Driving clinical research forward with globally harmonised flow cytometry solutions

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Introduction

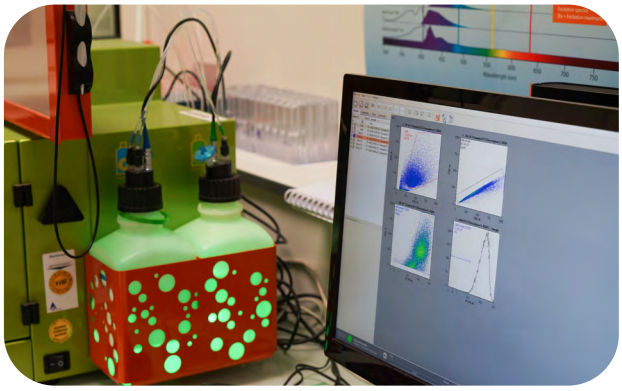
The critical role of flow cytometry in clinical trials for targeted therapies

Targeted therapies, including those in immuno-oncology, autoimmunity, infectious disease, cell and gene therapy and vaccine development are being actively evaluated in clinical studies to assess immune responses, biomarkers, and treatment effects.

These novel targeted therapies are the source of medical breakthroughs, and the sales of these new medicines are rapidly increasing. Critically assessing the efficacy and safety of a targeted therapy in clinical trials is essential. Flow cytometry is a sophisticated technology that provides specific information on how biologics and other targeted therapies interact with cells from treated participants in clinical trials.

Flow cytometry is a powerful technology for multiparametric cellular analysis, providing clinically relevant and essential information from early to late phases of clinical trials for new drug candidates. With laser technology and single-cell analysis capability, flow cytometry precisely measures targeted therapy binding to its intended cellular receptor. It also characterises cell subsets of interest that are impacted by the treatment. For example, receptor occupancy assessment may correlate with a study drug's therapeutic potential and clinical efficacy. In addition, flow cytometry can assess how clinical trial participants respond to treatment by measuring changes in relevant immune cell populations (immunophenotyping) or by analysing how cells behave or respond through functional assays, such as cytokine production, proliferation, or cytotoxic activity. In cell therapy, flow cytometry plays an important role in monitoring persistence and functional status of the drug product. Together, these capabilities make flow cytometric assays invaluable for characterising and evaluating preclinical research, demonstrating proof-of-concept, and monitoring patient outcomes in clinical trials.

Many standardised flow cytometric assays have been validated for common tests, and are available off-the-shelf, to quantify immune cells such as T, B, natural killer, and regulatory T-lymphocytes, for example. With the advent of high parameter flow cytometry, conventional or spectral, standardised immunoprofiling panels now provide an even more comprehensive assessment of key immune cell subpopulations. However, many advanced programs often require custom assay development tailored to the specific molecule and its mechanism of action. For example, detecting the presence of molecules, such as bi-specific monoclonal antibodies or checkpoint inhibitors bound to specific receptors. (Table A & Table C)



Given the cost, time and expertise needed to develop and qualify robust internal capabilities in flow cytometry, many sponsors find strategic partnering with clinical research organisation (CRO) laboratories the best solution. A partner with the scientific expertise, global resources and commitment required to effectively develop and uniformly execute flow cytometric assays can help drive successful clinical trials forward, while increasing the overall efficiency of a pharmaceutical sponsor's drug development program.

Effectively deploying complex flow cytometric assays in global studies requires an infrastructure of laboratories capable of ensuring comparable results for tests, regardless of where and when they are done. For early phase and phase 1 studies, close-proximity between clinical sites and laboratories is essential. Beyond sample collection and transportation monitoring, this global capability demands specialised expertise and rigorous quality control.

This paper presents ICON's best practices for developing and implementing flow cytometric assays in clinical studies and highlights the advantages of partnering with a strategic CRO laboratory to manage these complex assays. An important consideration in selecting the right laboratory is choosing one with the expertise to support targeted therapy development through a customised approach by flow cytometry. Regulatory compliance is also an essential consideration, to ensure assays meet CAP/CLIA, or GCLP standards based on their intended use. Finally, a laboratory with the global reach to support clinical trials around the world is also paramount.

A customised approach to flow cytometry

Customised assays used in research and early clinical trials are key in support of targeted therapy development. Because of the specificity of these customised assays, they can powerfully predict the performance potential of targeted compounds in vivo. Multiple types of custom flow cytometric assays and how they can be used to predict and assess targeted therapy performance are detailed below.

Receptor occupancy assays

The potential effectiveness of drugs and biologics that target cell receptors can be assessed using receptor occupancy (RO) assays, which measure how efficiently the compound binds to surface or intracellular receptors on selected immune cell populations of interest.

The classic approach to RO assays, is to develop two monoclonal antibodies that bind the target receptor: one that is non-competitive, meaning it binds to all target receptors even if already occupied by the test compound; and one that is competitive, meaning it only binds to unoccupied target receptors, since both the test compound and competitive antibody bind the same epitope. The non-competitive and competitive antibodies are tagged with different fluorochromes; the competitive antibody may be a labeled version of the drug itself. When added to a sample that has been treated with the test compound, the non-competitive antibody binds to all target receptors, allowing quantification of the total number of potential receptors in the samples. The competitive antibody only binds unoccupied receptors, and the ratio between unoccupied receptors and total receptors reveals the proportion of receptors bound by the test compound (see figure 1).

An alternative approach involves sequentially adding labeled competitive antibodies binding the target and non-competitive antibodies that bind the compound when it is receptor-bound, enabling direct measurement of both bound and unbound receptors (see figure 2). In general, a higher proportion of bound receptors correlates with greater potential efficacy, and this method has proven successful for test compounds of the IgG4 subclass and at least in certain cases for compounds of the IgG1 subclass.

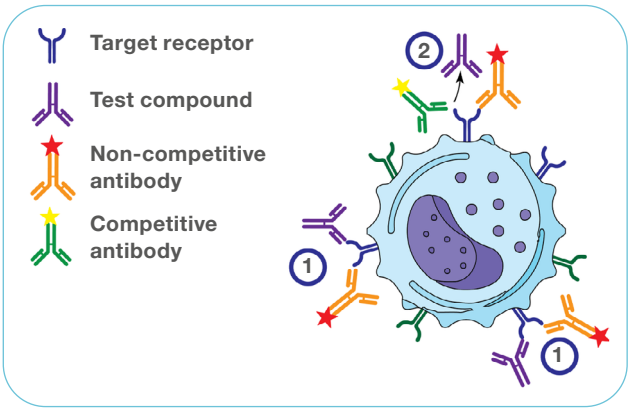


Figure 1. Determination of receptor occupancy using competitive and non-competitive antibodies.

A cell-surface receptor is targeted by two antibodies: a non-competitive antibody ( ) and a competitive antibody ( ), the latter recognising the same epitope as the test compound ( ). A saturating dose of unconjugated test compound can be used as a pretreatment to occupy all available target epitopes and define maximal receptor occupancy. Ideally, this binding is comparable to that measured using the non-competitive antibody. **(1)** When the test compound is bound to the receptor, the non-competitive antibody can bind simultaneously to a distinct epitope. The fluorescent signal from the non-competitive antibody therefore reflects total receptor expression, independent of drug binding. **(2)** In contrast, binding of the competitive antibody is reduced or abolished when the test drug occupies the shared epitope. The decrease in competitive antibody signal provides a measure of receptor occupancy by the test compound.

Running RO tests on samples treated with different concentrations and exposure times in drug development and preclinical trials can generate useful pharmacodynamic information on which compounds are likely to be successful. Flow cytometry RO tests in clinical trials can be used to inform go-no-go decisions in early clinical trials and on dosage levels in later trials to assess clinical effectiveness. RO methods are most often used in phase 1, phase 1/2, and phase 2 studies. Since every target of a test compound is receptor-specific, a customised RO assay is required for every compound tested.

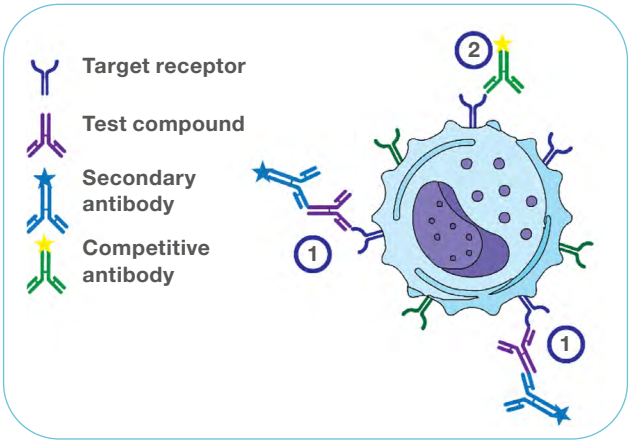


Figure 2. Receptor occupancy assay experimental design using a direct detection approach.

A cell-surface receptor serves as the target for an antibody that is competitive ( ) for the epitope recognised by the test compound ( ). Wherever free target epitopes are available, the competitive antibody can bind. Unconjugated, receptor-bound test compound is detected using a secondary antibody ( ). A saturating dose of unconjugated test compound may be used as a pretreatment to occupy all target epitopes and define maximal binding. The amount of free vs bound receptor is quantified, and percent receptor occupancy is determined.

(1) The competitive antibody binds to unoccupied target epitopes, outcompeting the test compound where the epitope is free.
(2) The secondary antibody binds to receptor-bound test compound, enabling direct detection of compound-associated receptors.

Immunophenotyping assays

Binding of a targeted compound to a specific cell type may trigger intracellular signaling that influences other immune cells and overall immune responses, with effects that may either be therapeutic or potentially harmful. Therefore, immunophenotyping assays are often run alongside RO tests to monitor these effects.

Immunophenotyping involves identifying a range of markers to identify immune cell subsets in peripheral blood, bone marrow or tissue samples. These subsets include T cells, B cells and other white blood cell types with specific biomarkers. Like RO assays, these tests use antibodies tagged with fluorochromes that bind to specific molecular targets, allowing cells to be identified and counted by type. Many of these assays are standard and commonly used, though custom assays for identifying specific antigens are frequently required.

In addition to validated immunophenotyping panels using conventional flow cytometry, spectral flow cytometry is increasingly applied for high-dimensional analysis of immune cell populations. This relatively new technique enables simultaneous detection of many markers with high resolution, allowing higher-parameter analysis and more comprehensive immune profiling. For example, an off-the-shelf validated 25-color immunoprofiling assay uses spectral flow to identify major human immune subpopulations, including T cells, B cells, NK cells, monocytes, dendritic cells, and basophils, which are critical for both innate and adaptive immune responses. Notably, the panel is designed for use with four lasers, leaving sufficient room to 'drop-in- markers to facilitate customised analyses on our five laser instruments.

Table A

Sample types	Examples
Blood and blood-derived	Whole blood, PBMCs, plasma, serum, bone marrow, cord blood, fixed whole blood e.g. Cyto-Chex
Solid tissue–derived	Tumor tissue, liver, lung, spleen, brain, lymph nodes, skin biopsies
Cell culture systems	Primary cells, cell lines, stem cells, co-cultures, organoids
Body fluids	CSF, BAL fluid, synovial fluid, ascites, pleural effusions, urine, saliva

Functional assays

Functional assays aim to characterise the presence of specific immune cells, and how these cells react to the presence of a candidate compound, such as through cytokine production, proliferation or cytotoxic activity. Clinical trial participants are treated with the compound, and flow cytometry can be used to assess changes before and after treatment in immune cell subpopulations. For example, intracellular cytokine production can be measured, or phosphorylated proteins, providing an indication of the type and magnitude of response. This gives additional insight into the pharmacodynamics, potential efficacy and side effects of candidate compounds. Functional flow cytometry assays frequently demand rapid turnaround times and close coordination with clinical sites; as a result, laboratory co-location is essential for optimal performance.

Cell and gene therapy

Flow cytometry is a vital analytical technology in cell and gene therapy, enabling high-resolution evaluation of cell identity, purity, potency, and functional attributes from early development through patient monitoring. As therapies become more complex, including the rapid growth of autoimmune CAR-T programs in conditions such as systemic lupus erythematosus (SLE), scleroderma, and myositis, there is an increasing need for highly reliable, high-parameter assays capable of characterising heterogeneous cell populations and maintaining reproducibility across instruments, sites, and study phases. Meeting these requirements demands laboratory partners with deep scientific expertise, the ability to develop and validate assays under regulatory standards such as GCP, and the operational infrastructure to ensure global harmonisation. ICON supports these needs through standardised instrumentation, mature quality systems incorporating Total Error Allowable and Statistical Process Controls, and extensive experience developing and deploying complex flow cytometry assays across clinical programs, including multiple approved CAR-T products. As a member of the NIST Flow Cytometry Standards Consortium, ICON contributes to industry-wide efforts to improve measurement comparability, participating in initiatives such as high-parameter phenotyping of CD19 CAR-T cells and orthogonal characterisation using validated ddPCR vector copy number analysis, thereby helping advance the adoption of quantitative, standardised flow cytometry in the biomanufacturing and clinical development of cell and gene therapies.

Peripheral blood mononuclear cell (PBMC) isolation

Many flow cytometry assays utilise whole blood as the analytical matrix and, under optimal conditions, samples are analysed within a short time window following collection. Over time, however, whole blood undergoes degradation due to ongoing biological processes, leading to cell death, alterations in marker expression, cellular activation, and cytokine release. Importantly, susceptibility to time-dependent changes varies across cell populations. As a result, evaluation of whole-blood stability is a critical component of flow cytometry method validation.

For phase 1/2a studies with limited samples stability, it may be necessary for clinical sites to be located in close proximity to the analytical laboratory. This requirement becomes increasingly challenging in global clinical trials, where maintaining sample integrity depends on a robust and tightly controlled transportation network linking multiple clinical sites to designated analytical laboratories. In some cases, the intrinsic stability of the target cell populations may be insufficient to accommodate these logistical constraints, necessitating the use of alternative handling strategies or matrix stabilisation approaches.

Sample stability can be extended through the use of specialised blood collection media containing fixatives (e.g., Cyto-Chex®). Alternatively, when granulocytes are not of interest, mononuclear cells can be isolated from whole blood or bone marrow (PBMCs or BMMCs) immediately after collection at the clinical site or ICON laboratories and subsequently cryopreserved in liquid or vapor phase nitrogen. Mononuclear cell isolation is generally easier to implement at clinical sites than full flow cytometry analysis and can be readily standardised across multiple locations.

The use of cryopreserved cells offers several advantages. Once frozen, samples remain stable for extended periods and can be shipped to a central laboratory for analysis. This enables all samples from an individual trial participant to be analysed within the same run, thereby reducing analytical variability. In addition, flow cytometry analysis becomes more standardised, and less dependent on ad hoc scheduling or local laboratory constraints.

Traditionally, mononuclear cells are isolated using density gradient separation methods such as Ficoll, performed either manually or using specialised collection and separation tubes, such as cell preparation tubes (CPT) and Leucosep tubes. More recently, automated PBMC isolation platforms have gained prominence, offering improved reproducibility, higher cell yields, and enhanced cell viability. In general, heparin or EDTA whole blood is recommended for PBMC-based flow cytometry assays, while EDTA is preferred for downstream molecular testing.

ICON Laboratory Solutions has well-established, standardised, and harmonised global procedures for PBMC isolation from whole blood. PBMCs are routinely isolated at ICON laboratories in Dublin, New York, Singapore, Lenexa, Assen, and China. Upon receipt, samples are inspected for collection date and time, blood volume, and evidence of hemolysis or clotting. PBMC isolation preferably are done within 24–48 hours of sample collection. Following isolation, cell counts and viability are performed. Isolated cells are stored either as cell pellets or in cryopreservation media in liquid nitrogen. For cryopreservation, ICON supports multiple serum-based and serum-free freezing media. An overview of the global PBCM capabilities is indicated in Table B.

Table B

Sample processing method	US	EU	APac	China	Sample type
PBMC isolation by CPT, BD vacutainer (mononuclear cell preparation tube [CPT])	✓	✓	✓	✓	WB
PBMC and BMMC by Leucosep[1] (Density centrifugation with inbuilt porous barrier)	✓	✓	✓	✓	WB, BM
PBMC and cell enrichment Miltenyi AutoMACS NEO	✓	✓			WB, BM

Table C

Applications	Standardisation and harmonisation
– Cell surface – Intracellular – Functional – Cell enrichment – Cell lines	– Global flow cytometer platforms standardised including fluorescence – Customised, standardised, global acquisition templates – Customised sponsor specific analysis templates design and training, using FCS Express with database reporting – Customised, standardised assay SOP training and implementation
Global custom assay validation or qualification expertise	
PK/PD	Receptor occupancy assays, antibody-dependent cell-mediated cytotoxicity (ADCC) assays, phosphorylation, cell-cycle, basophil activation, activation markers
Cell-based ADA, Neutralising antibodies	Anti-CAR antibodies, Nab assays using flow cytometry read out
Ultra-rare and rare events enumeration	Tetramer assays for antigen-specific T lymphocytes, myeloid derived suppressor cells, (MDSC), dendritic cell subpopulations, blasts, gamme-delta T-cells, plasma cells
Monitoring and Identifying	Chimeric antigen receptor (CAR-), checkpoint inhibitors
Cell maturation phase assays	T cells: Naïve, central memory, effector memory, effector, regulatory, activated, exhaustion B cell: Naïve, switched memory, unswitched memory, double negative, plasma
Immunophenotyping	Monocytes, basophils, eosinophils, T regulatory cells, natural killer cells, reticulocytes
Intracellular cytokines / phosphorylation assays	In Vitro stimulation of IL-2, -4, -6, -13, -17, y-IFN, NFkB, p38 pERK, pSTATs, histone acetylation
Cell enrichment	Miltenyi MACS magnetic based enrichment for leukocytes
Off-the-shelf assays	
High parameter flow 25-color immune-profiling assay (Cytek Aurora)	
Immunophenotyping panels for T-cells, B-cells and NK-cells	
Regulatory T-cells: CD4, CD25, CD127, FoxP3	
B cell depletion detection [LLOD/LLOQ]	
Checkpoint panel: CTLA-4, PD-1, Ki67, CD4, CD45, CD3, CD278 (ICOS), CD8	
BD Multi-test TBNK with Trucounttubes: CD3, CD4, CD8, CD45, CD19, CD16/CD56	
BD Multi-test TBNK with Trucounttubes: CD20 or CD14	
MRB assay: Minimal residual B cells (can detect B cells at the theoretical lower level of < 1 B cell/ul)	

Best practices for developing and implementing flow cytometric assays in clinical development programs

Due to the complexity and highly technical nature of developing custom flow cytometric assays and performing standardised assays, many sponsors choose to outsource this to experts in the field. Regardless of whether assay design and execution are outsourced or undertaken internally, a close working partnership between product researchers, clinical study design and operations, regulatory and flow cytometry experts is essential for success.

Communication, early, often and ongoing

Open communication between the sponsor and analytical experts involved with setting up a validation of the method is essential to ensure that assay strategies are aligned with specific study objectives. Whether the need is for consistent execution of standardised assay panels, refinement and validation of existing custom assays, or development of new assays, early alignment on goals, methods, and technical details helps establish a shared understanding of the assay's intended context of use. This early clarity streamlines workflows and supports efficient decision-making throughout the program. Because clinical development is inherently iterative, continued collaboration is necessary to ensure assays remain fit for purpose as study goals and data evolve.

As compounds advance through development, differences between the populations used during assay development and those enrolled in clinical studies may necessitate adjustments to assay protocols or data interpretation. In addition, the intended application of the assay—research use, clinical trials, or clinical decision-making—determines the regulatory framework that must be considered, including relevant guidance from agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

For multi-site and global studies, assay success depends on access to harmonised flow cytometry and PBMC isolation capabilities across regions. Aligning laboratory infrastructure and operational standards helps ensure consistent sample handling and data quality, regardless of geographic location. For organisations managing multiple development programs, a strategic and coordinated communication approach across all stages can maximise the value of early testing. This ensures that data generated in early development meaningfully inform clinical trial design and support objective decision-making when prioritising candidates with the greatest potential for success.

Method validation based on context of use

Demonstrating the scientific integrity of a study, not to mention winning regulatory approval, requires the presentation of methodologically and statistically reliable clinical evidence. Because flow cytometric assays provide evidence supporting product development, test programs must be designed to ensure they address relevant research and clinical questions in a way that will pass scientific and statistical scrutiny. Therefore, it is necessary to ensure assays are validated for their intended use. The CLSI H62 guideline provides recommended validation strategies for different regulatory settings and intended use of the data. These range from fit-for-purpose validation for exploratory endpoints, to analytical validation for primary clinical trial endpoints, CLIA-compliant validation for patient management and care, and ultimately the most rigorous validation and regulatory approval processes for companion diagnostic tests supporting drug treatment.

While the guidelines provide general scenarios and recommendations, the wide range of flow cytometry applications and assay types across different stages of drug development necessitates that each assay and scenario be evaluated individually for appropriate level of validation and proper assessment.

For example, assays intended for research use only may be validated for use within a single laboratory and study site, with an initial demonstration of precision in the range of 20% to 30% using standard cell samples across two runs. While assays positioned at the other end of the patient risk spectrum- such as supporting patient treatment decisions in clinical trials or serving as in vitro diagnostic tests for monitoring clinical treatment- require more rigorous Validation, which includes a more thorough precision assessment with a greater number of runs and replicates using clinical disease-state samples, cross-lab validation, and evaluation of additional parameters such as stability, limit of detection/lower limit of quantitation, linearity, selectivity and others.

For all flow cytometric methods to be implemented in clinical trials, the validation process should include:

A detailed validation plan containing:

- Background, scope and intended use of the assay
- Validation parameters with experimental outlines, validation samples, reportable results and associated acceptance criteria
- Data analysis and gating strategy
- Equipment, software, critical reagents including QC samples, antibodies and cells/cell lines, as well as other required supplies
- A full description of the method

Execution of validation experiments as described in the validation plan. Any deviation from the validation plan is documented with an impact assessment. During each run, all assay steps, instrumentation and its settings, and reagents/materials used are documented to enable full reconstruction. Post-run reviews by management, quality control and quality assurance are conducted per SOPs.

A validation report is generated, including the same sections as the validation plan, with results for each validation parameter and discussion of any deviations or results not meeting acceptance criteria.

Selecting and validating an appropriate assay tailored to a specific clinical application requires both scientific judgement and regulatory awareness. Expertise in developing, optimising and validating complex flow cytometric assays based on the context of use – combined with the ability to troubleshoot issues effectively – is essential for moving development programs forward and the success of clinical trials.

Robust data reporting, analysis and validation processes

Demonstrating assay data integrity and scientific relevance is critical for establishing overall study credibility and meeting regulatory requirements. Details of data collection methods, raw data outputs, gating hierarchy, statistical frameworks, assumptions and calculations should be clearly outlined, consistently applied, and properly documented to ensure compliance and reproducibility.

Quality control

Quality control measures are integral to ensuring assay reliability and data integrity in flow cytometry. Several essential categories of quality control should be considered:

Instrument quality control

This includes daily verification using vendor-provided control beads, routine checks of laser performance and detector linearity and periodic vendor maintenance. Together, these measures ensure that instrument performance remains stable, sensitive, and reproducible over time, supporting reliable data acquisition and consistent results across studies and laboratories.

Fluorescence quality control

This ensures that fluorescent tags used to identify cells or cell-associated biomarkers remain consistent over time and across laboratories, and that antibodies targeting the intended antigens are reliable and specific. Stained cells or calibration beads are used for this purpose. These controls are also routinely applied to establish fluorescence compensation or unmixing, as they provide well-defined single-fluorochrome signals that allow accurate correction for spectral overlap between detection channels.

Assay controls samples

Assay control samples include unstained controls, isotype controls, and positive control samples, which are essential for proper gating, background subtraction, and verification of staining specificity and overall assay performance. Collectively, these controls support accurate identification of target cell populations and consistent data interpretation. In addition, assay-specific quality control and validation ensure that customised assays and processes, such as the use of specialised cell lines, unique sample preparation methods, and quantitative or qualitative readouts are appropriately developed and scientifically and statistically validated to demonstrate the intended biological effect.

Process quality control

This includes ensuring proper sample collection, timely transportation, and maintenance of required temperature or environmental conditions to preserve sample integrity. It also involves standardised procedures for sample preparation, staining, acquisition, and analysis to ensure consistency across laboratories. To enhance efficiency, traceability, and regulatory compliance, ICOLIMS, an ICON custom-developed software, is used for sample tracking, data capture, workflow management, quality control, and reporting.

Case study: Supporting development of a new biological

The challenge

A sponsor with exclusively small-molecule experience purchased a monoclonal antibody drug candidate. Customised cellular assays were needed to assess the drug and were required for clinical trial testing.

The solution

With no experience in developing flow cytometry assays, the sponsor turned to ICON. Drawing on decades of experience and accredited facilities, ICON developed and validated assays that enabled demonstration of proof-of-concept, mechanism-of-action and receptor binding.

In addition, a robust, cell-based biomarker assay and standard operating procedures were developed in compliance with regulatory standards for use in clinical trials. The test was implemented in central laboratories in the United States, Europe and Asia in support of global trials over several years. A custom QC process was developed to monitor the fluorescence intensity of key custom reagents whose stability was unknown.

The outcome

Continuous communication to address data review for multiple trial cohorts provided high-quality data sets to the sponsor, suitable for regulatory submission. The client was highly satisfied with the results as the therapy moved toward approval.

Conclusion

Many sponsors choose to outsource customised assays and need a partner with the expertise to address their trial requirements. ICON has the scientific expertise to implement a broad range of flow cytometric assays in clinical trials. We cultivate a partnership with sponsors to provide scientific expertise, full-service assay development, and validation, followed by high- quality sample analysis to drive successful clinical trials forward.

For more information or to discuss your project requirements, please visit ICONplc.com/labs or email: Globalflowcytometryrequests@iconplc.com

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