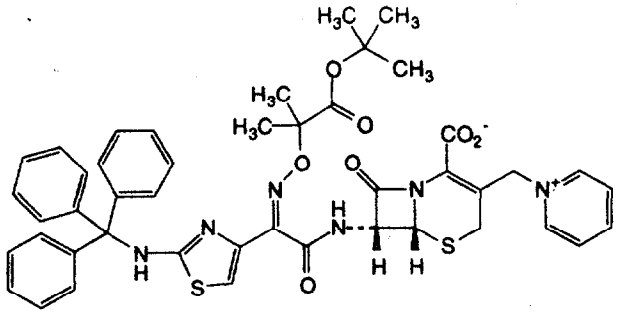
EUROPEAN PHARMACOPOEIA

Third Edition

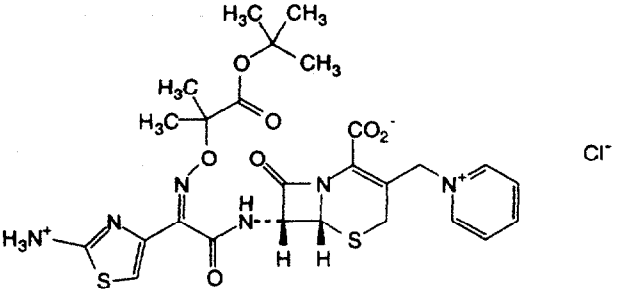
Supplement 2001

Published in accordance with the
Convention on the Elaboration of a European Pharmacopoeia
(European Treaty Series No. 50)

Council of Europe
Strasbourg



D. (6*R*,7*R*)-7-[[(*Z*)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]-2-[2-[(triphenylmethyl)amino]thiazol-4-yl]acetyl]amino]-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,



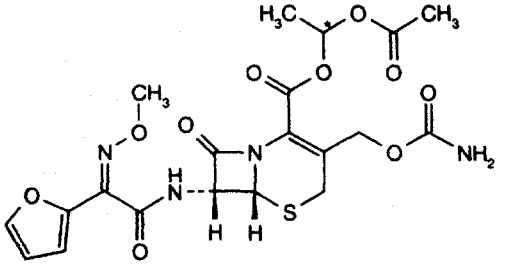
E. (6*R*,7*R*)-7-[[(*Z*)-2-(2-ammoniothiazol-4-yl)-2-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]acetyl]amino]-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct- 2-ene-2-carboxylate chloride,

F. pyridine.

1999:1300
corrected 2001

CEFUROXIME AXETIL

Cefuroximum axetili



$C_{20}H_{22}N_4O_{10}S$ M_r 510.5

DEFINITION

Cefuroxime axetil contains not less than 96.0 per cent and not more than the equivalent of 102.0 per cent of a mixture of the two diastereoisomers of (1*RS*)-1-[(acetyl)oxy]ethyl (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate, calculated with reference to the anhydrous and acetone-free substance.

CHARACTERS

A white or almost white, amorphous powder, slightly soluble in water, soluble in acetone, in ethyl acetate and in methanol, slightly soluble in alcohol.

IDENTIFICATION

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *cefuroxime axetil CRS*.

B. Examine the chromatograms obtained in the Assay. The retention time and size of the principal peaks in the chromatogram obtained with the test solution are the same as those of the peaks due to diastereoisomers A and B of cefuroxime axetil in the chromatogram obtained with reference solution (d).

TESTS

Diastereoisomer ratio. Examine by liquid chromatography (*2.2.29*) as described under Assay. In the chromatogram obtained with the test solution, the ratio of the peak due to cefuroxime axetil diastereoisomer A to the sum of the peaks due to cefuroxime axetil diastereoisomers A and B is between 0.48 and 0.55 by the normalisation procedure.

Related substances. Examine by liquid chromatography (*2.2.29*) as described under Assay. Calculate the percentage content of related substances from the areas of the peaks in the chromatogram obtained with the test solution by the normalisation procedure, disregarding any peak with an area less than 0.05 times that of the two principal peaks in the chromatogram obtained with reference solution (a). The percentage sum of the pair of peaks corresponding to the (*E*)-isomers located by comparison with the chromatogram obtained with reference solution (c) is not greater than 1.0 per cent, the percentage sum of the pair of peaks corresponding to the Δ^3-isomers located by comparison with the chromatogram obtained with reference solution (b) is not greater than 1.5 per cent and the area of any other secondary peak is not greater than 0.5 per cent. The sum of related substances is not greater than 3.0 per cent.

Acetone (*2.4.24*). Not more than 1.1 per cent.

Water (*2.5.12*). Not more than 1.5 per cent, determined on 0.400 g by the semi-micro determination of water.

ASSAY

Examine by liquid chromatography (*2.2.29*).

Test solution. Prepare the solution immediately before use. Dissolve 10.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the mobile phase.

Reference solution (b). Heat 5 ml of the test solution at 60 °C for 1 h to generate the Δ^3-isomers.

Reference solution (c). Expose 5 ml of the test solution to ultraviolet light at 254 nm for 24 h to generate (*E*) isomers.

Reference solution (d). Prepare the solution immediately before use. Dissolve 10.0 mg of *cefuroxime axetil CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

- a column 0.25 m long and 4.6 mm in internal diameter packed with *trimethylsilyl silica gel for chromatography R* (5 µm),
- as mobile phase at a flow rate of 1.0 ml/min a mixture of 38 volumes of *methanol R* and 62 volumes of a 23 g/l solution of *ammonium dihydrogen phosphate R*,
- as detector a spectrophotometer set at 278 nm.

Inject 20 µl each of reference solutions (a), (b), (c) and (d). When the chromatograms are recorded in the prescribed conditions the retention times relative to cefuroxime axetil diastereoisomer A (second peak) are approximately 0.9 for cefuroxime axetil diastereoisomer B, 1.2 for the cefuroxime axetil Δ^3-isomers and 1.7 and 2.1 for the (*E*) isomers. The test is not valid unless in the chromatogram obtained with reference solution (d), the resolution between the peaks corresponding to cefuroxime axetil diastereoisomers A and B is at least 1.5. In the chromatogram obtained with reference solution (b), the resolution between the peaks corresponding to cefuroxime axetil diastereoisomer A and cefuroxime axetil Δ^3-isomer is at least 1.5.

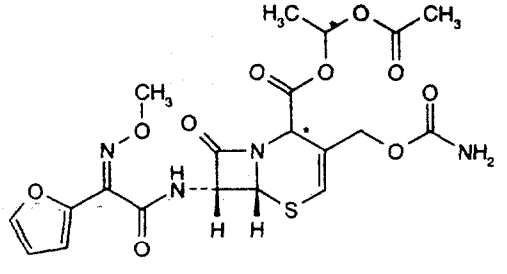
Inject reference solution (d) solution six times. The assay is not valid unless the relative standard deviation of the sum of the peaks corresponding to cefuroxime axetil diastereoisomers A and B is at most 2.0 per cent.

Calculate the percentage content of $C_{20}H_{22}N_4O_{10}S$ from the sum of areas of the two diastereoisomer peaks and the declared content of $C_{20}H_{22}N_4O_{10}S$ in *cefuroxime axetil CRS*.

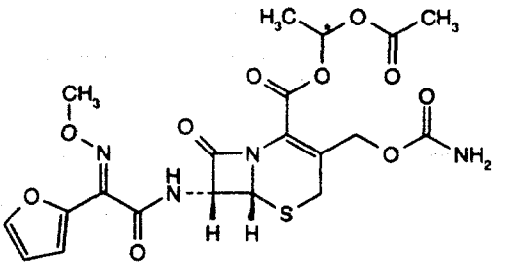
STORAGE

Store in an airtight container, protected from light.

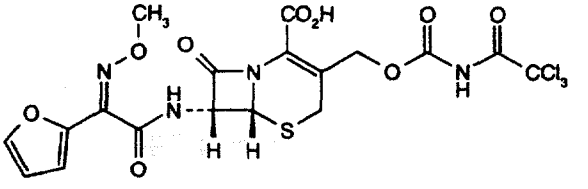
IMPURITIES



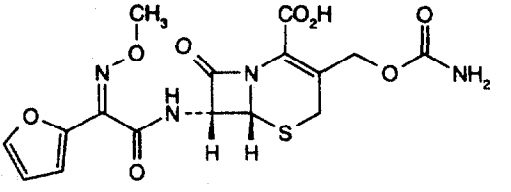
A. (1*RS*)-1-[(acetyl)oxy]ethyl (2*RS*,6*R*,7*R*)-3-[(carbamoyloxy)-methyl]-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate (Δ^3-isomers),



B. (1*RS*)-1-[(acetyl)oxy]ethyl (6*R*,7*R*)-3-[(carbamoyloxy)-methyl]-7-[[(*E*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate ((*E*)-isomers),



C. (6*R*,7*R*)-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]-amino]-8-oxo-3-[[[(trichloroacetyl)carbamoyl]oxy]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



D. (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid (cefuroxime).

2000:0887

CELLULOSE ACETATE

Cellulosi acetas

DEFINITION

Cellulose acetate is partly or completely *O*-acetylated cellulose. It contains not less than 29.0 per cent and not more than 44.8 per cent of acetyl groups (C_2H_3O), calculated with reference to the dried substance. The acetyl content is not less than 90.0 per cent and not more than 110.0 per cent of that stated on the label, calculated with reference to the dried substance.

CHARACTERS

A white, yellowish-white or greyish-white powder or granules, hygroscopic, practically insoluble in water and in alcohol,

British Pharmacopoeia 2001

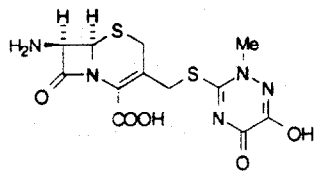
Volume I

Published on the recommendation of the Medicines Commission pursuant to the Medicines Act 1968 and notified in draft to the European Commission in accordance with Directive 98/34/EEC

The monographs of the Third Edition of the European Pharmacopoeia (1997), as amended by the Supplement 2001 published by the Council of Europe in September 2000, are reproduced either in this edition of the British Pharmacopoeia or in the associated edition of the British Pharmacopoeia (Veterinary)
see General Notices, page 3

Effective date: 1 December 2001
see Notices, page vi

London: The Stationery Office

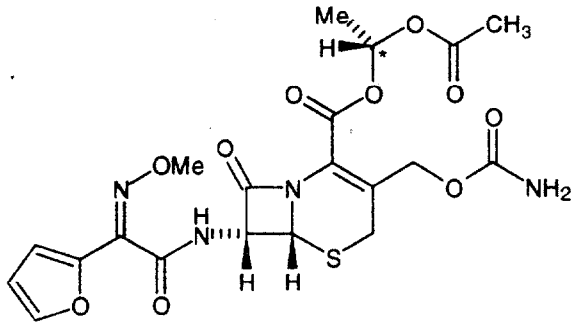


E. (6*R*,7*R*)-7-amino-3-[[(2,5,-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid.

Ph Eur

Cefuroxime Axetil

corrected 1/01



and epimer at C*

$C_{20}H_{22}N_4O_{10}S$ 510.5 *64544-07-6*

Cefuroxime Axetil complies with the requirements of the 3rd edition of the European Pharmacopoeia [1300]. These requirements are reproduced after the heading 'Definition' below.

Action and use Antibacterial.

Preparation
Cefuroxime Axetil Tablets

Ph Eur

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B. Examine the chromatograms obtained in the Assay. The retention time and size of the principal peaks in the chromatogram obtained with the test solution are the same as those of the peaks due to diastereoisomers A and B of cefuroxime axetil in the chromatogram obtained with reference solution (d).

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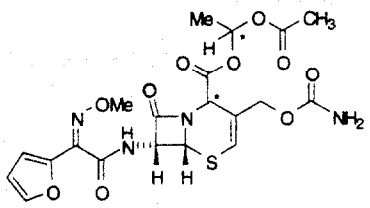
STORAGE

Store in an airtight container, protected from light.

IMPURITIES



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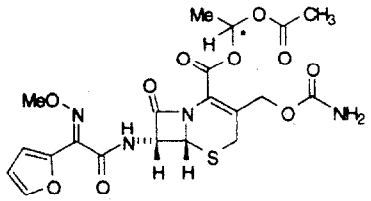
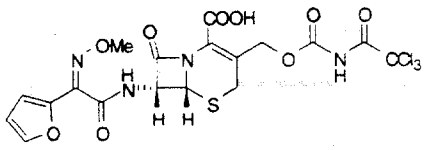
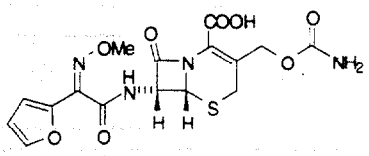


B. (1*RS*)-1-[(acetyl)oxy]ethyl (6*R*,7*R*)-3-[(carbamoyloxy)methyl]-7-[[(*E*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate ((E)-*isomers*),



C. (6*R*,7*R*)-7-[[(*Z*)-2-(furan-2-yl)-2-(methoxyimino)acetyl]amino]-8-oxo-3-[[[(trichloroacetyl)carbamoyl]oxy]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,



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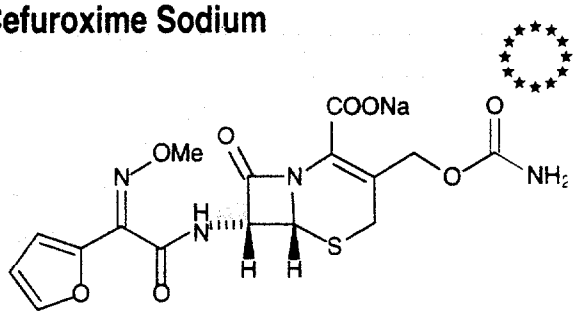
Ph Eur

Cefuroxime Sodium



$C_{16}H_{15}N_4NaO_8S$ 446.4 *56238-63-2*

Cefuroxime Sodium complies with the requirements of the 3rd edition of the European Pharmacopoeia [0992]. These requirements are reproduced after the heading 'Definition' below.

Action and use Antibacterial.

Preparation

Cefuroxime Injection

Ph Eur

DEFINITION

Cefuroxime sodium contains not less than 96.0 per cent and not more than the equivalent of 101.0 per cent of sodium (*Z*)-(6*R*,7*R*)-3-(carbamoyloxymethyl)-7-[2-(2-furyl)-2-(methoxy-imino)acetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, calculated with reference to the anhydrous substance.

CHARACTERS

A white or almost white powder, slightly hygroscopic, freely soluble in water, very slightly soluble in alcohol, practically insoluble in ether.

IDENTIFICATION

First identification: A, D.
Second identification: B, C, D.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *cefuroxime sodium CRS*.

B. Examine by thin-layer chromatography (*2.2.27*), using *silanised silica gel HF_{254} R* as the coating substance.

Test solution. Dissolve 20 mg of the substance to be examined in 5 ml of a mixture of equal volumes of *methanol R* and *0.067M phosphate buffer solution pH 7.0 R*.

Reference solution (a). Dissolve 20 mg of *cefuroxime sodium CRS* in 5 ml of a mixture of equal volumes of *methanol R* and *0.067M phosphate buffer solution pH 7.0 R*.

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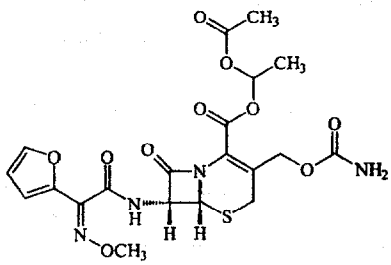
Strength Calculated as $C_{18}H_{18}N_8O_7S_3$
(1) 0.25 g (2) 0.5 g (3) 1.0 g (4) 2.0 g

Storage Preserve in well closed containers, stored in a cool and dry place and protected from light.

Cefuroxime Axetil



$C_{20}H_{22}N_4O_{10}S$ 510.48 [64544-07-6]

Cefuroxime axetil is a mixture of (*RS*)-1-Hydroxyethyl (6*R*,7*R*)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7²-(*Z*)-(*O*-methyloxime), 1-acetate 3-carbamate. It contains not less than 75.0% of cefuroxime ($C_{16}H_{16}N_4O_8S$), calculated on the anhydrous basis.

Description A white or almost white powder; almost odourless; taste, bitter.
Freely soluble in acetone; soluble in chloroform; sparingly soluble in methanol or ethanol; slightly soluble in ether; insoluble in water.

Specific absorbance Measure the absorbance of a solution of 15 μg per ml in methanol at 271 nm(Appendix Ⅳ A), the value of $A(1\%, 1\text{ cm})$ is 390～420.

Identification (1) The retention times of the principal peaks of the diastereoisomers of cefuroxime axetil in the substance being examined in the chromatogram obtained in the Assay are identical with those of the principal peaks of diastereoisomers of cefuroxime axetil CRS in the chromatogram of the reference solution correspondingly.
(2) The infrared absorption spectrum (Appendix Ⅵ C) is concordant with the spectrum of cefuroxime axetil CRS (Appendix Ⅻ).

Crystallinity No birefringence or extinction positions is produced (Appendix Ⅸ D).

Diastereoisomer Carry out the method and use the solution as described under Assay. The relative retention time of diastereoisomer B of cefuroxime axetil is about 0.85 and that of diastereoisomer A of cefuroxime axetil is 1.0. The ratio of diastereoisomer A of cefuroxime axetil to the sum of the diastereoisomers A and B of cefuroxime axetil is between 0.48～0.55, calculated with reference to the peak area obtained in the chromatogram.

Water Not more than 1.5% (Appendix Ⅶ M, method 1 A).

Related substance Dissolve an accurately weighed quantity in mobile phase to produce a test solution of about 0.2 mg per ml, dilute an accurately measured quantity with mobile phase to produce a test solution of about 6 μg per ml. Carry out the method as described under Assay. Inject 20 μl of the reference solution into the column. Adjust the attenuation so that the principal peak height in the chromatogram is about 10% of full scale of the chart. Inject separately 20 μl into the column and record the chromatograms for 2.5 times of the retention time of the principal peak. The sum of the area of all impurity peaks in the chromatogram obtained with the test solution is not greater than the area of the principal peaks in the chromatogram obtained with the reference solution.

Residue on ignition Not more than 0.2% (Appendix Ⅶ N), using 1.0 g.

Heavy metals Carry out the limit test for heavy metals (Appendix Ⅶ H, method 2), using the residue obtained in the test for Residue on ignition: not more than 0.002%.

Assay Carry out the method for high performance liquid chromatography (Appendix Ⅴ D), using a column packed with octadecylsilane bonded silica gel and a mixture of methanol-0.2 mol/L ammonium dihydrogen phosphate solution (38 : 62) as the mobile phase. The detection wavelength is 278 nm. Dissolve an accurately weighed quantity of cefuroxime CRS in mobile phase to produce a test solution of 0.2 mg per ml (ultrasonicate when necessary), heat the solution in a water bath at 60℃ at least for 1 hr to obtain some Δ^2 isomer of cefuroxime axetil. Inject 20 μl into the column. The resolution factor between peaks of the diastereoisomer A and B, the diastereoisomer A and the Δ^2 isomer of cefuroxime axetil complies with the related requirements. The number of the theoretical plates of the column is not less than 1500, calculated with reference to the peak of diastereoisomer A of cefuroxime axetil.

Procedure Weight accurately a quantity equivalent to 50 mg of cefuroxime to a 100 ml volumetric flask, add methanol, shake to dissolve, dilute to volume and mix well. Measure accurately to a 20 ml volumetric flask, diluted with the mobile phase to volume, mix well. Inject 20 μl into the column and record the chromatogram. Repeat the operation, using cefuroxime axetil CRS instead of the substance being examined, calculate the content of $C_{16}H_{16}N_4O_8S$ with respect to the peak area obtained in the chromatogram by the external standard method.

Category Antibiotic

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Preparation (1) Cefuroxime Axetil Capsules
(2) Cefuroxime Axetil Tablets

Cefuroxime Axetil Capsules

Cefuroxime Axetil Capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$).

Description Hard capsules containing almost white powder.

Identification The retention times of the principal peaks of the diastereoisomers of cefuroxime axetil in the substance being examined in the chromatogram obtained in the Assay are identical with those of the principal peaks of cefuroxime axetil CRS in the chromatogram of the reference solution correspondingly.

Diastereoisomer Carry out the method and use the solution as described under Assay. The relative retention time of diastereoisomer B of cefuroxime axetil is about 0.85 and that of diastereoisomer A of cefuroxime axetil is 1.0. The ratio of diastereoisomer A of cefuroxime axetil to the sum

of the diastereoisomers A and B of cefuroxime axetil is between 0.48～0.55, calculated with reference to the peak area obtained in the chromatogram.

Water Not more than 6.0% (Appendix Ⅷ M, method 1 A).

Dissolution Carry out the dissolution test (Appendix Ⅹ C method 2), using 0.07 mol/L of hydrochloride solution as the solvent, adjust the rotational speed of the paddle to 55 rpm. Withdraw 5 ml of the solution after exact 15 minutes and 45 minutes, filter and supply 5 ml of the above solvent accordingly in the vessel immediately. Dilute an accurately measured quantity of the successive filtrate with the same solvent to produce a test solution of about 15 μg per ml. Dissolve an accurately weighed quantity of the mixed contents in the test for weight variation of contents in water to produce a reference solution of about 15 μg per ml of cefuroxime axetil ($C_{20}H_{22}N_4O_{10}S$) according to the labelled amount. Measure the absorbance of the resulting solutions at 278 nm (Appendix Ⅳ A). Calculate the dissolution of $C_{20}H_{22}N_4O_{10}S$ from each capsules. Not less than 60% in 15 minutes and not less than 75% in 45 minutes of the labelled amount are dissolved.

Other requirements Comply with the general requirements for capsules (Appendix Ⅰ A).

Assay Dissolve an accurately weighed quantity of the mixed and finely powdered, contents in the test for weight variation of contents equivalent to about 125 mg of cefuroxime in methanol in a 50 ml volumetric flask, dilute to volume, mix well and filter. Measure accurately 5 ml of the successive filtrate to a 50 ml volumetric flask, dilute with mobile phase to volume. Inject 20 μl into the column, carry out the method for the Assay described under Cefuroxime Axetil.

Category As described under Cefuroxime Axetil.

Strength 0.125 g (calculated as $C_{16}H_{16}N_4O_8S$)

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Cefuroxime Axetil Tablets

Cefuroxime Axetil Tabletes contain not less than 90.0% and not more than 110.0% of the labelled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$).

Description Film coated tablets with almost white core.

Identification The retention times of the principal peaks of the diastereoisomers of cefuroxime axetil in the substance being examined in the chromatogram obtained in the Assay are identical with those of the principal peaks of cefuroxime axetil CRS in the chromatogram of the reference solution correspondingly.

Diastereoisomer Carry out the method and use the solution as described under Assay. The relative retention time of diastereoisomer B of cefuroxime axetil is about 0.85 and that of diastereoisomer A of cefuroxime axetil is 1.0. The ratio of diastereoisomer A of cefuroxime axetil to the sum of the diastereoisomers A and B of cefuroxime axetil is between 0.48～0.55, calculated with reference to the peak area obtained in the chromatogram.

Water Not more than 6.0% (Appendix Ⅷ M, method 1 A).

Dissolution Carry out the dissolution test (Appendix Ⅹ C method 2), using 0.07 mol/L of hydrochloride solution as the solvent, adjust the rotational speed of the paddle to 55 rpm. Withdraw 5 ml of the solution after exact 15 minutes and 45 minutes, filter and supply 5 ml of the above solvent accordingly in the vessel immediately. Dilute an accurately measured quantity of the successive filtrate with the same solvent to produce a test solution of about 15 μg per ml. Powder finely 10 tablets, dissolve an accurately weighed quantity of the powdered tablets in the hydrochloric acid solution to produce a reference solution of about 15 μg per ml of cefuroxime axetil ($C_{20}H_{22}N_4O_{10}S$) according to the labelled amount. Measure the absorbance of the resulting solutions at 278 nm (Appendix Ⅳ A). Calculate the dissolution of $C_{20}H_{22}N_4O_{10}S$ from each tablet. Not less than 60% in 15 minutes and not less than 75% in 45 minutes of the labelled amount are dissolved.

Other requirements Comply with the general requirements for tablets (Appendix Ⅰ A).

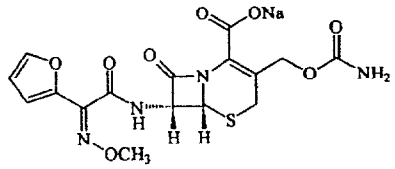
Assay Weigh accurately and powder finely 10 tablets. Dissolve an accurately weighed quantity of powdered tablets equivalent to about 125 mg of cefuroxime in methanol to produce a solution of 2.5 mg per ml of cefuroxime according the labelled amount, mix well and filter. Dilute the successive filtrate with mobile phase to produce a solution of 0.25 mg per ml. Carry out the method for the Assay described under Cefuroxime Axetil.

Category As described under Cefuroxime Axetil.

Strength Calculated as $C_{16}H_{16}N_4O_8S$
(1) 0.125 g (2) 0.25 g

Storage Preserve in tightly closed containers, stored in a cool place and protected from light.

Cefuroxime Sodium



$C_{16}H_{15}N_4NaO_8S$ 446.37 [56238-63-2]

Cefuroxime Sodium is sodium (6*R*, 7*R*)-7-[2(2-furyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It contains not less than 86.0% of cefuroxime ($C_{16}H_{16}N_4O_8S$), calculated on the anhydrous basis.

Description A white or almost white or slightly yellow powder or crystalline powder; odourless; taste, bitter; hygroscopic.
Freely soluble in water; sparingly soluble in methanol; insoluble in ethanol and chloroform.

Specific optical rotation +55° to +65°, in a solution of 10 mg per ml in water (Appendix Ⅵ E).

Specific absorbance Measure the absorbance of a solution of 10 mg per ml in water at 274 nm (Appendix Ⅳ A), the value of $A(1\%, 1cm)$ is 390～425.

Identification (1) The retention time of principal peak of cefuroxime in the substance being examined in the chromatogram obtained in the Assay are identical with that of the principal peak of cefuroxime CRS in the chromatogram of the reference solution correspondingly.
(2) The infrared absorption spectrum (Appendix Ⅵ C) is

ICH Topics and Guidelines
Quality Topics

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Quality Topics: Checklist

Q1: Stability:	Q1A(R): Stability Testing of New Drugs and Products **(Revised Guideline)**	Q1B: Photostability Testing	Q1C: Stability Testing for New Dosage Forms
	Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products		
Q2: Analytical Validation:	Q2A: Text on Validation of Analytical Procedures	Q2B: Methodology	
Q3: Impurities:	Q3A(R): Impurities in New Drug Substances **(Revised Guideline)**	Q3B(R): Impurities in New Drug Products **(Revised Guideline)**	Q3C: Impurities: Residual Solvents
Q4: Pharmacopoeias:	Q4: Pharmacopoeial Harmonisation		
Q5: Biotechnological quality	**Q5A**: Viral Safety Evaluation **(please check for correction on the text, click here)**	Q5B: Genetic Stability	Q5C: Stability of Products
	Q5D: Cell Substrates		
Q6: Specifications	Q6A: Chemical Substances with its Decision Trees	Q6B: Biotechnological Substances	
Q7: GMP	Q7A: GMP for Active Pharmaceutical Ingredients		

[redacted]
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Q1: STABILITY TESTING		
Q1A	**Stability Testing of New Drug Substances and Products**	***Step 5***
This guideline is now being revised under topic code Q1A(R). See below.		
Q1A(R)	**Stability Testing of New Drugs and Products (Revised guideline)**	***Step 5***
This revised Guideline has reached Step 4 of the ICH process on 8 November 2000. This gives recommendations on the stability testing protocols which should be followed to assess the stability of new drug substances and products. Recommendations are given on temperature and humidity levels as well as the duration of trials. ***Implementation (Step 5):*** **EU:** Adopted by CPMP, November 2000, issued as CPMP/ICH/2736/99 **MHLW:** To be notified **FDA:** To be notified		
Q1B	**Photostability Testing**	***Step 5***
The tripartite harmonised ICH guideline was finalised *(Step 4)* in **November 1996**. This forms an annex to the main stability guideline, and give guidance on the basic testing protocol required to evaluate the light sensitivity and stability of new drugs and products. ***Implementation (Step 5):*** **EU:** Adopted by CPMP, December 96, issued as CPMP/ICH/279/95 **MHLW**: Adopted May 97, PAB/PCD Notification No.422 **FDA:** Published in the Federal Register, Vol. 62, No. 95, May 16, 1997, pages 27115-27122.		
Q1C	**Stability Testing for New Dosage Forms**	***Step 5***
The tripartite harmonised ICH guideline was finalised *(Step 4)* in **November 1996.** It extends the main stability guideline and defines the circumstances under which reduced stability data can be accepted, at the time of filing an application, in the case of new formulations of already approved medicines. ***Implementation (Step 5):*** **EU**: Adopted by CPMP, December 96, issued as CPMP/ICH/280/95 **MHLW**: Adopted May 97, PAB/PCD Notification No.425 **FDA**: Published in the Federal Register, Vol. 62, No. 90, May 9, 1997, pages 25634-25635		
Q1D, Q1E, Q1F, Q1G, Q1H		
The ICH Steering Committee agreed that the main Stability Guideline should be complemented by the following topics : Matrixing and Bracketing (Q1D), Statistical Analysis and Interpretation of Data (Q1E), Data Package for Registration in Climatic Zones III and IV (Q1F), Generics (Q1G), and Labeling (Q1H). It is expected that *Step 2* should be reached at San Diego (November 2000) for Q1D-F topics.		
Q1D	**Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products**	***Step 3***
The Guideline was released for consultation under *Step 2* of the ICH process in November 2000. ***Consultation (Step 3):***		

EU: Released for consultation, November 2000, issued as CPMP/ICH/4104/00 - ICH Q1D
MHLW: To be notified
FDA: To be notified

Q2: VALIDATION OF ANALYTICAL PROCEDURES

Q2A	**Text on Validations of Analytical Procedures**	***Step 5***

The tripartite harmonised ICH text was finalised *(Step 4)* in **October 1994.** This identifies the validation parameters needed for a variety of analytical methods. It also discusses the characteristics that must be considered during the validation of the analytical procedures which are included as part of registration applications.

Implementation (Step 5):

EU: Adopted by CPMP, November 94, issued as CPMP/ICH/381/95
MHLW: Adopted July 95, PAB/PCD Notification No.755
FDA: Published in the Federal Register, Vol. 60, March 1, 1995, pages 11260

Q2B	**Methodology**	***Step 5***

The tripartite harmonised ICH text was finalised *(Step 4)* in **November 1996**. It extends the previous text to include the actual experimental data required, along with the statistical interpretation, for the validation of analytical procedures.

Implementation (Step 5):

EU: Adopted by CPMP, December 96, issued as CPMP/ICH281/95
MHLW: Adopted October 97. PMSB/ELD Notification No.338
FDA: Published in the Federal Register, Vol. 62, No. 96, May 19, 1997, pages 27463-27467

Q3: IMPURITY TESTING

Q3A	**Impurities in New Drug Substances**	***Step 5***

This Guideline is now being revised under topic code Q3A (R), see below.

Q3A(R)	**Impurities in New Drug Substances (Revised Guideline)**	***Step 3***

This Guideline is now under revision and therefore a draft was released for consultation at *Step* 2 of the process in October 1999. This provides guidance on limits and qualification of impurities in new drug substances, produced by chemical synthesis. The guideline is being widely followed by companies involved in new drug development, to ensure that a single drug substance specification is developed which is acceptable in all three regions.

Consultation (Step 3):

EU: Released for consultation, November 1999, issued as CPMP/ICH/2737/99.
MHLW: Released for consultation, PAB/PCD Notification n° 1829, 17 December 1999, deadline for comments on 31 March 2000.
FDA: Published in the Federal Register, Vol. 65, No. 140, Thursday, July 20, 2000, p. 45085 to 45090

Q3B	**Impurities in New Drug Products**	***Step 5***

This Guideline is now being revised under topic code Q3B(R), see below.

Q3B(R)	**Impurities in New Drug Products (Revised Guideline)**	***Step 3***

This Guideline is now under revision and therefore a draft was released for consultation at *Step* 2 of

the process in October 1999. This is an extension of the main guideline on impurities in new drug substances and makes recommendations on the content and qualification of impurities that may arise in the drug products due to degradation of the active ingredient or interaction with other components.
Consultation (Step 3):
EU: Released for consultation, November 1999, issued as CPMP/ICH/2738/99.
MHLW: Released for consultation, PAB/PCD Notification n° 1829, 17 December 1999, deadline for comments on 31 March 2000.
FDA: Published in the Federal Register, Vol. 65, No 139, Wednesday, July 19, 2000, p. 44791 to 44797

Q3C	**Impurities: Residual Solvents**	***Step 5***

The tripartite harmonised ICH guideline was finalised *(Step 4)* in **July 1997**. This recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms, and sets pharmaceutically acceptable limits for residual solvents (organic volatile impurities) in drug products.

Implementation (Step 5):
EU: Adopted by CPMP, September 97, issued as CPMP/ICH/283/95
MHLW: Adopted March 1998, PMSB/ELD Notification No.307
FDA: Published in the Federal Register, Vol. 62, No. 247, December 24, 1997, page 67377

Q3C (M)

A Maintenance process is now in place to revise PDEs as new toxicological data for solvents becomes available. Two draft documents were released for consultation at *Step 2* of the process in July 2000 for the following solvents : N-Methylpyrrolidone and Tetrahydrofuran.

Q3C (M)	**Impurities : Residual Solvents (Maintenance)** **PDE for N-Methylpyrrolidone (NMP)**	***Step 3***
Q3C (M)	**Impurities : Residual Solvents (Maintenance)** **PDE for Tetrahydrofuran**	***Step 3***
Q4	**Pharmacopoeial Harmonisation**	

The Pharmacopoeial authorities have been closely involved with the work of ICH since the outset and harmonisation between the major Pharmacopoeias, which started before ICH, has proceeded in parallel. The ICH Steering Committee receives regular reports on pharmacopoeial harmonisation at its meetings.

Q5: QUALITY OF BIOTECHNOLOGICAL PRODUCTS

Q5A	**Viral Safety Evaluation**	***Step 5***

The tripartite harmonised ICH guideline, entitled *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* was finalised *(Step 4)* in **March 1997**. This is concerned with testing and evaluation of the viral safety of biotechnology products derived from characterised cell lines of human or animal origin. The purpose is to provide a general framework for virus testing experiments for the evaluation of virus clearance and the design of viral tests and clearance evaluation studies. **(Please note that a typographic error has been corrected (Sept. 23, 1999) on Table A-1. the Genome of the Reovirus 3 is RNA (and not DNA as previously printed)).**
Implementation (Step 5):
EU: Adopted by CPMP, April 97, issued as CPMP/ICH/295/95

MHLW: Adopted, PMSB/ELD, Notification n° 329, 22 February 2000
FDA: Published in the Federal Register, Vol. 63, No. 185, September 24, 1998, page 51074

Q5B	**Genetic Stability**	***Step 5***

The tripartite harmonised ICH guideline, entitled *Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products,* was finalised *(Step 4)* in **November 1995**. It advises on the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant DNA derived proteins.
Implementation (Step 5):
EU: Adopted by CPMP, December 95, issued as CPMP/ICH/139/95
MHLW: Adopted January 98, PMSB/ELD Notification No.3
FDA: Published in the Federal Register, Vol. 61, February 23, 1996, page 7006

Q5C	**Stability of Products**	***Step 5***

The tripartite harmonised ICH guideline was finalised *(Step 4)* in **November 1995**. This forms an annex to the main ICH Stability Guideline (Q1A above) and deals with the particular aspects of stability test procedures needed to take account of the special characteristics of products, in which the active components are typically proteins and/or polypeptides.
Implementation (Step 5):
EU: Adopted by CPMP, December 95, issued as CPMP/ICH/138/95
MHLW: Adopted January 98, PMSB/ELD Notification No.6
FDA: Published in the Federal Register, Vol. 61, July 10, 1996, page 36466

Q5D	**Cell Substrates**	***Step 5***

Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
The tripartite harmonised ICH guideline was finalised *(Step 4)* in July 1997. This provides broad guidance on appropriate standards for the derivation of human and animal cell lines and microbes used to prepare biotechnological/biological products and for the preparation and characterisation of cell banks to be used for production.
Implementation (Step 5):
EU: Adopted by CPMP, September 98, issued as CPMP/ICH/294/95
MHLW: In preparation, will be published by the next Steering Committee
FDA: Published in the Federal Register, Vol. 62, No. 85, May 2, 1997, pages 24311-24317

Q6: SPECIFICATIONS FOR NEW DRUG SUBSTANCES AND PRODUCTS

Bulk drug substance and final product specifications are key parts of the core documentation for world-wide product license applications. However, there is little international guidance on how to set such specifications with a result that regulators and manufacturers often find themselves setting or agreeing to conflicting standards for the same product, as part of the registration in different regions. This leads to increased expenses and opportunities for error as well as a potential cause for interruption of product supply.
Work is therefore underway to provide harmonised guidance in this area. The Topic is divided into two parts: Chemical Substances (Q6A) and Biotechnological/Biological Substances (Q6B).

The harmonisation of about 10 compendial test chapters have been considered as critical by the ICH Steering Committee to attaining full utility of the ICH Q6A guideline. These chapters are at various stages of harmonisation among the three pharmacopeial organisations (USP, JP & EP). The three

organisations conduct their harmonisation efforts through a tripartite pharmacopeial harmonisation program known as the Pharmacopoeial Discussion Group (**PDG**). The representatives of the PDG were participants in the ICH Q6A EWG and continue to collaborate with the Q6A EWG on completion of the harmonisation for the test chapters.
The members of the PDG are also proposing to the ICH Steering Committee mechanisms for the continued participation in the ICH process for compendial harmonisation topics.

Q6A + Decision Trees	**Chemical Substances**	***Step 5***

The tripartite harmonised ICH guideline was finalised (*Step 4*) in October 1999. This addresses the process of selecting tests and methods and setting specifications for the testing of drug substances and dosage forms. Account has been taken of the considerable guidance and background information which are present in existing regional documents.
Implementation (Step 5):
EU: Adopted by CPMP, November 1999, issued as CPMP/ICH/367/96
MHLW: To be notified
FDA: Published in the Federal Register, December 29, 2000, Volume 65, Number 251, Notices, Page 83041-83063

Q6B	**Biotechnological Substances**	***Step 5***

Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
The tripartite harmonised ICH guideline was finalised (Step 4) in March 1999. This provides guidance on justifying and setting specifications for proteins and polypeptides which are derived from recombinant or non-recombinant cell cultures. The principles The scope of this part of the Topic are initially be limited to well characterised biotechnological products although the concepts may be applicable to other biologicals, which are not well characterised. In view of the nature of the products, the topic of specifications include in-process controls, bulk drug, final product and stability specifications and give guidance for a harmonised approach to determining appropriate specifications based on safety, process consistency, purity, analytical methodology, product administration and clinical data considerations.
Implementation (Step 5):
EU: Adopted by CPMP, March 99, issued as CPMP/ICH/365/96
MHLW: To be notified
FDA: Published in the Federal Register, August 18, 1999: 64FR Page 44928

Q7: GMP FOR PHARMACEUTICAL INGREDIENTS

Early in the ICH Process it was agreed that there was adequate international agreement on the technical aspects of Good Manufacturing Practices (GMP) for Pharmaceutical Products and that further harmonisation action through ICH was not needed. Recently, however, attention has focused on the need to formalise GMP requirements for the components of pharmaceutical products - both active and inactive. In February 1998, the ICH Steering Committee agreed that GMP for Active Pharmaceutical Ingredients (APIs) should be adopted as an ICH Topic

Q7A	**Good Manufacturing Practices for Active Pharmaceutical Ingredients**	***Step 5***

When this topic was adopted, the Steering Committee took steps to ensure that due account was taken of the work already in progress by PIC/S, FDA and other parties. In view of the unusually wide implications of this Topic, a much extended EWG has been established which includes, in addition to the six ICH parties and the Observers, experts representing IGPA (generics industry), WSMI (self

medication industry) and PIC/S. With respect to the latter representatives from China, India and Australia have been invited to participate.

Implementation (Step 5):

EU: Adopted by CPMP, November 2000, issued as CPMP/ICH/4106/00

MHLW: To be notified

FDA: To be notified

Notes on implementation in the three ICH Regions

EU	ICH guidelines are submitted to the Committee for Proprietary Medicinal Products (CPMP) for endorsement once they have reached *Step 2* or *Step 4* of the ICH Process. The CPMP decides on the duration for consultation with interested parties (usually 6 months). The European Agency for the Evaluation of Medicinal Products (EMEA) publishes and distrubutes the *Step 2* guidelines for comments. At *Step 4* the guidelines are endorsed by the CPMP and a timeframe for implementation is established (usually 6 months). The guidelines are subsequently published by the European Commission in Volume III of the *Rules Governing Medicinal Products in the European Union. Step 2* and *Step 4* guidelins are available from the Eudranet site on the Internet: http://www.eudra.org/emea.html Volume III is available from the *Office for Official Publications of the European Communities* and on the DG III website: http://dg3.eudra.org/
MHLW	When Step 2 or Step 4 has been reached, the ICH texts are translated into Japanese. Subsequently Pharmaceutical and Medical Safety Bureau (PMSB) Notification for the promulgation or consultation of guidelines written in Japanese is issued with a deadline for comments in the case of consultation drafts, or an implementation date for finalised guidelines. The notifications on guidelines in Japanese and also English attachments (ICH Texts) are available from PMSB or on the Internet by the National Institute of Health and Science. http://www.nihs.go.jp/dig/ich/ichindex.htm
FDA	When *Step 2* or *Step 4* has been reached, FDA publishes a notice with the full text of the guidance in the Federal Register. Notices for Step 2 guidances include a date for receipt of written comment; Step 4 guidances are available for use on the date they are published in the Federal Register. FDA guidances and guidelines are available on the Internet: CDER: http://www.fda.gov/cder/guidance/index.htm CBER: http://www.fda.gov/cber/guidelines.htm

Quality Topics	Safety Topics	Efficacy Topics	Regulatory Communications

Guidance for Industry

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

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)
August 2001
ICH

Guidance for Industry

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
(Internet) 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
Internet: http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
Mail: the 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)
August 2001
ICH

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Guidance for Industry[1]
Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

This guidance represents 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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION (1)

A. Objective (1.1)

This document is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess.

In this guidance, the term *manufacturing* is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of APIs and the related controls. In this guidance, the term *should* identifies recommendations that, when followed, will ensure compliance with CGMPs. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes. For the purposes of this guidance, the terms *current good manufacturing practices* and *good manufacturing practices* are equivalent.

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[1] This guidance was developed within the Expert Working Group (Q7A) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2000. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Arabic numbers in subheadings reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2000.

The guidance as a whole does not cover safety aspects for the personnel engaged in manufacturing, nor aspects related to protecting the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guidance is not intended to define registration and/or filing requirements or modify pharmacopoeial requirements. This guidance does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents should be met.

B. Regulatory Applicability (1.2)

Within the world community, materials may vary as to their legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this guidance.

C. Scope (1.3)

This guidance applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidances for drug (medicinal) products as defined by local authorities.

This guidance covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in Section XVIII (18).

This guidance excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guidance. In addition, the guidance does not apply to medical gases, bulk-packaged drug (medicinal) products (e.g., tablets or capsules in bulk containers), or radiopharmaceuticals.

Section XIX (19) contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An *API starting material* is a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material

purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which API starting materials are entered into the process. For other processes (e.g., fermentation, extraction, purification), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API starting material is normally introduced into the process.

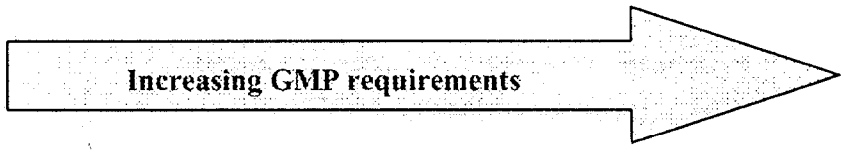
From this point on, appropriate GMP as defined in this guidance should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 1. However, all steps shown may not need to be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g., milling, micronizing) should be conducted according to this guidance.

This GMP guidance does not apply to steps prior to the introduction of the defined API starting material.

Table 1: Application of this Guidance to API Manufacturing

Type of Manufacturing	Application of this guidance to steps (shown in gray) used in this type of manufacturing				
Chemical Manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establish-ment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establish-ment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



II. QUALITY MANAGEMENT (2)

A. Principles (2.1)

Quality should be the responsibility of all persons involved in manufacturing.

Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.

There should be a quality unit(s) that is independent of production and that fulfills both quality assurance *(QA)* and quality control *(QC)* responsibilities. The quality unit can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

The persons authorized to release intermediates and APIs should be specified.

All quality-related activities should be recorded at the time they are performed.

Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in Section X (10) or the use of raw materials or intermediates pending completion of evaluation).

Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality-related complaints, recalls, and regulatory actions).

B. Responsibilities of the Quality Unit(s) (2.2)

The quality unit(s) should be involved in all quality-related matters.

The quality unit(s) should review and approve all appropriate quality-related documents.

The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include, but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company

2. Establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials

3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution

4. Making sure that critical deviations are investigated and resolved

5. Approving all specifications and master production instructions

6. Approving all procedures affecting the quality of intermediates or APIs

7. Making sure that internal audits (self-inspections) are performed

8. Approving intermediate and API contract manufacturers

9. Approving changes that potentially affect intermediate or API quality

10. Reviewing and approving validation protocols and reports

11. Making sure that quality-related complaints are investigated and resolved

12. Making sure that effective systems are used for maintaining and calibrating critical equipment

13. Making sure that materials are appropriately tested and the results are reported

14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates, where appropriate

15. Performing product quality reviews (as defined in Section 2.5)

C. Responsibility for Production Activities (2.3)

The responsibility for production activities should be described in writing and should include, but not necessarily be limited to:

1. Preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures

2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions

3. Reviewing all production batch records and ensuring that these are completed and signed

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded

5. Making sure that production facilities are clean and, when appropriate, disinfected

6. Making sure that the necessary calibrations are performed and records kept

7. Making sure that the premises and equipment are maintained and records kept

8. Making sure that validation protocols and reports are reviewed and approved

9. Evaluating proposed changes in product, process or equipment

10. Making sure that new and, when appropriate, modified facilities and equipment are qualified

D. Internal Audits (Self Inspection) (2.4)

To verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

E. Product Quality Review (2.5)

Regular quality-reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results
- A review of all batches that failed to meet established specification(s)
- A review of all critical deviations or nonconformances and related investigations
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program

- A review of all quality-related returns, complaints and recalls
- A review of adequacy of corrective actions

The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

III. PERSONNEL (3)

A. Personnel Qualifications (3.1)

There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs.

The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

B. Personnel Hygiene (3.2)

Personnel should practice good sanitation and health habits.

Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed, when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn, when necessary, to protect intermediates and APIs from contamination.

Personnel should avoid direct contact with intermediates or APIs.

Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

C. Consultants (3.3)

Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

IV. BUILDINGS AND FACILITIES (4)

A. Design and Construction (4.1)

Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants, as appropriate.

Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection
- Quarantine before release or rejection of intermediates and APIs
- Sampling of intermediates and APIs
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
- Storage of released materials
- Production operations
- Packaging and labeling operations
- Laboratory operations

Adequate and clean washing and toilet facilities should be provided for personnel. These facilities should be equipped with hot and cold water, as appropriate, soap or detergent, air

dryers, or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process, intermediate, or API.

B. Utilities (4.2)

All utilities that could affect product quality (e.g., steam, gas, compressed air, heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

C. Water (4.3)

Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

If drinking (potable) water is insufficient to ensure API quality and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms, and/or endotoxins should be established.

Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

Where the manufacturer of a nonsterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

D. Containment (4.4)

Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

The use of dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

Appropriate measures should be established and implemented to prevent cross-contamination from personnel and materials moving from one dedicated area to another.

Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials, such as herbicides and pesticides, should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

E. Lighting (4.5)

Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

F. Sewage and Refuse (4.6)

Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

G. Sanitation and Maintenance (4.7)

Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

V. PROCESS EQUIPMENT (5)

A. Design and Construction (5.1)

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitation (where appropriate), and maintenance.

Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Production equipment should only be used within its qualified operating range.

Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter the quality of APIs or intermediates beyond the official or other established specifications. Any deviations from this practice should be evaluated to ensure that there are no detrimental effects on the material's fitness for use. Wherever possible, food grade lubricants and oils should be used.

Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

B. Equipment Maintenance and Cleaning (5.2)

Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

Written procedures should be established for cleaning equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment
- Cleaning schedules, including, where appropriate, sanitizing schedules
- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning
- Instructions for the removal or obliteration of previous batch identification
- Instructions for the protection of clean equipment from contamination prior to use
- Inspection of equipment for cleanliness immediately before use, if practical
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate

Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g., degradants or objectionable levels of microorganisms).

Nondedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

Equipment should be identified as to its contents and its cleanliness status by appropriate means.

C. Calibration (5.3)

Control, weighing, measuring, monitoring, and testing equipment critical for ensuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

Equipment calibrations should be performed using standards traceable to certified standards, if they exist.

Records of these calibrations should be maintained.

The current calibration status of critical equipment should be known and verifiable.

Instruments that do not meet calibration criteria should not be used.

Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an effect on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

D. Computerized Systems (5.4)

GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.

Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.

Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

Written procedures should be available for the operation and maintenance of computerized systems.

Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

Changes to computerized systems should be made according to a change procedure and should be formally authorized, documented, and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software, and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

Data can be recorded by a second means in addition to the computer system.

VI. DOCUMENTATION AND RECORDS (6)

A. Documentation System and Specifications (6.1)

All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be in paper or electronic form.

The issuance, revision, superseding, and withdrawal of all documents should be controlled by maintaining revision histories.

A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still legible.

During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically affect quality. Acceptance criteria should be established and documented for in-process controls.

If electronic signatures are used on documents, they should be authenticated and secure.

B. Equipment Cleaning and Use Record (6.2)

Records of major equipment use, cleaning, sanitation, and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

If equipment is dedicated to manufacturing one intermediate or API, individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

C. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials (6.3)

Records should be maintained including:

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
- The results of any test or examination performed and the conclusions derived from this
- Records tracing the use of materials
- Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications
- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials

Master (approved) labels should be maintained for comparison to issued labels.

D. Master Production Instructions (Master Production and Control Records) (6.4)

To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for

each batch size or rate of production should be included. Variations to quantities should be included where they are justified

- The production location and major production equipment to be used
- Detailed production instructions, including the:
  - sequences to be followed
  - ranges of process parameters to be used
  - sampling instructions and in-process controls with their acceptance criteria, where appropriate
  - time limits for completion of individual processing steps and/or the total process, where appropriate
  - expected yield ranges at appropriate phases of processing or time
- Where appropriate, special notations and precautions to be followed, or cross-references to these
- The instructions for storage of the intermediate or API to ensure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

E. Batch Production Records (Batch Production and Control Records) (6.5)

Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to ensure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed

- Signatures of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label for intermediate or API
- Representative label of API or intermediate if made commercially available
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
- Results of release testing

Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

F. Laboratory Control Records (6.6)

Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing
- A statement of or reference to each test method used
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions
- A complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors
- A statement of the test results and how they compare with established acceptance criteria
- The signature of the person who performed each test and the date(s) the tests were performed
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards

Complete records should also be maintained for:

- Any modifications to an established analytical method
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices

- All stability testing performed on APIs
- Out-of-specification (OOS) investigations

G. Batch Production Record Review (6.7)

Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

VII. MATERIALS MANAGEMENT (7)

A. General Controls (7.1)

There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

Materials should be purchased against an agreed specification, from a supplier, or suppliers, approved by the quality unit(s).

If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

B. Receipt and Quarantine (7.2)

Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the

supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested, as appropriate, and released for use.

Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

If bulk deliveries are made in nondedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning
- testing for trace impurities
- audit of the supplier

Large storage containers and their attendant manifolds, filling, and discharge lines should be appropriately identified.

Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

C. Sampling and Testing of Incoming Production Materials (7.3)

At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below. A *supplier's certificate of analysis* can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Complete analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a complete analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals.

Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based on a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

D. Storage (7.4)

Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

E. Re-evaluation (7.5)

Materials should be re-evaluated, as appropriate, to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

VIII. PRODUCTION AND IN-PROCESS CONTROLS (8)

A. Production Operations (8.1)

Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code
- Receiving or control number
- Weight or measure of material in the new container
- Re-evaluation or retest date if appropriate

Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

Other critical activities should be witnessed or subjected to an equivalent control.

Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

Any deviation should be documented and explained. Any critical deviation should be investigated.

The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

B. Time Limits (8.2)

If time limits are specified in the master production instruction (see 6.40), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

C. In-process Sampling and Controls (8.3)

Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the developmental stage or from historical data.

The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

Critical in-process controls (and critical process monitoring), including control points and methods, should be stated in writing and approved by the quality unit(s).

In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

D. Blending Batches of Intermediates or APIs (8.4)

For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

Out-of-specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

Acceptable blending operations include, but are not limited to:

- Blending of small batches to increase batch size
- Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch

Blending processes should be adequately controlled and documented, and the blended batch should be tested for conformance to established specifications, where appropriate.

The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

E. Contamination Control (8.5)

Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

Production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials.

Precautions to avoid contamination should be taken when APIs are handled after purification.

IX. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES (9)

A. General (9.1)

There should be written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing, release, and handling of packaging and labeling materials.

Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

B. Packaging Materials (9.2)

Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

If containers are reused, they should be cleaned in accordance with documented procedures, and all previous labels should be removed or defaced.

C. Label Issuance and Control (9.3)

Access to the label storage areas should be limited to authorized personnel.

Procedures should be established to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

Obsolete and out-dated labels should be destroyed.

Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

A printed label representative of those used should be included in the batch production record.

D. Packaging and Labeling Operations (9.4)

There should be documented procedures designed to ensure that correct packaging materials and labels are used.

Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

Labels used on containers of intermediates or APIs should indicate the name or identifying code, batch number, and storage conditions when such information is critical to ensure the quality of intermediate or API.

If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, special transport conditions, and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

X. STORAGE AND DISTRIBUTION (10)

A. Warehousing Procedures (10.1)

Facilities should be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been made.

B. Distribution Procedures (10.2)

APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Special transport or storage conditions for an API or intermediate should be stated on the label.

The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

XI. LABORATORY CONTROLS (11)

A. General Controls (11.1)

The independent quality unit(s) should have at its disposal adequate laboratory facilities.

There should be documented procedures describing sampling, testing, approval, or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include control of impurities (e.g., organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.

Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should include analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

Reagents and standard solutions should be prepared and labeled following written procedures. *Use by* dates should be applied, as appropriate, for analytical reagents or standard solutions.

Primary reference standards should be obtained, as appropriate, for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

Where a primary reference standard is not available from an officially recognized source, an *in-house primary standard* should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

B. Testing of Intermediates and APIs (11.2)

For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed, and classification of each identified impurity (e.g., inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH guidance Q6B.

The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data to detect changes to the API

resulting from modifications in raw materials, equipment operating parameters, or the production process.

Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

C. Validation of Analytical Procedures - See Section 12. (11.3)

D. Certificates of Analysis (11.4)

Authentic certificates of analysis should be issued for each batch of intermediate or API on request.

Information on the name of the intermediate or API including, where appropriate, its grade, the batch number, and the date of release should be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the certificate of analysis should show the name, address, and telephone number of the repacker/reprocessor and reference the name of the original manufacturer.

If new certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

E. Stability Monitoring of APIs (11.5)

A documented, on-going testing program should be established to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

The test procedures used in stability testing should be validated and be stability indicating.

Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of

the same material and in small-scale drums of similar or identical material composition to the market drums.

Normally, the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least 2 years, fewer than three batches can be used.

Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first 3 months, and at 3-month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., 9-month testing) can be considered.

Where appropriate, the stability storage conditions should be consistent with the ICH guidances on stability.

F. Expiry and Retest Dating (11.6)

When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g., published data, test results).

An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and (2) the quality of the API represents the material to be made on a commercial scale.

A representative sample should be taken for the purpose of performing a retest.

G. Reserve/Retention Samples (11.7)

The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

Appropriately identified reserve samples of each API batch should be retained for 1 year after the expiry date of the batch assigned by the manufacturer, or for 3 years after distribution of the

batch, whichever is longer. For APIs with retest dates, similar reserve samples should be retained for 3 years after the batch is completely distributed by the manufacturer.

The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

XII. VALIDATION (12)

A. Validation Policy (12.1)

The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.

The critical parameters/attributes should normally be identified during the development stage or from historical data, and the necessary ranges for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes
- Identifying process parameters that could affect the critical quality attributes of the API
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control

Validation should extend to those operations determined to be critical to the quality and purity of the API.

B. Validation Documentation (12.2)

A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g., retrospective, prospective, concurrent) and the number of process runs.

A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

Any variations from the validation protocol should be documented with appropriate justification.

C. Qualification (12.3)

Before initiating process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose

- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements

- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges

- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications

D. Approaches to Process Validation (12.4)

Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

There are three approaches to validation. Prospective validation is the preferred approach, but there are situations where the other approaches can be used. These approaches and their applicability are discussed here.

Prospective validation should normally be performed for all API processes as defined in 12.1. Prospective validation of an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

An exception can be made for retrospective validation of well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

1. Critical quality attributes and critical process parameters have been identified

2. Appropriate in-process acceptance criteria and controls have been established

3. There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability

4. Impurity profiles have been established for the existing API

Batches selected for retrospective validation should be representative of all batches produced during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

E. Process Validation Program (12.5)

The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to, or better than, historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

F. Periodic Review of Validated Systems (12.6)

Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

G. Cleaning Validation (12.7)

Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.

Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable, and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

Equipment cleaning/sanitation studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

H. Validation of Analytical Methods (12.8)

Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

Methods should be validated to include consideration of characteristics included within the ICH guidances on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

Appropriate qualification of analytical equipment should be considered before initiating validation of analytical methods.

Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

XIII. CHANGE CONTROL (13)

A formal change control system should be established to evaluate all changes that could affect the production and control of the intermediate or API.

Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.

Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).

The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

Current dosage form manufacturers should be notified of changes from established production and process control procedures that can affect the quality of the API.

XIV. REJECTION AND RE-USE OF MATERIALS (14)

A. Rejection (14.1)

Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

B. Reprocessing (14.2)

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and over-reacted materials.

C. Reworking (14.3)

Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.

Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, a report can be written and the batch released once it is found to be acceptable.

Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

D. Recovery of Materials and Solvents (14.4)

Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or commingling with other approved materials.

Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

E. Returns (14.5)

Returned intermediates or APIs should be identified as such and quarantined.

If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

XV. COMPLAINTS AND RECALLS (15)

All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

Complaint records should include:

- Name and address of complainant
- Name (and, where appropriate, title) and phone number of person submitting the complaint
- Complaint nature (including name and batch number of the API)
- Date complaint is received
- Action initially taken (including dates and identity of person taking the action);
- Any follow-up action taken
- Response provided to the originator of complaint (including date response sent)
- Final decision on intermediate or API batch or lot

Records of complaints should be retained to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

XVI. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES) (16)

All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

Companies should evaluate any contractors (including laboratories) to ensure GMP compliance of the specific operations occurring at the contractor sites.

There should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including the quality measures, of each party.

A contract should permit a company to audit its contractor's facilities for compliance with GMP.

Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it under the contract without the company's prior evaluation and approval of the arrangements.

Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

XVII. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS (17)

A. Applicability (17.1)

This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.

All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this guidance.

B. Traceability of Distributed APIs and Intermediates (17.2)

Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

C. Quality Management (17.3)

Agents, brokers, traders, distributors, repackers, or relabelers should establish, document and implement an effective system of managing quality, as specified in Section 2.

D. Repackaging, Relabeling, and Holding of APIs and Intermediates (17.4)

Repackaging, relabeling, and holding APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this guidance, to avoid mix-ups and loss of API or intermediate identity or purity.

(e.g., cell banking) should be performed under appropriate process controls. This guidance covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for determining environmental quality and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

In general, process controls should take into account:

- Maintenance of the working cell bank (where appropriate)
- Proper inoculation and expansion of the culture
- Control of the critical operating parameters during fermentation/cell culture
- Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity, where appropriate
- Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality
- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production
- Viral safety concerns as described in ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*

Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

B. Cell Bank Maintenance and Record Keeping (18.2)

Access to cell banks should be limited to authorized personnel.

Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

Records of the use of the vials from the cell banks and storage conditions should be maintained.

Where appropriate, cell banks should be periodically monitored to determine suitability for use.

See ICH guidance Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

C. Cell Culture/Fermentation (18.3)

Where cell substrates, media, buffers, and gases are to be added under aseptic conditions, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

Personnel should be appropriately gowned and take special precautions handling the cultures.

Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, sanitized, or sterilized.

Culture media should be sterilized before use, when necessary, to protect the quality of the API.

Appropriate procedures should be in place to detect contamination and determine the course of action to be taken. Procedures should be available to determine the impact of the contamination on the product and to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified, as appropriate, and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

Records of contamination events should be maintained.

Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

D. Harvesting, Isolation and Purification (18.4)

Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption should be performed in equipment and areas designed to minimize the risk of contamination.

Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

E. Viral Removal/Inactivation steps (18.5)

See ICH guidance Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

Appropriate precautions should be taken to prevent potential viral contamination from previral to postviral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g., through equipment or environment) from previous steps.

XIX. APIs FOR USE IN CLINICAL TRIALS (19)

A. General (19.1)

Not all the controls in the previous sections of this guidance are appropriate for the manufacture of a new API for investigational use during its development. Section XIX (19) provides specific guidance unique to these circumstances.

The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

B. Quality (19.2)

Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for approval of each batch.

A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

Process and quality problems should be evaluated.

Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

C. Equipment and Facilities (19.3)

During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.

Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

D. Control of Raw Materials (19.4)

Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

E. Production (19.5)

The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

F. Validation (19.6)

Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification ensures API quality during this development phase.

Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

G. Changes (19.7)

Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

H. Laboratory Controls (19.8)

While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

I. Documentation (19.9)

A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

GLOSSARY (20)

Acceptance Criteria: Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) ***(or Drug Substance):*** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

Batch (or Lot): A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number): A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden: The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with results produced by a reference or traceable standard over an appropriate range of measurements.

Computer System: A group of hardware components and associated software designed and assembled to perform a specific function or group of functions.

Computerized System: A process or operation integrated with a computer system.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging, or repackaging, storage or transport.

Contract Manufacturer: A manufacturer who performs some aspect of manufacturing on behalf of the original manufacturer.

Critical: Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination: Contamination of a material or product with another material or product.

Deviation: Departure from an approved instruction or established standard.

Drug (Medicinal) Product: The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance: See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date): The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions and after which it should not be used.

Impurity: Any component present in the intermediate or API that is not the desired entity.

Impurity Profile: A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control): Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this guidance only addresses those intermediates produced after the point that a company has defined as the point at which the production of the API begins.)

Lot: See Batch

Lot Number: See *Batch Number*

Manufacture: All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Material: A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor: The residual liquid that remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It can be used for further processing.

Packaging Material: Any material intended to protect an intermediate or API during storage and transport.

Procedure: A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids: Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon).

Process Control: See ***In-Process Control.***

Production: All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA): The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC): Checking or testing that specifications are met.

Quality Unit(s): An organizational unit independent of production that fulfills both quality assurance and quality control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine: The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material: A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary: A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary: A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing: Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete, is considered to be part of the normal process, and is not reprocessing.

Retest Date: The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking: Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed): See definition for signed.

Signed (signature): The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent: An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. *Conformance to specification* means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation: A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Validation Protocol: A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and/or operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected: The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical: The quantity that would be produced at any appropriate phase of production based upon the quantity of material to be used, in the absence of any loss or error in actual production.

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5 Packaging

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