A report: "Reagents for the 1990's"

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A meeting1 sponsored by the United States Food and Drug Administration (FDA) in cooperation with the International Society of Blood Transfusion (ISBT) and the International Committee for Standardization in Haematology (ICSH), addressed key aspects of monoclonal reagent manufacture, including antibody characterization, specificity and potency tests, and assessment of product stability. The diverse background of the invited speakers and respondents ensured that similarities and differences in practice were exposed, thus enabling areas of consensus to be identified.

Workshop participants affirmed the need for continued international collaboration with a view to developing and instituting standards for—
1. The selection, description, and identification of cell lines
2. Cell line stability and safe cell line storage protocols
3. Incorporation of good manufacturing practices (GMP) and quality control at all stages of production
4. Development of reagent performance criteria
5. Serological test procedures for antibody specificity and quantification including grading, scoring, and interpreting reaction strength

For example, the inherent variability of the immediate spin technique was acknowledged, and it was agreed that, for potency estimations of blood grouping reagents, this technique should be replaced by a 5-minute incubation 'spin' procedure.

Product Characterization

There was also agreement that the identity of monoclonal cell lines used in the manufacture of blood grouping reagents should be stated in the package insert so that when the use of two reagents is mandated, products from two different cell lines can be employed.

Of the more specific issues raised, hemagglutination was considered the single most useful predictor of monoclonal antibody suitability for use as a blood grouping reagent. However, it was also observed that techniques such as immunoglobulin quantification might be useful in monitoring production. Specificity testing by hemagglutination was considered mandatory, but it was acknowledged that immunochemical characterization can disclose unexpected differences in specificity, and, therefore, should form an integral part of initial cell line characterization. The need to optimize and control the pH of the final product and of the test procedure was emphasized by several speakers.

Stability Testing

In assessing the stability of monoclonal reagents, it was noted that real-time stability studies are essential. Accelerated degradation studies, e.g., at 20°C, 37°C, and 56°C, merely give an indication of probable stability and do not always correlate well with real-time studies, although they may be useful in product development. There was agreement that red cells with weaker antigenic expression, and cells with lower site density, e.g., group A2B (H positive) for anti-A reagents, more effectively demonstrate product deterioration during storage; therefore, use of such cells is valuable in the assessment of product stability. Some participants expressed the belief that a panel of well-characterized red cells exhibiting low antigen site density, perhaps in the form of an international reference cell panel, should be used whenever possible.

Reference Preparations

Several useful points of consensus were reached on the subject of reference preparations. These should be either international standards or national/in-house minimum potency standards matched to international standards.

ABO reagents

The development and widespread use of quality monoclonal anti-A, anti-B, and anti-A,B (labeled as anti-A+B, or anti-A and B in some countries) has made it
easy to establish standards for these reagents. The FDA polyclonal reagent standards are of higher potency than the World Health Organization (WHO) polyclonal standards and were considered appropriate for international use. The need for an anti-A,B standard was left in abeyance. Current potency reference reagents do not adequately address reactivity of anti-A,B reagents with subgroups of A and B. Because these reagents are of a less critical nature and the reactivity question can best be answered with an internationally accepted cell panel, which will require a large effort to assemble, participants gave this a relatively low priority.

The ISBT/ICSH Expert Working Party on Blood Group Serology is setting up a program to evaluate monoclonal anti-A and anti-B standards adjusted to equal the potency titer of the FDA polyclonal reference preparations. It has been proposed that these new standards would replace the WHO reference preparations as the preferred standards, although it is acknowledged that the WHO standards may remain in use in countries that produce polyclonal reagents but have fewer resources.

**Anti-D reagents**

The development of potent, directly agglutinating, monoclonal IgM anti-D reagents, without potentiators, has brought simple low protein Rh(D) grouping into routine use. These reagents are excellent for testing patients’ samples but may miss some examples of weak D (Dn) and some D variants in which one or more epitopes of the D antigen are absent or reduced in site density. There was a perceived need for an IgM monoclonal anti-D reference preparation, and the proposal that this should provide a titer of 64 to 128 against R1r red cells was well received.

**Anti-human globulin reagents**

The FDA has minimum potency reference preparations for anti-IgG and anti-C3d polyclonal reagents, while the ISBT/ICSH Working Party on Anti-Human Globulin (AHG) Reagents has established two polyspecific AHG reference reagents (RIIIM and R3P) for tube tests. RIIIM defines the maximum potency of anti-IgG which will not cause prozones with weakly sensitized red cells and which contains monoclonal anti-C3c and anti-C3d antibodies that exceed the potency of polyclonal reagent anti-C3c and anti-C3d. R3P defines the minimum anti-IgG potency (which exceeds the FDA IgG reference preparation) and which also contains polyclonal anti-C3c and anti-C3d. It was noted that the anti-IgG component of the current ISBT/ICSH AHG reference reagents is less susceptible to neutralization than the FDA anti-IgG minimum potency standard. However, most participants were satisfied with the current FDA minimum potency standard.

**Other reference preparations**

An ISBT/ICSH standard enzyme (activated papain) is presently being formulated and evaluated (see discussion under “International enzyme standard”). Additionally, a weak anti-D standard reagent is planned for the near future (see discussion under “Proficiency testing”). Reference cell panels (addressed under “Requirements for Anti-D Reagents”) will also be helpful in standardizing monoclonal reagents.

**Requirements for Anti-D Reagents**

The discussion of specificity and reactivity for present and future reagents included particular emphasis on anti-D. The complexity of the Rh antigen D, although recognized for a long time, has recently become the focus of renewed attention owing to the exposure of a number of hitherto undescribed variants by many monoclonal anti-D. This has raised concern about the suitability of anti-D reagents derived from a single cell line as the sole reagent for routine Rh(D) grouping.

While monoclonal D antibodies usually react well with red cells having normal D antigen expression, their ability to react with red cells lacking some of the normal D epitopes (partial D antigen) varies considerably. Thus, many IgG monoclonal D antibodies do not react with DVI red cells, while others fail to react with DVI, or with red cells in other established categories. Furthermore, current IgM monoclonal anti-D antibodies have shown a general tendency not to agglutinate DVI red cells and to react less well, if at all, with categories DV and DVIII. The situation is further complicated by quantitative variations in D expression and by results that are largely dependent upon the particular test procedure chosen.

European and North American manufacturers have addressed this problem in different ways. In general, Europeans use two different anti-D reagents, often a monoclonal IgM reagent and either a monoclonal IgG or an IgG/IgM monoclonal blend. Many have opted for the inclusion of a polyclonal IgG anti-D reagent in their Rho(D) grouping protocol. In several countries, a simple direct hemagglutination test is thought to be adequate for determining the Rh group of patients and previously
tested blood donors; first-time blood donors and antenatal samples are further tested with an anti-D blend that has demonstrated effectiveness against a panel of weak D and D-category red cells. North Americans, on the other hand, generally favor a single reagent which is a blend of monoclonal IgM and polyclonal IgG anti-D. When manufacturing a blended reagent of this type, particular care is needed to balance the proportion of each component to avoid competition for D sites between the IgG and IgM components, which could result in false negative results in direct hemagglutination tests. Some concern was expressed about the use of such IgM/IgG anti-D blends as the sole reagent for Rh\textsubscript{0}(D) grouping.

Irrespective of reagent formulation, it was clear that the presence of a prozone must be guarded against. Methods for reagent evaluation should include a procedure to detect prozones. (The FDA-proposed performance criteria now include such a test.) The importance of creating an international reference cell panel for characterizing monoclonal anti-D was again recognized. However, it was clear that realization of such an objective will be a difficult task and success will require continuing cooperation among countries.

Caution is particularly advised in evaluation of anti-D reagents if the antiglobulin test for Du is to be omitted in manual tests on Rh\textsubscript{0}(D)-negative donor samples. Experience in the Netherlands, where this option has been pursued, has shown the importance of including rigorous evaluation of anti-D reagents. Prior to the implementation of their reagent quality assessment program, at least one case of primary immunization of an Rh\textsubscript{0}(D)-negative woman by transfusion of weak D red cells (donor "341," labeled as Rh\textsubscript{0}(D)-negative on the basis of polyclonal anti-D testing) had occurred. Because routine follow-up after transfusion is not done in most circumstances, it is possible that other undetected immunizations may occur with unknown frequency. Since the development and implementation of the reagent quality assessment program, which utilizes a panel of weak D and D-category cells, including donor "341," no new cases of immunization have been recorded. Many workers feel that until such a panel of cells is accepted and available internationally for validating proposed anti-D reagents, the antiglobulin test for Du must continue to be used for critical determinations.

The properties of the latest generation of anti-D reagents have caused an increase in the proportion of individuals previously regarded as being Du (weak D, positive by the indirect antiglobulin test [IAT]) being grouped now by direct hemagglutination test as frank Rh\textsubscript{0}(D)-positive. Much discussion centered around the minimum D-site density per red cell that could be regarded as critical in terms of primary immunization and whether it was important for anti-D reagents to detect partial D antigens for which specific markers have not so far been recognized. Though not unanimous, the majority view was that the IAT is no longer essential for the detection of weak D positives (D\textsuperscript{u}), and that it is not necessary for anti-D reagents to detect all examples of red cells with weak D or partial D phenotypes. The workshop concluded that the primary requirement of anti-D reagents should be accurate and unambiguous agglutination of red cells that apparently express a full complement of D epitopes. The development of an internationally accepted cell panel to define the critical reactivity will be essential to the future evaluation of anti-D reagents. One unresolved controversy was the minimum reaction strength acceptable for marketing anti-D reagents if detection of weak D and D variants is to be assured. Some participants felt that "one-plus" reactions are satisfactory. Others indicated that "two-plus" reactions are preferable, as they provide a better margin of safety against poor test performance and potential decrease in potency over the shelf-life.

**Labeling concerns**

Although initially discussed in regard to anti-D reagents, the following comments can be applied to other products as well. It was felt that statements regarding the reactivity of anti-D reagents with cells representing various D categories or subcategories, whether produced from a single cell line or multiple cell lines, should be included in the package insert. For example, "This product reacted with three out of four examples of D\textsuperscript{VI} cells tested." There was also a consensus that manufacturers should emphasize in the package insert both the minimum and the maximum incubation times for use with their reagents. Instances were cited of reaction strength peaking at 5 minutes and disappearing after 15 minutes. There was general agreement that tests in tubes are preferable to tests on slides, especially for Rh\textsubscript{0}(D) grouping. A suggestion was made that manufacturers might consider formulating two reagents—one for rapid tube tests and one for slide tests—rather than the single all-purpose reagent currently provided.
It was acknowledged that in cases where the user chooses to modify the diagnostic reagent manufacturer's approved methods for use, e.g., by dilution or by use in an unapproved system, the user assumes liability for the reagent's performance. The user must ensure that data validating such modifications are collected, maintained, and readily available.

**Blood Grouping Reagent Performance Criteria**

Prior to the workshop, the organizers collected reagent performance criteria from a number of countries, including Canada, France, Germany, Japan, the United Kingdom, and the United States (FDA). (The document from the U.K. was noted to be an unconfirmed draft.) Copies of these documents were issued to delegates who welcomed the concept of working towards international performance criteria.

An initiative towards this objective had already been taken by the FDA who, in the preparation of their draft documents *Proposed Revised Performance Criteria for Blood Grouping Reagents* and *Proposed Revised Performance Criteria for Anti-Human Globulin Reagents* (August 1990), had taken national and international considerations into account. While numerous aspects of performance criteria were addressed, the discussion focused on the FDA draft documents and their further revision. Many aspects of performance evaluation of reagents were discussed. For example, there was some evidence that the entire range of pH over which a particular antibody sample is reactive should be explored, and that many other factors (such as electrical conductivity, protein concentration, reaction stability and reaction strength plotted against time, and the optimal temperature range) should be part of the initial characterization of all new reagents. It was also recognized that there are two different settings for performance evaluation: (1) the evaluation performed to characterize and assess the source material and the initial lots of product in support of an FDA license application or amendment for a new product, and (2) the testing done to assure conformance with standards for each lot of product before release for use. Most of the information required for characterization and assessment of source material and initial lots for approval of new products was covered in the FDA's *Proposed Revised Points to Consider in the Manufacture of In Vitro Monoclonal Antibody Products* (first draft, September 1990). Further revisions to this document are being considered, and input was requested from the attendees.

Also discussed in detail was the document pertaining to the testing required by the FDA for product lot release: *Proposed Revised Performance Criteria for Blood Grouping Reagents* (first draft, August 1990). The salient conclusions are reflected in the December 1990 second draft of the document. Some of the most notable changes include revision of the age requirements for cells for testing purposes, deletion of the requirements to routinely include cord cells as test cells, addition of weak and variant D cells for testing anti-D reagents, inclusion of a test to detect prozones in Rh reagents, and deletion of many rare cells as required test cells. Other changes have been made as well. Workshop participants and others are encouraged to submit comments on the document.

**Anti-Human Globulin Reagent Performance Criteria**

In anti-human globulin reagent discussions, there was general acknowledgment, with special regard to monoclonal anti-IgG, that the anti-IgG component should be capable of detecting cell-bound IgG1 and IgG3, while failure to detect cell-bound IgG4 was not considered to be a disadvantage. It was also suggested that IgG of known Gm allotype should be used in the evaluation process in order to avoid mistaking an anti-isoallotype for anti-IgG.

Differences in the terminology currently used by the FDA for antibodies against particular complement components and terminology used commonly outside the U.S.A. were discussed, without resolution. The possible significance of C3 polymorphisms resulting in negative direct antiglobulin tests with monoclonal anti-C3d in cases of acquired immune hemolytic anemia was noted. Also discussed was a test for false positive reactions which was developed by the ISBT/ICSH and adopted by the FDA. Implementation of this test, coupled with the use of monoclonal anti-C3c and anti-C3d, has virtually eliminated false positives caused by excessive anti-C3d in the polyspecific anti-human globulin reagents used in routine work. With the advent of "cleaner" reagents, the problem of poor worker performance, caused by harsh shaking techniques developed to overcome the false positives seen with earlier polyspecific anti-human globulin reagents, must now be addressed through education coupled with proficiency testing. Technologists must be taught that gentle reading techniques can now be used without fear of
false positive reactions.

As with the blood grouping reagents, criteria for evaluation of new products as well as lot-to-lot surveillance are needed. Detection of subgroups and allotypes, as well as other issues of product characterization, can be covered in the initial product evaluation and documentation, while testing on products for FDA lot release should follow Proposed Revised Performance Criteria for Anti-Human Globulin Reagents. The first draft (August 1990) was discussed, and suggestions were subsequently incorporated into the revised second draft (December 1990). The most notable change is the inclusion of the warm, low ionic method for complement coating red blood cells as an alternative method. Other minor changes have also been made. Comments are still sought on the issues of a test to detect prozones, a test for resistance to inhibition, and tests with antibody-induced complement-coated cells, since agreement was not reached during the workshop.

Field Trials

The session on the design of field trials concentrated primarily on two areas of discussion. First, what is the purpose of a field trial, and second, how many and what kinds of samples must be tested? It became clear that there were several different interpretations of the purpose of a field trial. Some expressed the belief that it was sufficient to test just enough samples to gain statistical confidence that the reagent would perform satisfactorily in actual use. Others stated that it was necessary to test as many samples as possible to ensure specificity or to test enough samples to encounter all of the various antigenic expressions that exist in the populations studied. Still others thought that a field trial should show that the product works appropriately in the hands of non-manufacturers and non-experts. It rapidly became apparent that depending on the interpretation of the reason for doing field trials, the numbers and kinds of required samples would vary greatly. The only area of field trial design in which a consensus was reached was that the numbers and kinds of samples must be kept to a minimum to make trials feasible for manufacturers to perform.

In summation, it was generally agreed that field trials, especially for ABO, Rh(D), and anti-human globulin reagents, should commence only after the manufacturer has determined, either through in-house or contract testing of approximately 300 or more samples, that the reagent is of appropriate potency and specificity. At least two lots of the reagent under test and an approved reference reagent should be tested in parallel and should be blind-coded. At least three test sites are recommended, but more sites may be desirable. Ideally, the sites should vary in regard to geographic region, population distribution, size; and function. The samples should include specimens of variable age in different collection media from both patients and donors. A minimum of 3,000 unselected samples, supplemented with 100 samples in each of several special categories, is usually adequate (e.g., elderly people, pregnant women, stored donor units, cord samples, various disease groups, frozen cells, clotted samples, anticoagulated samples, various ethnic groups). All methods in the manufacturer's directions must be covered during the field trial, but each site does not have to perform every method. It is essential that good manufacturing practices be followed with regard to recordkeeping so that results acquired through testing in other countries can be considered. Finally, it is necessary to study and resolve discrepancies and to store samples with aberrant results for future reference. Additional items of agreement are included in a new FDA document, Points to Consider for Field Trial Design and Implementation, which will be widely circulated for additional comments.

International Coordination

This session brought together the views and experience of a few ISBT/ICSH and World Health Organization/Global Blood Safety Initiative (GBSI) experts who have contributed to the running of training courses in a variety of countries. It also reaffirmed that international coordination in regard to reagent standards and standardization of techniques is essential.

Global Blood Safety Initiative Reagents

Providing a supply of high-quality blood grouping reagents in countries that do not currently have a well-established national blood transfusion program is a challenge, owing to a number of problems including, but not exclusively, insufficient funds and foreign exchange; inadequate ordering, delivery, and distribution; and unreliable information.

The Global Blood Safety Initiative (GBSI) was launched in 1988 to promote blood safety on a global basis. It receives funding from the United Nations Development Programme (UNDP) and the WHO Global Programme for AIDS, and assistance from ISBT and
organizations such as the World Federation of Hemophilia. It also receives direction from the League of Red Cross and Red Crescent Societies Blood Program and from different WHO units, including Health Laboratory Technology and Blood Safety.

Before the development of the GBSI in 1988, WHO endeavored to solve reagent supply problems by encouraging and sponsoring local reagent production. Now, several countries successfully make polyclonal ABO reagents, while a few also produce anti-D, anti-M, anti-N, lectins, and anti-human globulin reagents. Although this approach works well in many countries, it is not without problems. Donor selection criteria are not always well established. Additionally, there are many problems with transfusion-transmissible infectious diseases such as hepatitis B, human immunodeficiency virus (HIV), and malaria. In some countries, the infectious disease rate is very high while the ability to screen for and detect suitable markers in infected donors is low, owing to factors such as lagging technology and unavailability of test kits.

Since its inception, GBSI has advocated “twinning” arrangements between non-commercial institutions of western European countries and blood centers in other countries as a means of acquiring reagents at reduced cost and improving technology, with resultant improvement in safety in blood transfusion practice. One example of a twinning arrangement currently under evaluation is a Belgian Red Cross blood transfusion center that has supplied training and established cell lines for a group in Thailand. The project has proven costly to set up, and it still has to be determined whether the low labor costs will result in overall savings. Additionally, there have been some technical problems that still have to be dealt with.

An alternative approach is to arrange for bulk purchase of approved monoclonal or other quality reagents from commercial sources. Although this approach eliminates the major hurdle of specificity evaluation, other factors such as funding, bottling, quality control, and distribution remain to be addressed. It is hoped that WHO and GBSI will achieve success once these issues are resolved. The problem of distribution throughout countries lacking centrally managed networks remains a major obstacle to the progress of such a program. Some small countries have found programs of this nature profitable. For example, Finland found their acquisition program could reduce reagent cost by 50 percent while increasing reagent quality.

**Blood transfusion**

Ensuring safe blood transfusion in these same countries is a problem, not only because of lack of blood grouping reagents, but also because of lagging education and technology owing to the lack of resources such as textbooks, reference materials, supplies, and equipment. Specialists going to these countries for the purpose of educating staff must be prepared for the difficult conditions sometimes encountered. The lack of resources can lead to problems such as clerical errors in ABO grouping and infusion of blood prior to availability of HIV test results.

A realistic approach must be taken, and transfer of expertise must focus on teaching techniques and systems that can be applied at the local level under local conditions. This sometimes consists of the fundamentals, i.e., sample labeling, accurate recordkeeping, double-check systems, basic ABO grouping, etc. Priorities for countries establishing a national blood transfusion program should be as follows:

1. **Accurate ABO grouping and HIV testing**
2. **Procurement of plasma volume expanders** (It is necessary to have these for urgent cases so that untested blood does not have to be used.)
3. **Indirect antiglobulin crossmatch** (The benefits of the crossmatch are low compared to the serious consequences of ABO incompatibility or HIV infection, and, therefore, this should be implemented only after accurate ABO grouping and HIV testing are in place.)
4. **Rh(D) grouping** (This can sometimes take a low priority in the early phase of development of a transfusion service. For example, the incidence of Rh(D)-negatives in many African countries is less than 2 percent, so Rh(D) grouping is not an immediate priority.)
5. **Antibody screening** (Antibody screening is a luxury found in countries with abundant resources. It is not usually considered for countries with few resources.)

**International Standardization**

**Standards and techniques**

The earlier consensus on acceptable international standards was reaffirmed. It was agreed that along with efforts to establish international reagent standards, steps should also be taken to establish international tech-
niques for blood grouping reagents and other laboratory methods. This standardization could begin with reagent manufacturers citing the international technique in their package inserts. International standardization will facilitate the training of staff in all countries.

It was thought that the sale of inferior-quality reagents (perceived to be a problem in some countries) would be abolished if only those reagents meeting specific standards were approved for distribution, e.g., standards set by the control authority in the country of origin or the ISBT/ICSH. Reagent labels and package inserts would reflect this information.

Central clone registry

The advantages and disadvantages of maintaining a central registry of all clones proven to produce potent and specific antibodies were briefly discussed. Some people felt that such a registry would be beneficial in providing reagents for countries with fewer resources at a reasonable cost by eliminating much of the specificity testing required when preparing reagents. However, it was also pointed out that the specificity of the final product is very often dependent on the dilution factor, the diluent, and other factors, as discussed previously. Thus, given the availability of technical resources in some countries, the simple purchase of a registered clone or an antibody from a registered clone may not solve all reagent problems. The matter was left in abeyance. It is not clear whether all manufacturers are willing to inform the consumer of a clone's identity. There was general agreement, however, that it would be very useful to identify the clone(s) in product labeling.

International enzyme standard

An international reference preparation for enzymes used for antibody screening, red cell panels, microplate testing, and automated blood grouping use has been developed and is in the evaluation stage. This preparation, the ISBT/ICSH standard enzyme, will be used in conjunction with a standard anti-D in a two-stage direct hemagglutination technique and will be used to standardize the reactivity of enzyme solutions, thus ensuring appropriate strength and eliminating problems of false positives due to excessive enzyme activity.

Antiglobulin control cells

Also addressed were possible changes in requirements for IgG sensitized cells used for the control of antiglobulin tests. It was overwhelmingly agreed that to be effective, "antiglobulin control cells" must be cells that are weakly coated with IgG so that neutralization of the anti-human globulin by poor washing or other problems in the test may be readily detected. It was also noted that most consumers prefer cells that are heavily coated with IgG (giving them a false sense of security), and seek a new supplier when only weakly sensitized cells are available from a given manufacturer. Many expressed the belief that if regulatory authorities set limits on the strength of reactivity with these cells, consumers would be forced to use cells with appropriate levels of IgG coating. A method for standardizing the level of sensitization of antiglobulin control cells was recommended that requires a negative test result when serum diluted 1 in 1,000 is added to unsensitized cells, followed by addition of anti-human globulin and the control cells. The control cells would then truly be controlling the antiglobulin tests, and poor technique (both washing and "shaking") would be exposed. With poor technique exposed, correct technique could then be taught. The consensus was that manufacturers should, as a group, take the steps to effect a change in the market along with national control authority intervention. It was also agreed that the manufacturers alone probably cannot institute such a change without the help of professional organizations such as the American Association of Blood Banks (AABB) and the ISBT. It was also suggested that memoranda from the FDA might be effective in the U.S. market.

Proficiency testing

Discussions on worker proficiency and automated cell washer quality control included consideration of the use of a standardized, weak anti-D as a means for testing and improving technologist proficiency as well as for checking the efficacy of automated cell washers used in the antiglobulin test. (This anti-D will also be used in conjunction with the aforementioned standard enzyme preparation.) Anti-D was recommended because weak anti-D is more readily available than other weak antibodies such as anti-Kidd and also because it can be more easily standardized. It was acknowledged, however, that other weak antibodies may be preferred. It was also pointed out that testing worker proficiency must be done in-house on all technologists and not just in large laboratories where often only the best technologist performs the testing. It was acknowledged that the proposed proficiency evaluation program could not address all problems in the field, but that at least
it would provide a start in improving the standard of testing.

**Slide testing**

The issue of slide testing was addressed from two different angles. First, it was noted that in order for a manufacturer to produce a product that works well on slides, particularly a product of monoclonal origin, it is often necessary to have an excessive amount of antibody in the product. This can be costly and can also contribute to problems of prozone and site "blocking" in tube testing. There are also sample identification concerns, as slides are difficult to label properly. And, finally, there are enormous biosafety concerns, at least in the United States, owing to the fact that slide edges are sharp and the method itself tends to be messy. It was generally agreed that in countries with well-established blood transfusion services, slide testing could probably be abandoned with little problem since slide tests are usually only performed as a screening test, a rechecking method, or an emergency test. However, for countries with fewer resources, where availability of electricity, equipment, and other materials is variable, slide testing is still often the only method that can be used widely. It was also pointed out that many countries in Europe use slide or slide/well tests, and elimination of slide reagents in this region may be difficult. One alternative is for manufacturers to produce two different kinds of reagents—one for tube test only and one for slide and tube test, leaving the choice to the consumer.

**Biosafety**

Biosafety was addressed very briefly. The view was presented that, whenever possible, consumers should be educated in ways of reducing biosafety hazards. In the United States, "universal precautions" as defined by the Centers for Disease Control are applicable. A few novel methods of reducing biosafety hazards were mentioned (e.g., leaving the needle in the pilot tube until the tube is transferred to the laboratory; disposal of needles, glass pipets, and slides into rigid carboys), and it was suggested that ideas of this type could be referred to the FDA, who will compile them into a "helpful hints" type of document. Pleas for the use of common sense in including suggestions in such a document were expressed. It was agreed that this is an area where discretion must be used. A compilation of the mailing restrictions used by different governments for samples will also be a helpful tool.

**FDA process**

The process for filing and reviewing medical device applications and amendments was reviewed with special emphasis on computer-controlled devices. An outline of suggested approaches for meeting FDA requirements in this area can be obtained from the Food and Drug Administration.

Copies of the complete transcript of the meeting may be obtained for the approximate cost of $60 (U.S.) through the Freedom of Information Office (FOI) at the following address: Food and Drug Administration, HFI-35, 5600 Fishers Lane, Rockville, MD 20857, U.S.A.

Copies of all FDA documents described herein may be obtained at no charge at the following address: Food and Drug Administration, CBER/DTS/LBBP/HFB-900, 8800 Rockville Pike, Bethesda, MD 20892, U.S.A. Facsimile: (301) 480-3254.

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