

HOW DO YOU MAKE BETTER DEVELOPMENT DECISIONS FASTER?

WHITE PAPER

Antibody Drug Conjugate Development: Keys to Rapid IND Submission and Approval

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EXECUTIVE SUMMARY

Antibody drug conjugates (ADCs) are a relatively new type of drug that combines the targeting ability of a biologic with a highly potent cytotoxic agent. This powerful combination promises to become a game-changer in the fight against cancer—potentially replacing broad spectrum chemotherapies with more specific, less damaging options. At the same time, because ADCs' cell-killing drug payloads are thousands of times more toxic than conventional treatments, safety concerns are proportionally amplified. That makes gaining regulatory approval for first-in-man studies far more demanding than with a traditional biopharmaceutical.

While it's natural for pharmaceutical developers to focus on toxicological and pharmacological findings from animal studies, far too often, early stage ADC developers underestimate the importance of their filing's Chemistry Manufacturing and Controls (CMC) section. This may result in regulatory requests for additional information or unanticipated studies, which can delay or even permanently derail a promising program.

This white paper discusses a pragmatic approach to helping ADC developers ensure IND success. It highlights **two main challenges**:

1. **Complexity of the ADC molecule**
2. **Insufficient CMC data**

This publication outlines strategic and analytical approaches that can save time and effort, and help ensure that regulatory requirements for CMC data are satisfied. It suggests that the best way to accelerate the regulatory path to first-in-man studies is to focus the CMC development plan on three areas:

1. **Critical Quality Attributes (CQA)**
2. **Frequently overlooked studies**
3. **Platform approaches**

INTRODUCTION:

ANTIBODY DRUG CONJUGATES AND THE IND PROCESS

Before human clinical trials can commence in the United States, new drugs must go through a complicated and time-consuming Investigational New Drug (IND) application and approval process. An IND application must demonstrate complete pharmaceutical or biopharmaceutical analyses. In addition to extensive data from animal pharmacology, toxicology studies, clinical protocols and investigator information, it must include detailed Chemistry, Manufacturing and Controls (CMC) information on the manufacturing and stability of the clinical trial material (CTM).³

When it comes to clinical studies with ADCs, additional scrutiny of CTM is to be expected. The inherent instability of biologics, together with the level of toxicity associated with an ADC's small molecule payload have grave implications on patient safety. It is not surprising, then, that CMC data requirements and the level of analytical support needed to support an ADC program are substantially greater than with more traditional therapies.

According to ADC Review / Journal of Antibody Drug Conjugates:²

“One of the most critical aspects is to address all the unique issues involved in the submission of an IND completely, correctly, and in a timely fashion...”

Incomplete or incorrect information can result in requests for additional studies, delaying the filing of a successful IND or worse—the financially motivated end to an otherwise promising program. But with a well-planned approach to testing and diverse technical/analytical expertise on your team, ADC developers can avoid these pitfalls and help ensure a seamless path to the clinic.

2.0 WHY ADC DEVELOPMENT IS SO HARD

According to the 2016 Nice Insight CDMO Outsourcing Survey, 57% of companies surveyed said they were developing ADCs, compared to 51% who said they have naked monoclonal antibodies (mAbs) in development.^{4,5} Another source states that 182 companies around the world have ADCs in their pipeline.⁶

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Despite this surge, only four ADCs have been licensed to date. Plenty of examples exist of drugs that showed potential in early pre-clinical stages, but didn't progress, and were terminated. Many of these failures were due to toxicity or incomplete characterization data.^{7,8}

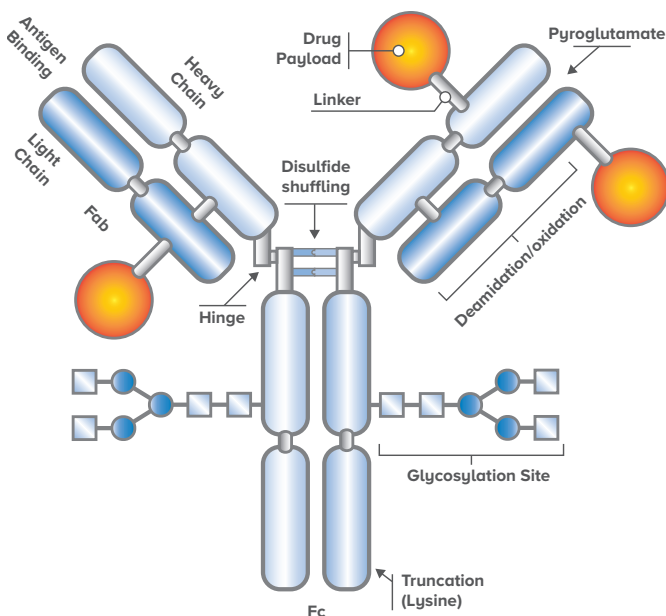
This white paper deals with two of the most common challenges relating to IND approval for ADCs. These are:

1. **The complexity of the ADC molecule itself, which is critical, as analysis of this complex structure informs decisions about its design and manufacture.**
2. **Lack of necessary CMC data on the clinical trial material**

2.1 CHALLENGE #1: THE COMPLEXITY OF THE ADC MOLECULE

The analytical challenges unique to ADC development are numerous, but chief among them are the complexity and stability of the mAb, the very difficult synthesis and characterization of the small molecule payload (cytotoxic agent) and linker, the chemical linking chemistry, and different conjugations that may be involved.^{9,10,13}

Figure 1. Schematic showing the complexity and various components of an antibody drug conjugate.



Understanding the structure and behavior of biologically derived molecules—and interpreting analytical findings to inform development decisions—requires a myriad of analytical techniques and experienced biopharmaceutical scientists.¹² Few contract manufacturing organizations (CMOs) have the breadth of testing services required for full biopharmaceutical analysis. Not surprisingly, an estimated 70%-80% of ADC analysis is outsourced.⁶

ADC analysis also requires expertise handling highly cytotoxic compounds. Because the potency of ADC payloads is much

greater than biologic drugs, it is crucial to truly understand the role that each part of the ADC – mAb, linker and cytotoxic agent – plays in the toxicity, stability and safety of a new drug.⁷

- **Linkers:** improvements in linker design focus on serum stability and drug-to-antibody ratio (DAR). The overall concern with linkers is to produce more homogenous ADC populations by studying the conjugation between linker and mAb.
- **Payloads:** choosing the right payload involves certain basic criteria, such as solubility, stability, and the likelihood of conjugation.¹¹ But ascertaining the correct drug potency also has proven to be a critical factor. According to McCombs et al, “poor clinical efficacy of first-generation ADCs is attributed to sub-therapeutic levels of drug reaching the target.”¹⁰

The IND analytical package must include not only assays and purity analyses, but also the drug-to-antibody ratio (DAR) and site(s) of conjugation. Only advanced biopharmaceutical analysis can supply this information.

Selecting the right analytical techniques is critical.¹³ Valliere-Douglass et al. suggest that conventional analytical methods used for standard biopharma characterization are not sufficient for ADCs.¹⁴ They outline the latest methods in mass spectrometry that have helped scientists fully characterize ADC drugs when conventional techniques fall short.

A list of analytical services and techniques necessary for ADC characterization is given in Part 4 of this white paper.

2.2 CHALLENGE #2: FAILURE TO PROVIDE SUFFICIENT CMC DATA

One of the primary reasons IND submissions for new ADCs are delayed is because the biopharma company (or their contract service provider) fails to perform analyses in accordance with Chemistry, Manufacturing and Controls (CMC) guidelines.¹⁵

This is because nine times out of ten, the drug developer lacks a clear plan for meeting CMC data requirements when mapping the development process.¹⁶ In fact, a key factor in streamlining your IND submission for a new ADC is finding a development partner who can help you articulate a well-planned CMC strategy early in the project.

Complete structural characterization, physico-chemical testing, and biophysical analysis of the antibody-drug conjugate are required. This includes the parent monoclonal antibody, as well as analysis of biological activity, toxicity, and stability of the drug product. Table 1 on the following page shows the structural analysis needed for the mAb intermediate.

As already mentioned, ADC analysis is more complex than traditional biopharmaceutical analysis. Multiple biopharma studies and analytical methods are required, as well as concurrent expertise in performing these techniques and interpreting the data.

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Analysis Needed	Appropriate Analytical Technique
Primary structure (complete sequence)	Peptide map-UPLC-UHR QToF
Disulfide linkages	Peptide map-UPLC/MS/MS
Secondary/tertiary structure	CD, Fluorescence, HDX-MS
Fragments Aggregates	SEC-MALS, MFI
Charge	icIEF
Glycosylation	Peptide map-UPLC/MS/MS or cleavage/labeling/UPLC
Other post translational modifications	Peptide map-UPLC-UHR-QToF
Antigen binding	ELISA, ECL, SPR
Biological activity, as appropriate	Cell bioassay (proliferation, cytotoxicity, effector)

Table 1. Necessary analysis of mAb to meet CMC guidelines, and corresponding analytical techniques

Bottom line: you may find traditional techniques used for biopharmaceutical analyses are quickly becoming obsolete. New, highly sensitive and specific technologies are becoming the standard, and are indispensable if you are to progress through the clinic ahead of your competition.¹⁷

3.0 WHY TRADITIONAL APPROACHES FALL SHORT

The complexity of the ADC molecule and lack of emphasis on CMC development strategy are the primary causes for delays in ADC IND approvals. But since most early stage developers lack internal analytical resources, they must partner with consultants or CROs who understand regulatory guidance and can help them navigate the IND process. They also need access to a full suite of cGLP and cGMP-compliant analytical testing services. But it can be difficult to find a partner with the experience and capabilities necessary to step into this role.

There are two primary reasons why the choice of outsourcing partners can be especially critical for ADC developers:¹⁷

- **Analytical Capabilities:** Older techniques are unable to provide the analyses necessary for ADC molecules – the stability of specific molecules cannot be determined, and a

deep understanding of the molecule may not be possible.

- **Absence of a Plan:** All too often, early stage developers lack a defined CMC strategy. When this is the case, archived samples often aren't set aside, validation reports and studies are inconclusive, and compatibility studies are overlooked—all of which can lead to delays and/or insufficient data. In the absence of a clearly defined testing strategy, analytical methods are not in place to ensure the identity, strength, quality, purity and potency of the drug. These are required for every New Drug Application (NDA).¹⁸

Finally, according to an article by Amer Alghabban in *Pharmaceutical Outsourcing*:¹⁹

“The way a pharmaceutical company contracts CROs/CMOs has a critical and direct impact on a company’s realization of its goal”

Alghabban states that many manufacturers – 45.6% in one survey--have reported quality problems with their vendors, inexperience with regulatory requirements, and 49.1% of vendors were not able to keep their promises.^{19, 20}

Ultimately, current practices fail to overcome the two challenges outlined in section 2 because ADC developers partner with the wrong CRO.

4.0 THREE WAYS TO STREAMLINE THE IND PROCESS FOR ADCS

There are proven ways to increase your chances of successfully filing an IND for a new ADC, and at the same time reduce the amount of effort and expense involved.

Complete characterization and protein analysis play the most important part in this process.¹³ This means characterizing attributes such as the drug-to-antibody ratio (DAR) and sites of conjugation. DAR is a critical factor for ADCs, because it represents the average number of drugs conjugated to the mAb. The DAR value influences the drug’s effectiveness, as low toxin loading lowers potency, and high toxin loading can negatively affect pharmacokinetics (PK) and toxicity. Sites of conjugation are important, because improving site-specific drug attachment can result in more homogeneous conjugates and allow control of the site of drug attachment.²¹

There are several considerations that can accelerate time-to-clinical trials for an ADC. These include:

- **Analyzing critical quality attributes, or CQA**
- **Developing a defined testing plan to ensure no necessary studies are overlooked, such as compatibility and residual solvent analysis—and a schedule that ensures the most efficient and timely completion**
- **Adopting platform approaches to ADC development**

The following sub-sections will address each of these in turn.

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4.1 CONDUCT DETAILED STUDIES OF CRITICAL QUALITY ATTRIBUTES

Critical quality attributes (CQA) are biological, chemical and physical attributes that are measured to ensure the final drug product maintains its quality, safety, and potency. The precursor to defining CQAs is complete characterization of the drug product and intermediates.

Currently, characterization of the mAb intermediate is already well defined, and includes studies such as:

- **Mass Analysis** — Intact, reduced, deglycosylated
- **Peptide Map (UPLC–UHR QToF MS):** sequencing, Post Translational Modifications (PTMs) and disulfide linkages
- **N-Glycan Profile Site, extent and structure of glycosylation**
- **Circular dichroism**
- **Differential scanning calorimetry**

CQAs (relating to safety and efficacy of the drug) for an ADC product also include the following additional assays:

Analysis needed	Appropriate analytical technique
Drug-to-antibody ratio (DAR)	HIC
Drug load distribution	Peptide map-UPLC-UHR QToF
Linkage sites	Peptide map-UPLC-UHR QToF
Linker and payload structure	FTIR, UPLC/ MS/MS, NMR

Table 2. CQAs for an ADC relating to safety and efficacy, and corresponding analytical techniques

Additional attributes considered CQA, due to their impact on health and efficacy include:

- **Free drug concentration**
- **Antigen binding**
- **Cytotoxic assays**

Free Drug Concentration

As mentioned earlier, the FDA is concerned primarily with human safety in regards to an IND submission. With ADCs, this means they are concerned with the concentration of free drug (toxin) in the final product — both on release and on stability. While the main advantage of ADCs is their targeted specificity, any free toxin introduced into the bloodstream is a serious threat to human health and safety. Therefore, any assay used to measure free drug concentration must be exceptionally sensitive (≤ 1 ng/

mL). This is typically performed by UPLC/MRM/MS.

Antigen Binding

Antigen binding is vital to the efficacy and specificity of an ADC. Non-specific binding results in the death of healthy cells and toxicity. Techniques to measure binding include:

- **Enzyme-linked immunosorbent assay (ELISA)** — a biochemical technique for detecting and quantifying peptides, proteins and antibodies. Multiple formats can be utilized, but all incorporate binding of an antibody to the analyte resulting in a subsequent signal (UV, fluorescence, phosphorescence)
- **Electro-chemiluminescence (ECL)** — a detection method based on luminescence from electrochemical reactions. ELISA and ECL can be used interchangeably, but ECL's greater sensitivity allows it to be used in other studies, streamlining the IND process
- **Surface Plasmon Resonance (SPR)** — a label-free method used to monitor noncovalent molecular interactions in real time. Generally considered a poor candidate for antigen binding, due to poor inter-day precision.

Cytotoxic Assays

While all of the physico-chemical analyses (CE, icIEF, SEC, etc.) provide an idea of the purity and stability of a single aspect of an ADC, they do not provide a measure of the functional stability of the entire molecule. Cell bioassays are the ultimate measure of an ADC's activity, stability and 3-dimensional structure, as they measure the effect of all degradation pathways. Bioassays, by their very nature, are variable and are technique-dependent, making them difficult to utilize as part of your IND submission. While research quality bioassays are sufficient for drug development; a qualified, accurate cell bioassay is an absolute requirement for an IND application. Optimizing these assays to make them precise and robust requires expert and experienced scientists. They provide a method that can be confidently used for stability and post-IND formulation development. Upon IND approval, these studies should be initiated immediately, shortening formulation/process optimization.

4.2 PERFORM STUDIES THAT ARE OFTEN OVERLOOKED

A successful IND depends on multiple studies — particularly relating to toxicology - that are often overlooked, or even neglected. This is due to a lack of planning early on in the process. And these oversights can result in delays of several months.

A number of overlooked studies should be performed prior to initiation of toxicology and other early clinical tests. These include:

- **Dose formulation**
- **Infusion set/syringe compatibility**
- **In-use stability**
- **Residual cytotoxins**

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Dose Formulation

Toxicology studies are performed at low doses and require greater sensitivity than release/stability assays. As required by the FDA, dose formulations must be assayed for toxicology studies, to ensure the correct dose is being delivered. The typical approach is ECL or ELISA. If ECL is developed for release, it is easily adapted to these studies, streamlining the overall IND process.

Infusion Set/Syringe Compatibility

Concern has been raised about the occurrence of critical incidents related to infusion sets. Every drug developer and CRO needs to establish a set of procedures to evaluate infusion sets from their vendors, particularly in terms of drug loss to surfaces. This includes filters, pre- and post-IV bags, and tubing. Multiple concentrations and durations should be tested.

In-use Stability

According to the FDA:²²

“The purpose of in-use stability testing is to establish a period of time during which a multiple-dose drug product may be used while retaining acceptable quality specifications once the container is opened”

The FDA recently announced a draft GIF #242 entitled “In-Use Stability Studies and Associated Labeling Statements for Multiple-Dose Injectable Animal Drug Products”. The draft will outline how to design and carry out in-use stability studies to support the in-use statements, for multiple-dose injectable drug products.²² While this focuses on animal and multi-dose studies, the draft also reflects the importance the FDA places on in-use stability for human trials, and yet they are often neglected during the IND process.

Multiple stability-indicating assays are required, including:

- **DAR**
- **ECL**
- **Size Exclusion Chromatography (SEC)**
- **Micro Flow Imaging (MFI)**

Residual Cytotoxins

The linkage of the payload to the monoclonal antibody is an organic chemical event involving many of the typical solvents and catalysts. Therefore, similar to traditional pharmaceuticals, both residual solvents and heavy metals must be monitored on release of the drug substance. Typical assays include:

- **DMA (Dimethylacetone)**
- **DMF (Dimethylformamide)**
- **THF (Tetrahydrofuran)**
- **Palladium**
- **Platinum**

4.3 ADOPT A “PLATFORM” APPROACH

The basic idea behind a platform approach is to leverage “prior

knowledge” to reduce the effort needed to start clinical trials. It begins with identifying a class of molecules that show comparable characteristics, such as physico-chemical properties and stability profiles.²³

New candidates with characteristics that match known molecules can be treated as a “next-in-class” candidates. Once comparable characteristics are validated, developers can focus additional testing on areas of difference between the new candidate and historical likenesses—reducing testing requirements and at the same time further adding to the body of shared knowledge related to the platform, and increasing the platform’s robustness.

Adopting a platform approach can significantly streamline IND testing requirements, accelerating time to clinic and reducing costs. According to Bradl et al., the platform approach enabled biopharmaceutical development for toxicological studies within 14 months after receiving DNA sequences.²⁴ After another six months, material from GMP facilities was provided for clinical studies. This resulted in a time requirement of 20 months from DNA to Investigational Medicinal Product Dossier.²⁴

Of course, a key element is actually identifying those molecules that match the definition of a “next-in-class” candidate. Careful planning in regards to methods, data, and documentation will provide a universal approach applicable to other antibody drug conjugates.

Standardization of instrumental parameters, data collection and data manipulation can speed up characterization. The necessary studies include:

1. **QToF** – An ultra-high resolution Quadrupole Time of Flight MS, coupled to a UPLC can provide the vast majority of characterization data. Powerful QToF software, designed specifically for proteins, deconvolutes complicated mass spectra, simplifying data interpretation. The QToF can determine:
 - **Complete sequence**
 - **Post translational modifications**
 - **Glycan profiles**
 - **Payload linkage sites**
 - **Disulfide linkages**
2. **Release and Stability:**
 - **The majority of assays are similar for all ADCs: SDS CE, icIEF, SEC, UV, and DAR. Generic assays can be qualified directly and only modified/optimized if qualification criteria are not met.**
 - **Design method qualifications appropriate to Phase I and template protocols**
 - **Binding assays should all utilize ECL. The sensitivity of this technique allows it to be used for toxicology and compatibility studies, as well as release and stability.**

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Other investigations typically include prophylactic studies in anticipation of agency questions. While they are not necessarily required for the IND filing, having data to support responses to agency questions will prevent delays. By preparing data in an IND-ready format, you'll ensure "drag and drop" of the data, greatly facilitating the process in the typical last minute rush to complete the IND.

5.0 BUYER'S GUIDE: CHOOSING THE RIGHT CRO FOR FAST IND SUBMISSION AND APPROVAL

According to a report by Global Industry Analysts, Inc., the global biopharma market is estimated to reach US\$306 billion by the year 2020.²⁵

With this continued market expansion, including antibody drug conjugate development, there is a greater need for contract lab support. Not only this, but there is a critical need for high-quality contract laboratory partners who understand the regulatory guidelines, can perform required risk assessments, and can develop, validate and execute challenging analytical procedures.

If you're looking for help from a CRO to reduce risk, and increase your chances of a successful IND submission, here's what you need to look for:

- 1. True loyalty and partnership.** You need a CRO that will take complete ownership of your product, and not just treat it like another sample. A CRO that partners with you closely – and isn't simply a vendor – means they form a core part of your team, and have a personal stake in your success. They're hands-on, and keep you updated every step of the way. Whatever CRO you choose, be sure they make their experts available to you at all times. They should take part in meetings, telecons, kick-off calls, and be involved in every stage of the process.
- 2. Scientific expertise.** Significant scientific expertise in biopharmaceutical development and biopharma services is a must. A large proportion of the CRO staff should be made up of Ph.D. scientists and biopharma veterans. The CRO should assign scientific advisors that act as connections between your team and theirs. Their expertise and scientific background means they can accurately map out the entire process, from development to IND submission.
- 3. The right experience.** Ideally, your CRO should have experience supporting successful IND submissions under tight deadlines. They should also have a solid track record of working on multiple biopharma products over several years. These drugs should span a wide range, from monoclonal antibodies and antibody-drug conjugates, to biosimilars and pegylated proteins. All projects need to be backed by an exceptional regulatory record.
- 4. Flexibility.** Flexibility is important when the unexpected happens. Your CRO needs to work closely with you to determine the best analytical approaches. Their

flexibility (and scientific expertise) means the CRO can think outside the box when things don't go according to plan. They can quickly identify alternative ways of getting things done. In fact, finding novel ways to characterize and understand biopharmaceutical behavior is often necessary to file a successful IND.

- 5. Full range of analytical biopharma services.** The complexity and heterogeneity of ADCs mean they are exceptionally challenging to characterize. A full suite of analytical services is necessary to do this. Be sure to ask your CRO about their capabilities, and what biopharma services they offer. As mentioned in this white paper, you need to be sure your CRO won't overlook anything, and can help you meet CMC regulations. Their scientists should be experts in these techniques and interpretation of their data. At a minimum, these techniques should include cell-based bioassay development and analysis by ultra high-resolution QToF, as well as routine release and stability testing.

6.0 CASE STUDY: CMC SUPPORT FOR ANTIBODY DRUG CONJUGATES

Situation

- Virtual client had very aggressive timelines for submitting INDs for two antibody drug conjugates within 12 months
- Client requested complete chemistry support for the CMC section of the IND

Solution

- In collaboration with the client's scientists, EAG proposed a fast-tracked method development and validation program to meet their timelines.
- EAG scientists performed complete characterization of the mAb and drug product, including complete sequencing, PTMs, and glycan analysis
- Developed and validated multiple methods for release and stability including: icIEF, ELISA, cell bioassay, DAR, free drug, N-linked Glycan, SEC, CE-SDS, and HCP

Outcome

- All data was delivered to the client within the deadline, and both INDs were submitted on schedule
- Both INDs were successful, and the FDA had no observations/remarks regarding the EAG's portion of the IND

Our client's priorities changed during the study, requiring additional studies beyond the scope of the original project. We were able to accommodate these changes and still meet their deadlines. EAG scientists were fully involved in project kick-offs.

7.0 CONCLUSIONS AND TAKING THE NEXT STEP

Finding a CRO who can partner with you to accelerate your antibody drug conjugate IND submission is challenging. It's not easy to determine which CROs can truly partner with you to help you achieve your objectives.

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This white paper has outlined two critical challenges with ADC development. Specifically, these challenges relate to successfully filing an IND. They are:

- **The complexity of the ADC molecule**
- **Failing to meet CMC regulations**

Given these challenges, there are 3 ways to streamline the IND process:

- **Characterize all critical quality attributes**
- **Perform studies that are often overlooked**
- **Adopt a platform approach**

By eliminating any CROs that don't measure up, you can narrow your choices down to a short list of two or three options. We hope you'll consider working with EAG Laboratories.

To find out how EAG Laboratories can help you overcome these challenges, and file a successful IND under tight deadlines, please contact us at +1.888.219.9187 or visit us online at eag.com.

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