POLICY AND PROCEDURES

Office of the Center Director

Procedure for Review and Clearance of ICH Guidelines

Table of Contents

PURPOSE

This Manual of Policies and Procedures (MAPP) describes the process for development, review, and clearance of internationally harmonized drug regulation recommendations produced under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and implemented by the Food and Drug Administration (FDA or Agency).

ICH guidelines[1] reflect both the FDA's views, and the views of more than 50 international regulatory authorities and industry associations who comprise ICH's members and observers. Development and implementation of harmonized guidances requires a significant degree of negotiation, collaboration, and cooperation within the Agency and among FDA's partners and stakeholders.

[1] ICH guidelines are considered guidance documents, as described in 21 CFR 10.115(b), when published by FDA.

This MAPP describes the processes for development of internationally harmonized drug recommendations and the FDA-specific procedures for internal and external review and clearance.

BACKGROUND

As a global leader in drug regulation, FDA collaborates with other international regulatory authorities and industry associations to harmonize global recommendations for the development of safe, effective, and high-quality medicines. These efforts are achieved through a consensus-driven process led by scientific and technical experts convened by ICH.

ICH was established in 1990 by representatives of the regulatory agencies and industry associations from the United States, Europe, and Japan. The ICH membership has grown and continues to expand well beyond its founding members. ICH includes more than 20 regulatory and industry association members and over 30 observers spanning six continents. The latest information on members and observers can be found at https://ich.org/page/members-observers.

ICH seeks to foster development of uniform, scientifically driven, international guidelines to improve the efficiency of new drug development and promote public health by, among other things, preventing duplication of clinical trials and minimizing the use of animal testing. Approximately 70 ICH guidelines have been issued on all aspects of human drug development. ICH also pioneered development of electronic standards for the transfer of regulatory information, creating an electronic common technical document that brings together information in a harmonized format, accepted by regulators in all ICH regions.

ICH relies on a transparent, science-based, and consensus-based process for guideline development that includes opportunities for public comment and a commitment of regulators, including FDA, to implement ICH guidelines and electronic standards. A summary of the process is provided in the "Procedures" section of this MAPP and on the ICH website (www.ich.org).

At any given time, approximately 30 or more active, multi-year ICH working groups are developing or revising guidelines on all aspects of drug development, including quality, safety, efficacy, multidisciplinary (cross-cutting), and electronic standards. More than 700 technical experts contribute directly to this work. FDA's scientific and medical experts actively engage in each working group, often leading the efforts.

ICH guidelines reflect the thinking (either proposed thinking, as in a draft guideline, or current thinking, as in a final guideline) of ICH members, including FDA. Therefore, in addition to ratifying ICH guidelines as an ICH regulatory Assembly member, FDA issues ICH guidelines as FDA guidances under the Agency's own auspices, in accordance with its good guidance practices regulation (21 CFR 110.15). In this document, we will use the term "ICH guideline" to refer to a document within ICH's guideline development process, and "FDA ICH guidance" to refer to a document within the FDA's guidance development process.

POLICY

- The development of internationally harmonized ICH drug guidelines promotes American and global public health, and fosters access to safe and effective medications.

- ICH guidelines, like all other FDA guidances, are consistent with United States' laws and regulations and Agency priorities and resources.

- ICH guidelines fall within a unique category of FDA guidances requiring a distinct clearance process outlined in this MAPP.

- Factors that make ICH guidelines unique include:

    - They are the product of more than 50 international regulatory authorities and industry associations developed over multiple years and approved by each.

    - International cooperation is essential to develop harmonized guidelines. This cooperation includes alignment on content as well as process. Regional regulatory authorities, including the FDA, seek to align the timing of public comment periods to support collective review by expert working group members. Long publication delays by any country or region, delay working group consideration and final guideline development — and can undermine the good will and trust that are the cornerstones of international collaboration.

    - Once approved by the ICH Assembly, ICH guidelines are publicly available on the ICH website (www.ich.org). Unlike other FDA guidances, this means that the content of the ICH guideline is publicly available before *Federal Register* (FR) publication of the Notice of Availability (NOA) of the corresponding FDA ICH guidance.

    - Any substantive changes to the guidelines following ICH member sign-off, when the Agency provides its official approval, can only be made through an elaborate process requiring sign-off from all parties.

- As a result of the distinguishing factors described above:

    - A*fter* ICH consensus has been achieved the Agency publishes the NOA and guideline (which is reformatted as an FDA guidance). Thus, by the time FDA is clearing the NOA and guidance as an FDA ICH guidance, the Agency, in its capacity as a regulatory ICH Assembly member, will have already approved the contents of the document in its form as an ICH guideline.

    - Although FDA's typical clearance process for an NOA and guidance allows for substantive comments from reviewing offices – including, potentially, significant policy changes – only minor editorial changes to ICH guidelines are permitted under ICH rules. Any changes that are more significant than that requires re-approval by all ICH parties. Thus, to respect the international consensus reflected in the ICH guideline, only minor editorial changes to FDA's ICH guidance can be permitted during the NOA and FDA ICH guidance clearance process (see Attachment II).

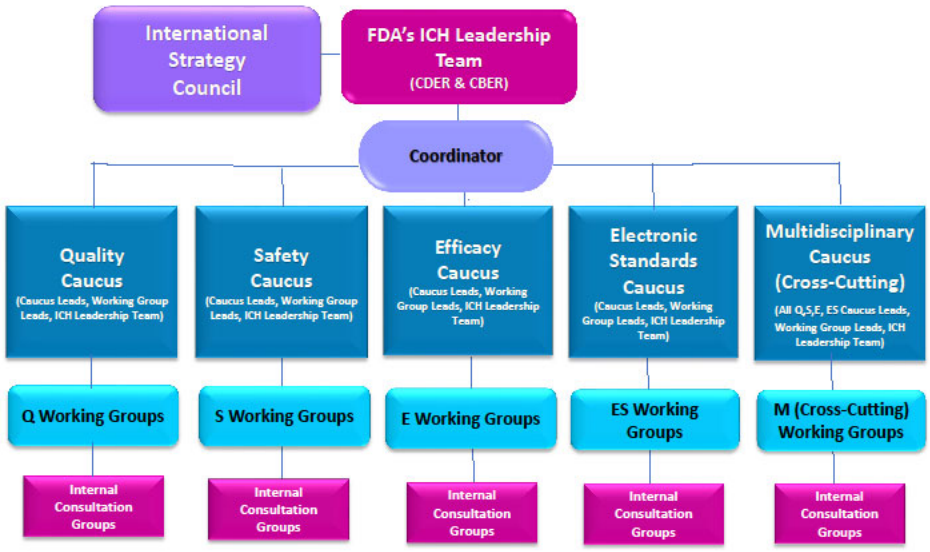
    - The ICH consensus process assumes that all parties agreeing to the contents of a guideline have consulted with necessary experts in their organizations and are putting forth their organizations' policy preferences and decisions on the subject. It is critical, then, that all FDA subject matter experts participating in the development of an ICH guideline – all of which later are issued as FDA guidances – communicate clearly and frequently about guideline development with all stakeholder offices in the Agency. FDA stakeholders are expected to be made aware of the contents of ICH guidelines as they develop, so that FDA representatives to ICH expert working groups can provide the international working group with input reflecting the entire Agency's views.

    - Expedited clearance for the NOA and FDA ICH guidance is necessary to align the United States' public comment period with other countries. Synchronized publication timing supports collective review by ICH expert working group members, facilitates resource planning, and enables timely implementation.

RESPONSIBILITIES

Efforts to develop and implement harmonized international drug guidelines require collaboration and coordination between senior staff and experts throughout the Center for Drug Evaluation and Reserarch (CDER), the Center for Biologics Evaluation and Research (CBER), and the Agency (see Figure 1 for the FDA ICH Collaboration Structure). Multiple layers of leadership and coordination assure that harmonized recommendations are consistent with FDA authorities and procedures and reflect its priorities and interests.

Figure 1: FDA ICH Collaboration Structure



FDA ICH LEADERSHIP TEAM

The FDA ICH leadership team consists of two official representatives to the ICH Management Committee and the Assembly,[2] assisted by FDA's designated ICH coordinator. One representative is designated by CDER and one by CBER, the two Centers charged with the responsibility for regulating human drug and biological products.

FDA ICH Leadership Team Responsibilities:

- Ensure collaboration and coordination between senior staff and experts throughout CDER, CBER, and the FDA, to develop and implement harmonized international drug guidelines.
- Ensure harmonized recommendations are consistent with FDA authorities and procedures and reflect its priorities and interests.
- Lead the annual review and prioritization of new topic proposals.

[2] See Definitions and References sections for additional information on the Management Committee and Assembly.

FDA Representatives to ICH Assembly and Management Committee Responsibilities:

- Provide strategic direction and guidance to advance the Agency's harmonization priorities.
- Update senior CDER and CBER leadership via the International Strategy Council (see below) and seek their input.
- Serve as FDA's official voice within the ICH Assembly and Management Committee.
- Nominate FDA's ICH working group leads based on recommendations from senior Center leaders and caucus leads. Designated experts include a topic lead and a deputy topic lead. A rapporteur or regulatory chair may also be selected to provide working group leadership. When an FDA rapporteur is chosen, a rapporteur supporter may also be designated.

ICH Coordinator Responsibilities:

- Serve as liaison between the ICH Secretariat, the FDA leadership team, and the working groups.
- Prepare FDA's ICH representatives for participation in ICH Management Committee and Assembly meetings.
- Provide guidance to working group leads throughout the harmonization process and assistance in advancing progress.
- Following ICH guideline approval, facilitate publication of draft and final FDA ICH guidances through the NOA and guidance clearance process.
- Coordinate review and prioritization of new topic proposals.
- Direct FDA's participation in annual FDA/Health Canada ICH regional public meeting.

INTERNATIONAL STRATEGY COUNCIL

The International Strategy Council is a group comprised of the CDER and CBER Center directors and relevant office leadership convened on a regular basis to provide overall strategic direction and guidance on international drug regulation activities. The ICH leadership team convenes International Strategy Council meetings to provide updates on important ICH activities and to seek strategic guidance as needed.

International Strategy Council Responsibilities:

- Review and help to prioritize new topic proposals submitted during the annual cycle.
- Assist in identifying which offices should be represented on internal consultation groups for new topics.

WORKING GROUP LEADS

Working groups are established by the Assembly following approval of a new topic proposal. There are several discrete forms that match specific stages of guideline development: an informal working group develops a concept paper; an expert working group develops a guideline; and an implementation working group develops training materials and other tools to support regional implementation of a final approved guideline.

As an ICH founding member, FDA has two official expert representatives on each working group, a topic lead and a deputy topic lead. These roles are filled by senior experts from CDER and CBER based on the applicability of the topic to each Center's products and the technical expertise required.

An additional FDA representative may serve as either the rapporteur or regulatory chair of a working group. Typically, a senior FDA expert fills the role of rapporteur when the agency proposes a new topic that is approved by the ICH Assembly. A rapporteur may enlist the help of a rapporteur supporter to serve as a project manager for the working group.

Working Group Lead Responsibilities: (Rapporteur or Regulatory Chair, if applicable; Topic Lead; and Deputy Topic Lead)

- Serve as the Agency's official voice in the working group to develop harmonized international recommendations related to a specific topic/technical guideline and negotiate with other working group members on FDA's behalf.
- Develop a guideline clearance plan (Attachment I) to assure that guidelines receive comprehensive, internal consideration and thorough vetting of issues. The guideline clearance plan is approved by relevant FDA Caucus lead(s) and is submitted to the FDA ICH leadership team at the launch of the expert working group.
- Prior to approving the Concept Paper, seek input from relevant caucus chairs, and other offices identified in the guideline clearance plan.
- Convene and lead the FDA internal consultation group to seek input, share progress, and review any significant drafts or revisions. Meetings should begin when the expert working group is formed.
- Provide timely reports to the ICH leadership team, flagging any significant issues or concerns.
- Raise potential legal or regulatory policy issues or concerns with Center or Agency counsel for advice and recommendations. Share any significant legal or regulatory policy issues or concerns with the FDA ICH leadership team.
- Reach out to CDER/Office of Regulatory Policy (ORP) Paperwork Reduction Act (PRA) staff (the ORP PRA/PTE Team) early in the guideline development

process to discuss any potential PRA considerations.[3] If a potential new information collection is anticipated, working group representatives should alert the ICH coordinator immediately to discuss alternative strategies to minimize disruption.
- Before expert working group sign-off of ICH draft and final guidelines, obtain sign-off from individuals identified in the guideline clearance plan.

Rapporteurs:

When FDA proposes a new topic that is approved by the ICH Assembly, it typically selects a senior expert to serve in the role of rapporteur.

Rapporteur Responsibilities:
- Lead the working group's work and develop a detailed work plan, typically in collaboration with the regulatory chair, to achieve the technical objectives outlined in the concept paper within specified, anticipated timeframes.
- Reconcile scientific and technical differences among working group members.
- Ensure the views of working group members are reflected in an appropriate and fair manner.
- Present reports to the Assembly on the technical and scientific aspects of the document(s) under development and challenges.
- Develop a Step 2 and Step 4 presentation (see the Procedures section for explanation of ICH steps), approved by all expert working group members, to be posted on the ICH website.

Regulatory Chairs:

An expert from a regulatory member of the Management Committee is appointed to serve in this role.

Regulatory Chair Responsibilities:
- Collaborate with the rapporteur to develop a work plan consistent with the scope and time frame outlined in the concept paper.
- Ensure time frames are met and work is completed within these parameters.
- Provide regular reports to the ICH Management Committee and Assembly on working group progress, in collaboration with the rapporteur, including adherence to time frames; scope; and conflicting views, if they arise.
- Work with the rapporteur to reconcile divergent views. If the regulatory chair and the rapporteur fail to achieve consensus, the regulatory chair elevates the issue to the Management Committee for resolution as early as possible.

[3] An NOA accompanying publication of a guidance in the FR is required to include a PRA section identifying new or existing information collections.

- Convene regulator-only discussions where the rapporteur is not a regulator and, as needed, help advance document development.
- Address the behavior of any expert within the working group who is disruptive or is not constructive, in consultation with the regulatory chair's coordinator.
- Decide, in consultation with the rapporteur, when it is necessary to document significant differences of position or conflicting views among working group members.

CAUCUS LEADS

FDA has established internal Agency caucuses for each of ICH's focus areas: quality, safety, efficacy, electronic standards, and non-electronic standards multidisciplinary topics. Each working group is assigned to a designated caucus based on its subject matter.

Senior scientific experts (often with prior experience as working group leads) serve as caucus leads, providing guidance and direction to FDA's leadership team and working group leads, and substantive clearance on the draft and final ICH guidelines.

By virtue of their cross-cutting nature, non-electronic standards, multidisciplinary caucus working groups are not assigned distinct caucus leads. Instead, all quality, safety, efficacy, and electronic standards caucus leads combine to serve as caucus leads for these expert working groups – and are invited to attend the non-electronic standards, multidisciplinary caucus.

Caucus Lead Responsibilities:

- Assist FDA's informal working group leads in developing a guideline clearance plan (Attachment I) by identifying representatives to serve on internal consultation groups and as clearing authorities. Note: If any legal or regulatory policy issues or concerns are identified, caucus leads are encouraged to recommend participation of legal and/or regulatory policy counsel.
- Approve the guideline clearance form before formation of an ICH expert working group.
- Review and clear draft and final versions of the ICH guideline for alignment with FDA statutory and regulatory requirements and policy, and other ICH documents before expert working group sign-off at Steps 1 and 3.
- Provide ongoing guidance and advice to the ICH leadership team and caucus experts.

INTERNAL CONSULTATION GROUPS

Early in the guideline development process, FDA's ICH working group leads establish an internal consultation group comprised of those FDA experts who are working group representatives, as well as a small group of senior FDA scientific and technical experts to

represent the other relevant and impacted Center scientific discipline perspectives. If appropriate, experts in other medical product centers, the Office of Regulatory Affairs, or the Commissioner's Office should also be invited to serve on the group. If development of the guideline raises legal or regulatory policy issues, working group representatives are also encouraged to include regulatory counsel. Continued dialogue and engagement with the internal consultation group during ICH guideline development enables early identification and effective management of potential issues and facilitates later guideline review and clearance.

Internal consultation group members are identified in the guideline clearance plan (Attachment I). The plan is approved by relevant Caucus leads and is submitted by FDA's informal working group leads to the FDA ICH leadership team at the launch of the expert working group.

Each CDER super office's representation is limited to senior subject matter experts who have both the technical expertise and authority to represent the office's position, and apportioned based on the relative importance of the subject matter to each office's responsibilities.

Expert working group leads work with their internal consultation group to establish an appropriate operating structure and meeting schedule.

Internal Consultation Group Responsibilities:

- Actively participate on a regular basis during guideline development to provide substantive input and ensure continuity.
- Flag important substantive issues (e.g., scientific, policy, legal, etc.), offer recommendations within requested time frames, and validate the guideline's approach. Comments and suggested edits should be confined to substantive issues only.
- Work cooperatively with FDA colleagues to reach alignment.
- Review drafts and clear, or obtain clearance of, documents for their offices.
- Keep their office leadership, including their designated clearing authority (if designated), informed of guideline progress and important developments.

CLEARING AUTHORITIES

When a super office is represented on an ICH internal consultation group, the super office director may serve as a clearing authority or may designate a staff member to serve in this role. Since internal consultation group members are authorized to speak on behalf of their super office, a clearing authority may be unnecessary.

Clearing Authority Responsibilities:

- Serve as a point of contact for their office's internal consultation group members to answer questions and resolve professional differences of opinion. Early and regular communication between the super office's internal consultation group

members and a designated clearing authority, minimizes the need for lengthy or intensive final review.
- Unless major concerns are identified, provide final approval within two weeks for a draft and final ICH guideline before expert working group sign-off.

Office of Regulatory Policy Responsibilities:

ORP Regulatory Counsel Responsibilities:
- Provide legal and regulatory counsel to FDA ICH leadership team and working group experts throughout guideline development.
- Where necessary, flag legal issues for Office of Chief Counsel consultation.

ORP PRA/PTE Team Responsibilities:
- Engage with working group leads early in the guideline development process to discuss potential PRA issues and recommend options. Since delays associated with a new information collection are likely to be so significant in the U.S. as to be incompatible with harmonization efforts, any potential new information collections must be flagged as early as possible.
- Provide PRA language for insertion in NOAs announcing FDA ICH guidances. See Attachment II for additional information.
  PRA language for insertion in the NOA will be provided:
  - Within14 days after submission of draft NOA and ICH-approved guideline to the ORP PRA/PTE team
  - Within 30 days after submission of final NOA and ICH-approved guideline to the ORP PRA/PTE team

  Please note that these timeframes are consistent with the editorial timeframes provided below – and should be coordinated with the editorial staff for transmission of a final integrated document to the ICH coordinator and other designated international programs staff within OCD.

ORP Editorial Staff

Staff provide editorial suggestions for all CDER guidances, including FDA ICH guidances, in accordance with the CDER Style Guide.

Since the substance of internationally harmonized guidelines must be approved by all parties before NOA and guidance publication, editorial suggestions are limited to superficial changes (e.g., spelling, grammar, punctuation, formatting).

ORP Editorial Staff Responsibilities:
- Review FDA ICH NOAs. Format draft FDA ICH guidances. Review and format final FDA ICH guidances. See Attachment II for additional information.
  Please note that FDA's good guidance practices exclude ICH draft guidances from requirements to have certain standard elements (e.g., disclaimer statements)

that otherwise would be present in an FDA-issued draft guidance.[4] As a result, draft FDA ICH guidances are released for public comment with formatting changes only. Final FDA ICH guidances, in contrast, are edited for conformance with the CDER Style Guide, and must include the standard elements present on all other FDA-issued final guidances.[5]

- Editorial recommendations/formatting will be provided:
  - Within14 days after submission of draft NOA and ICH-approved guideline.
  - Within 30 days after submission of final NOA and ICH-approved guideline.

ORP Project Management Staff Responsibilities:

- Help to expedite announcements of ICH guidelines in the FR.
- Provide timely notification of NOA and FDA ICH guidance publication and actionable intelligence (e.g., updates regarding delays, substantive concerns, etc., to enable further timely discussions to expedite review and publication) to ICH coordinator based on feedback received from the Commissioner's Office of Policy.

Office of Communications Responsibilities:

- Routinely send ICH guidelines to all relevant email distribution lists.
- Collaborate with the ICH coordinator and subject matter experts to develop additional communications materials when the need is identified.

PROCEDURES[6]

ICH GUIDELINE DEVELOPMENT: PRE-STEP PROCESS

Annual New Topic Selection Process

ICH considers proposals for new harmonized guideline topics on an annual cycle. The cycle begins in the fall and ends with the approval of new topics by the Assembly in the spring. In between, the Management Committee evaluates the proposals and provides a recommendation on new topics to the Assembly.

The Management Committee establishes the criteria for new topics during the fall biannual meeting scheduled in late October or early November. It may also ask Members to preview potential new topic proposals at the fall meeting as a means to gauge

[4] 21 CFR 10.115(i)(3).

[5] *Id.*

[6] Please see Attachment IV for a high-level timeline mapping ICH and FDA procedures throughout the guideline development process. Additional information is also available in the References section.

preliminary interest and to inform the approach and criteria for the new topic cycle. The availability of expert resources to support development of these topics will also be discussed. The ICH Secretariat launches a formal call for proposals shortly after the fall biannual meeting – with a short deadline (typically in early December).

CDER proposals are submitted to the ICH coordinator in the new topic template. The current version of the template is provided as an Appendix in the *Standard Operating Procedures of the ICH Working Groups* cited in the References section. Authors of new topic proposals are also required to provide a slide presentation for consideration by the Management Committee's New Topic Subcommittee – and to use the presentation as a basis for briefing Subcommittee Members. Subcommittee briefings typically occur in January.

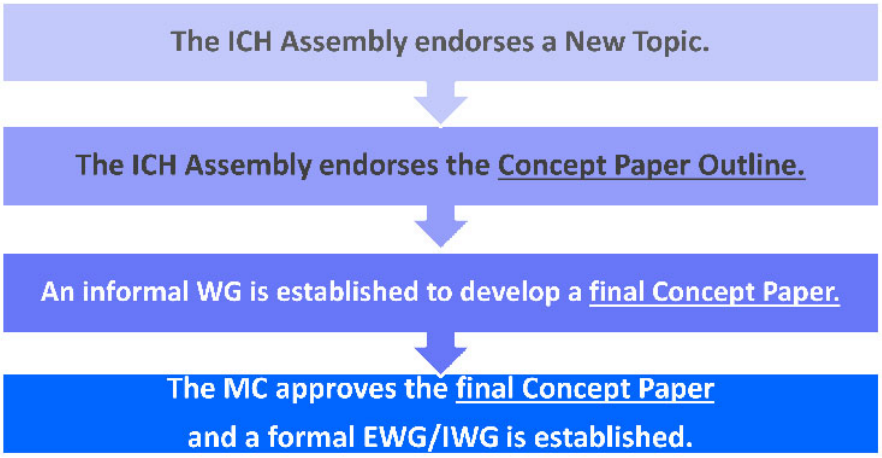
CDER staff are encouraged to contact the ICH coordinator to flag potential new topic proposals or seek advice.

Once the deadline for submission has closed, new topic proposals are circulated to appropriate caucus leads, office leaders, and subject matter experts for review and feedback on both the substantive merits and available resources required for development. The leadership team then convenes the International Strategy Council to seek senior leadership guidance and FDA prioritization of the proposals. The leadership team conveys FDA priority rankings to the Management Committee.

The Management Committee tallies the rankings from all Management Committee parties, reviews the overall rankings, and determines final collective recommendations at its interim meeting, typically conducted in March. The new topic proposals and recommendations are provided to the Assembly for consideration at the spring ICH biannual meeting.

When the Management Committee recommends a new topic for Assembly approval, the party who submitted the proposal is typically asked to develop a concept paper outline for Assembly consideration. Approval of the concept paper outline may occur concurrently with the new topic proposal or after (see Figure 2 for the ICH guideline pre-step process).

Figure 2: ICH Guideline Development: Pre-Step Process



Once the concept paper outline is approved by the Assembly, ICH establishes an informal working group to develop a concept paper. A concept paper describes the perceived problem and the issues to be resolved by a harmonization project and outlines the estimated timeline for meeting key milestones. It defines the scope and parameters of the guideline and guides its development. The template is provided as an Appendix in the *Standard Operating Procedures of the ICH Working Groups* cited in the References section.

Typically, the party that authors the new topic proposal serves as the rapporteur of the informal working group.[7] Formally, the Secretariat issues a call to Management Committee parties to nominate a regulatory chair and working group leads. The three founding regulatory members (FDA, United States; European Commission, Europe; Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices, Japan) are permitted to select up to two working group members: a topic lead and a deputy topic lead.[8] In general, other ICH parties may select only one representative. Founding regulatory members are required to appoint experts to a working group. Other parties may appoint experts but are not required to do so.

FDA's ICH leadership team nominates informal working group leads based on consultation with senior Center leadership and caucus leads.

To assure internal Agency consensus, FDA's working group leads develop a guideline clearance plan (Attachment I) to facilitate comprehensive consideration and thorough vetting of issues during development. The guideline clearance plan identifies internal

[7] The rapporteur may also enlist the help of a rapporteur supporter to serve as a project manager for the working group.
[8] A rapporteur, regulatory chair, and/or rapporteur supporter are not included in the founding members two-person per working group limit.

consultation group members and clearing authorities, and is informed by discussions within the International Strategy Council, follow-up discussions with offices, and advice provided by caucus leads. The plan is approved by the relevant Quality, Safety, Efficacy or Electronic Standards caucus lead(s), and is submitted to the FDA ICH leadership team when the informal working group completes its work. Non-electronic standards, multidisciplinary expert working groups should obtain approval from all caucus leads.

Within ICH, when all informal working group members reach consensus on a concept paper, it is submitted to the Management Committee for approval.

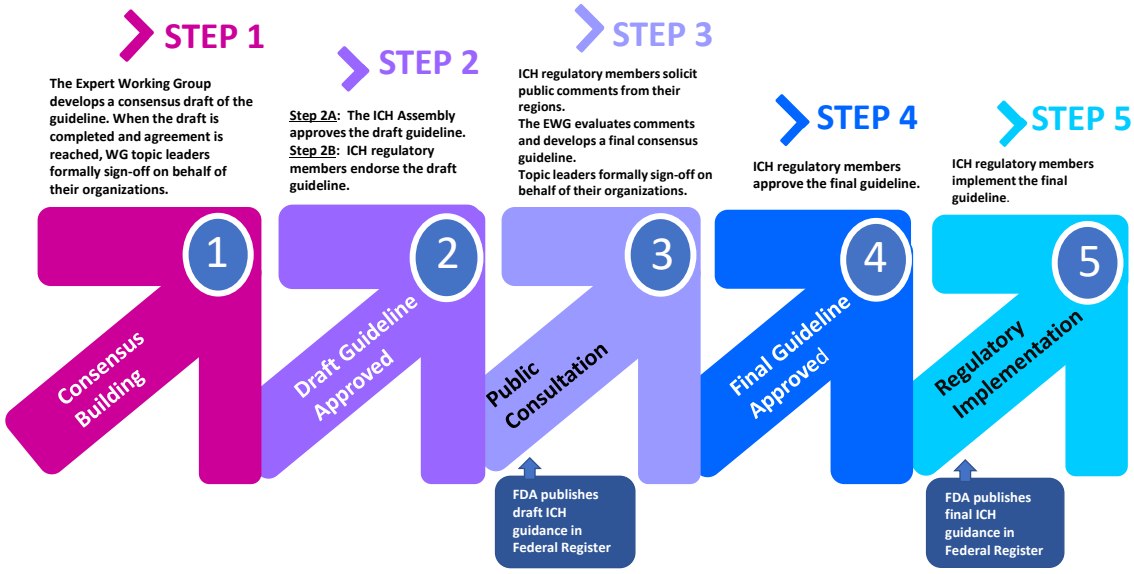
Once approved by the Management Committee, an expert working group is formed to develop the harmonized guideline based on the objectives in the concept paper. In practice, informal working group members typically transition to membership on the expert working group.

At this stage, FDA's expert working group leads are encouraged to discuss any potential PRA issues with the ORP's PRA/PTE Team to avoid creating administrative burden and adding significant delay to guideline development and clearance. If a potential new information collection is anticipated, FDA ICH working group representatives should alert the ICH coordinator immediately to discuss alternative strategies to minimize disruption.

ICH GUIDELINE DEVELOPMENT: FIVE STEP PROCESS

Figure 3 illustrates the five-step process for the development of ICH guidelines.

Figure 3: International Harmonization Process



Step 1: Consensus Building

During Step 1, the expert working group develops a consensus draft of the guideline based on the objectives outlined in the concept paper. FDA's working group leads actively participate in expert working group meetings and regularly consult with the internal consultation group on significant developments. Guideline drafts are shared for internal review, consideration, and Agency alignment. If significant substantive issues (e.g., scientific, policy, legal, etc.) arise requiring additional Center or Agency expertise, working group leads should flag these issues and seek appropriate counsel.

Before expert working group sign-off, FDA working group leads provide documents to the internal consultation group and their relevant caucus leads for approval. Once cleared, documents are shared with clearing authorities (identified in the guideline clearance plan) for a 2-week review. Unless major concerns are identified, the documents are approved for expert working group sign-off. FDA's topic lead is authorized to provide the Agency's endorsement at Step 1.

Formally, the ICH Secretariat circulates the expert working group documents to each party's topic lead for sign-off providing their organization's imprimatur of support. Once approved, the document(s) move to Step 2.

Step 2: Assembly Approval of Draft Guideline

The ICH Secretariat manages the process of moving document(s) through Step 2 consideration.

- **Step 2a:** Adoption of the draft guideline by the ICH Assembly
- **Step 2b:** Adoption of draft guideline by regulatory members of the Assembly

Once approved at Step 2 a and b, working group document(s) are posted on ICH's website: www.ich.org. The expert working group also develops a Step 2 presentation that is posted with the draft guideline and other relevant working group materials. Additional information on the Step 2 presentation is provided in the *Standard Operating Procedure of the ICH Working Groups* cited in the References section.

Step 3: Public Consultation

Step 3 occurs in three stages: Regional regulatory consultation, evaluation of regional comments, and development of a final guideline.

- **Step 3, Stage 1: Regional regulatory consultation**: ICH regulatory members solicit public comments from their regions. Regulatory authorities and industry associations in other regions may also comment on the draft guideline by submitting comments directly to the ICH Secretariat.

FDA begins this process by issuing a Notice of Availability (NOA) announcing the publication of the draft FDA ICH guidance in the *Federal Register* and posting the guidance on the FDA website.

FDA's expert working group leads begin the NOA and guidance clearance process by sending FDA's ICH coordinator a completed version of the draft guideline section of the "ICH Guideline Questionnaire for *Federal Register* Publication" (Attachment III). Based on the responses to the questionnaire, FDA's ICH coordinator, or other international programs' staff within the Office of the Center Director, draft an NOA to accompany publication of the draft guidance and coordinate Agency clearance.

See Attachment II for additional information on the NOA and FDA ICH guidance clearance process.

- **Step 3, Stage 2: Evaluation of regional consultation comments:** During this stage, the expert working group evaluates public comments to develop a consensus draft of the final guideline. Working group members are encouraged to share public comments from their region in the ICH template developed for this purpose (see template posted on FDA's ICH SharePoint page).

FDA's working group leads continue to actively participate in expert working group meetings and regularly consult with the internal consultation group on significant developments. Guideline drafts are shared for internal review, consideration, and Agency alignment. If significant substantive issues (e.g., scientific, policy, legal, etc.) arise requiring additional Center or Agency expertise, working group leads should flag these issues and seek appropriate counsel.

Before expert working group sign-off, FDA working group leads provide documents to the internal consultation group and their relevant caucus leads for approval. Once cleared, documents are then shared with clearing authorities (identified in the guideline clearance plan) for a two-week review. Unless major concerns are identified, the documents are approved for expert working group sign-off.

- **Step 3, Stage 3: Finalization of guideline:** Formally, the ICH Secretariat circulates the expert working group documents to each party's topic lead for sign-off on behalf of their organization. Once approved, the document(s) moves to Step 4.

Step 4: Adoption of ICH harmonized guideline

Regulatory members of the ICH Assembly approve the final guideline which is then posted on ICH's website.

The expert working group also develops a Step 4 presentation that is posted with the final guideline and other relevant working group materials. Additional information on the Step 4 presentation is provided in the *Standard Operating Procedure of the ICH Working Groups* cited in the References section.

Step 5: Implementation

ICH regulatory members implement the guideline according to procedures and requirements within their regions.

FDA completes the implementation process by issuing an NOA announcing the publication of the final guidance in the FR and posting the guidance on the FDA website. FDA's expert working group leads begin the NOA and FDA ICH guidance clearance process by sending the ICH coordinator a completed version of the final guideline section of the "ICH Guideline Questionnaire for *Federal Register* Publication" (Attachment III). Based on the responses to the questionnaire, FDA's ICH coordinator, or other international programs' staff within the Office of the Center Director, draft an NOA to accompany publication of the final guidance and coordinate Agency clearance. See Attachment II for additional information on this process.

You may also find it helpful to refer to Attachment IV which provides an overview of both ICH and FDA procedures for guideline development throughout the Step process.

REFERENCES

1. OMB, 1995. Paperwork Reduction Act.
2. ICH, *Standard Operating Procedure of the ICH Working Groups*, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.
3. ICH, Rules of Procedure of the Assembly, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

4. ICH, MedDRA Management Committee Rules of Procedure, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.
5. ICH, Articles of Association, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

DEFINITIONS

Assembly (ICH): The overarching governing body of ICH, including all Members and Observers who make decisions regarding the Articles of Association and its rules and procedures, admission of new members, election of Management Committee representatives, and adoption of ICH guidelines.

Concept Paper: Developed by an informal Working Group, this document describes the perceived problem, summarizes the issues to be resolved by a harmonization project, and provides an estimated timeline for reaching major milestones. The concept paper defines the scope and parameters of the final guideline and guide its development. A template is included as an appendix in *the Standard Operating Procedure of the ICH Working Group*s manual cited in the References section.

Concept Paper Outline: A brief proposed outline of a new topic proposal. Concept paper outlines are typically submitted to the Assembly for approval at the same time, or shortly after, a new topic proposal is recommended by the Management Committee.

Guideline Clearance Plan: An internal FDA document developed by informal working group leads to facilitate comprehensive consideration and thorough vetting of issues during guideline development (Guideline Clearance Plan, Attachment I). The plan identifies internal consultation group members and clearing authorities, and is informed by discussions within the International Strategy Council, follow-up discussions with offices, and advice provided by the FDA's ICH caucus leads. The plan is approved by the relevant Quality, Safety, Efficacy, or Electronic Standards caucus lead(s), and is submitted to the FDA ICH leadership team when the ICH informal working group completes its work.

Management Committee (ICH): Body that oversees operational aspects of ICH on behalf of all members, including administrative and financial matters and oversight of the working groups. The Management Committee provides recommendations on the selection of new topics for harmonization as well as on the adoption, withdrawal, or amendments of ICH guidelines.

Secretariat (ICH): ICH's administrative office located in Geneva, Switzerland. The ICH Secretariat is responsible for day-to-day management and coordination of ICH activities as well as providing support to the Assembly, the Management Committee and its Working Groups. The Secretariat also provides support for the ICH MedDRA Management Committee.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/24/2013	Initial	n/a
3/19/24	1	Change of title and content based on new internal process controls. Greater background provided.

ATTACHMENT I: ICH GUIDELINE CLEARANCE PLAN

This plan is submitted to the FDA ICH leadership team when an ICH expert working group is established. The ICH Guideline Clearance Plan is completed by FDA's informal working group leads in consultation with their office leadership and caucus lead(s), and approved by caucus lead(s) before submission.

Internal consultation group members are senior scientific experts, and, as appropriate, legal and regulatory policy experts, including working group leads, chosen to represent each relevant Center and Agency office impacted by the guideline. They form a small group to be consulted on any important issues or developments including approval of key working group drafts. Each subject matter expert is authorized to speak on behalf of their office, and is expected to flag significant issues or concerns for their office leadership.

Each super office director with representation on the internal consultation group may designate a single individual to serve as the super office's clearing authority. This person serves as a point of contact for their Internal Consultation Group members to answer questions, resolve differences of opinion, and provide final approval.

Early and regular communication between the super office's internal consultation group members and a designated clearing authority minimizes the need for lengthy or intensive final review. Prior to working group sign-off, clearing authorities are provided 14 days to review the Step 1 and Step 3 documents for any major concerns.

ICH Working Group Title		
Role	**Name**	**Center/Office**
FDA Working Group Leads		
Rapporteur/Reg. Chair (if applicable)		
Topic Lead		
Deputy Topic Lead		
Rapporteur Supporter (if applicable)		
Office Clearing Authorities		
Caucus Lead(s)[9]		

[9] For cross-cutting multidisciplinary topics, please include all relevant Caucus Leads.

Legal Review (if necessary)		

FDA INTERNAL CONSULTATION GROUP MEMBERS:

Name	Center/Office

ATTACHMENT II: *FEDERAL REGISTER* NOTICE AND FDA GUIDANCE CLEARANCE PROCESS

Internationally harmonized ICH guidelines are the product of more than 50 international regulatory authorities and industry associations developed over multiple years and approved by each. Once the Agency, and other parties, provide their official imprimatur of support, only minor editorial changes are permitted. Any non-superficial changes to a guideline can only be made through an elaborate process requiring sign-off from all parties in order to respect the international consensus reflected in ICH-approved guidelines.

Extensive internal Agency collaboration is required to develop and clear an ICH guideline, before the *Federal Register* (FR) notice of availability (NOA) and corresponding FDA ICH guidance clearance process begins. This is important, because, for the reasons discussed above, Agency stakeholders will not be able to use the NOA and guidance clearance process to provide substantive comments or advocate for policy changes.

Unlike other FDA guidances, ICH guidances also differ because they are publicly available prior to FR publication. Corresponding ICH guidelines are published earlier on ICH's website at Steps 2b and 4, described in the "Procedures" section.

International cooperation is essential to develop harmonized guidelines – and accelerated NOA and FDA ICH guideance clearance is an important component of this cooperation. Regional regulatory authorities, including the FDA, seek to align the timing of public comment periods to support collective review by expert working group members. Long delays by individual parties in publishing draft guidelines to initiate public comment, delay working group consideration and final guideline development. Accelerated NOA/FDA ICH guidance clearance is necessary to minimize disruption and delay in producing final, harmonized recommendations and to assure their timely implementation.

CDER REVIEW AND CLEARANCE OF CDER-LED FDA ICH GUIDANCES[10]

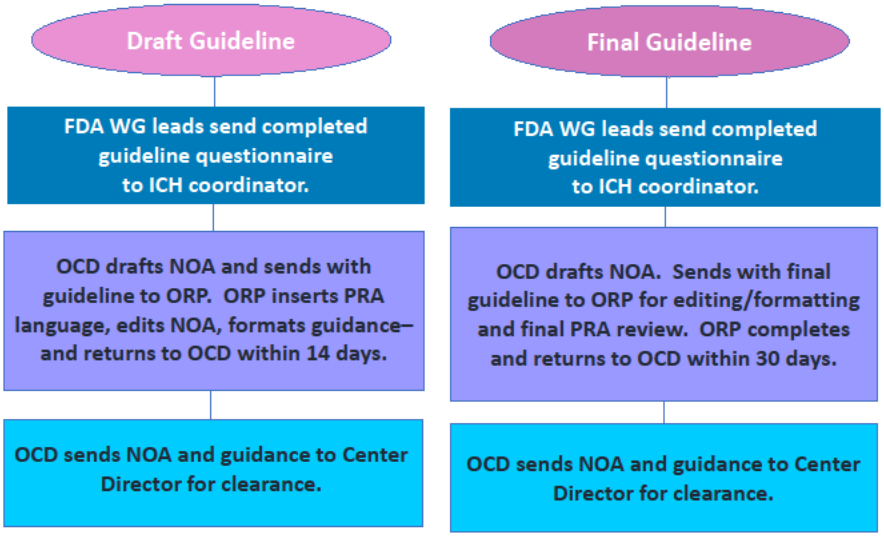
The ICH coordinator, with the assistance of colleagues in the International Programs Office within the Office of Center Director International Programs (OCD IP) lead this process -- working in close consultation with working group leads. See Figure 5 below for an illustration of the NOA and guidance clearance process.

[10] CBER-led ICH guidances are cleared through a similar process led by the Office of the Director's Regulations and Policy Staff.

ICH Guideline Questionnaire for *Federal Register* Notice Publication

FDA's expert working group leads begin the FR clearance process by completing the draft or final guideline section of the "ICH Guideline Questionnaire for *Federal Register* Notice Publication" (Attachment III) and sending it to the ICH coordinator. The questionnaire captures key information to facilitate development of the notice of availability and to respond to routine questions posed during the Agency clearance process.

Figure 4:
Expedited CDER Clearance Process for ICH FR Publication



Draft Guidelines:

Based on the responses to the questionnaire, OCD IP staff draft an NOA to accompany publication of the draft guidance. The draft NOA is then shared with the expert working group leads for review.

Next, OCD IP staff send the NOA and the draft guideline (to be published as a draft FDA ICH guidance) to the ORP editorial and PRA/PTE Team for review. ORP editorial staff edit the NOA in accordance with the CDER Style Guide. They also format the draft ICH guideline as an FDA guidance. These actions are completed within 14 days.

Please note that FDA's good guidance practices exclude ICH draft guidances from requirements to have certain standard elements (e.g., disclaimer statements) that

otherwise would be present in an FDA-issued draft guidance.[11] As a result, draft FDA ICH guidances are released for public comment with formatting changes only. Final FDA ICH guidances, in contrast, are edited for conformance with the CDER Style Guide, and must include the standard elements present on all other FDA-issued final guidances.[12]

Concurrently, ORP's PRA/PTE team review the guideline and provide language for insertion in the mandatory PRA section of the NOA. The language identifies any existing or new public information collections.[13]

A final, integrated NOA and formatted FDA ICH guidance are returned to OCD. The ICH coordinator then submits the NOA and draft guidance to the Center Director for clearance.

Once cleared, OCD transmits the documents to the Commissioner's Office of Policy, along with background materials (drafted based on responses provided by working group leads to the questionnaire) for clearance and publication. Substantive editorial suggestions provided during the clearance process are shared with the working group leads for review.

The ORP editorial team may also provide suggested edits to the guideline for consideration by FDA experts during the public comment period. These editorial suggestions do not require immediate consideration and are not bound by the FR clearance timeframe.

Final Guidelines:

Based on the responses to the questionnaire, OCD IP staff draft an NOA to accompany publication of the final guidance. The NOA is then shared with the expert working group leads for review.

Next, the NOA and the final ICH guideline are sent to the ORP editorial and PRA/PTE teams for review. The editorial team reviews the NOA and the final guideline and edits in accordance with the CDER Style Guide. Unlike the draft guidance which is published essentially unedited from the version posted on ICH's website, the final FDA ICH guidance may include minor, editorial changes (e.g., substituting British English with American English). Since the editorial team reviews the final FDA ICH guidance more closely than the draft, review may take up to 30 days.

---

[11] 21 CFR 10.115(i)(3).
[12] *Id.*
[13] As noted earlier in the MAPP, delays associated with new information collections are likely to be so long as to be incompatible with harmonization efforts.

The ORP PRA/PTE team provides the PRA language for insertion in the NOA within the same time period.

The ICH coordinator then submits the NOA and draft guidance to the Center Director for clearance. Once cleared, OCD transmits the documents to the Commissioner's Office of Policy, along with background materials (drafted based on responses provided by working group leads to the questionnaire) for clearance and publication. Substantive editorial suggestions provided during the clearance process are shared with the working group leads for review.

ATTACHMENT III: ICH GUIDELINE QUESTIONNAIRE FOR *FEDERAL REGISTER* PUBLICATION

Purpose: This document contains a list of questions required to prepare the Notice of Availability (NOA) announcing publication of an FDA ICH guidance and to facilitate Agency clearance and publication at Steps 3 and 5.

For DRAFT Guidelines/Guidances:

1. Provide a list below of clearing authorities and subject matter experts involved in development and review of a document. Note: The lists provided below should be consistent with the approved guideline clearance plan (Attachment I) submitted by expert working group leads to the leadership team at the expert working group's formation.

CLEARANCE HISTORY			
Name	**Role**	**Center/Office**	**Date**
	Clearing Authority		
	Clearing Authority		
	Clearing Authority		
	CDER Caucus Lead		
	CBER Caucus Lead		
	Legal Review (if necessary)		

INTERNAL CONSULTATION GROUP	
Name	**Office**

2. Provide a brief one- to two-sentence summary of the guideline/guidance for the NOA. Please note that a succinct summary will facilitate clearance.

3. What's the intent of guideline? Note the NOA includes a sentence beginning with "The intent of this guideline is to…"

4. Why is this important? (e.g., What's the public health value?)

5. What policies are being announced? Are there changes? Why are we making these changes? Note: if this is redundant of questions 1-3, there's no need to provide a response.

6. Beyond the interest in aligning public comment periods with other regulatory authorities, are there any notable time pressures or considerations (e.g., public meetings) related to the document?

7. List any stakeholders besides ICH members and any notable anticipated support or opposition:

8. Is there an outreach strategy (communication plan)? If one isn't planned, but it would be helpful, please indicate.

9. Does the guideline directly impact other HHS entities (e.g., NIH or BARDA), or other Federal agencies? If yes, these entities may need to review the guidelines.

FOR FINAL GUIDELINES/GUIDANCES:

Provide a list below of clearing authorities and subject matter experts involved in development and review of a document. Note: The lists provided below should be consistent with the approved guideline clearance plan (Attachment I) submitted by expert working group leads to the leadership team at the expert working group's formation.

CLEARANCE HISTORY			
Name	**Role**	**Center/Office**	**Date**
	Clearing Authority		
	Clearing Authority		
	Clearing Authority		
	CDER Caucus Lead		
	CBER Caucus Lead		
	Legal Review (if necessary)		

INTERNAL CONSULTATION GROUP	
Name	**Office**

2. What significant comments were received?

3. What significant changes were made from the draft version to final version?

4. If any notable anticipated support or opposition from stakeholders is associated with changes made since the draft was published, please indicate.

5. Beyond the interest in early implementation and alignment with other regulatory authorities, are there any notable time pressures or considerations (e.g., externally planned events) related to the document?

ATTACHMENT IV: ICH GUIDELINE DEVELOPMENT OVERVIEW